**Updates in Hypertension and Cardiovascular Protection**
*Series Editors:* Giuseppe Mancia · Enrico Agabiti Rosei

Adel E. Berbari
Giuseppe Mancia *Editors*

# Disorders of Blood Pressure Regulation

## Phenotypes, Mechanisms, Therapeutic Options

ESH European Society of Hypertension

Springer

# Updates in Hypertension and Cardiovascular Protection

The aim of this series is to provide informative updates on both the knowledge and the clinical management of a disease that, if uncontrolled, can very seriously damage the human body and is still among the leading causes of death worldwide. Although hypertension is associated mainly with cardiovascular, endocrine, and renal disorders, it is highly relevant to a wide range of medical specialties and fields – from family medicine to physiology, genetics, and pharmacology. The topics addressed by volumes in the series *Updates in Hypertension and Cardiovascular Protection* have been selected for their broad significance and will be of interest to all who are involved with this disease, whether residents, fellows, practitioners, or researchers.

More information about this series at http://www.springer.com/series/15049

Adel E. Berbari • Giuseppe Mancia
Editors

# Disorders of Blood Pressure Regulation

## Phenotypes, Mechanisms, Therapeutic Options

ESH European Society of Hypertension

Springer

*Editors*
Adel E. Berbari
Internal Medicine
American University of Beirut
Medical Center
Beirut
Lebanon

Giuseppe Mancia
Emeritus Professor of Medicine
University of Milano-Bicocca
Monza
Italy

ISSN 2366-4606 ISSN 2366-4614 (electronic)
Updates in Hypertension and Cardiovascular Protection
ISBN 978-3-319-59917-5 ISBN 978-3-319-59918-2 (eBook)
https://doi.org/10.1007/978-3-319-59918-2

Library of Congress Control Number: 2017955687



Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

# Preface

Over the last decades progress in our understanding of the pathophysiology, epidemiology, and therapeutic approaches to hypertension has led this condition to be viewed differently from the past. Hypertension, initially classified as primary and secondary, is now subdivided into a much larger number of phenotypes based on demographics, comorbidities, presence or absence of other risk factors, or target organ involvement. Genetic involvement is also now clearer. The aim of this book is to discuss the multiple new aspects (some of which novel) of the hypertension disease. Sections are devoted to the general aspects of hypertension including the clinical importance of blood pressure values different from the conventional office ones, the relevance to pathophysiology and prognosis of circadian rhythm and seasonal variations in blood pressure, the temporal evolution of treated and untreated hypertension, and the factors involved in the appearance and progression of a blood pressure elevation, including the possible contribution of single or, for essential hypertension, multiple genes. Other sections deal with the clinical aspects of hypertension, and the specific therapeutic options for each hypertension phenotype. This extends to prehypertension as well as to white coat, masked, renovascular, endocrine, pediatric, and gestational hypertension. Finally, the book reviews hypertension phenotypes that are less well known and dealt with by classical textbooks, i.e., calculus renal disease, stress-induced hypertension, pseudo-hypertension, paroxysmal pseudo-pheochromocytoma, and other rare causes of blood pressure elevation such as Turner syndrome, hypertension due to herbal and medicinal compounds and drugs, to call attention to these rarer conditions which are nevertheless mechanistically and clinically relevant.

We hope that physicians and investigators interested in hypertension will find the content of the book stimulating and useful to their professional activity.

Beirut, Lebanon — Adel E. Berbari
Monza, Italy — Giuseppe Mancia

# Contents

# Part I

# General Aspects

# Introduction: Definition and Classification of Arterial Pressure Phenotypes

1

Lawrence R. Krakoff

## 1.1 Introduction

The title of this book and the range of topics that are covered in its chapters indicate a large, complex, and ever-growing body of medical science related to blood pressure and, in particular, the application of that science to care of a very large fraction of the globe's human population [1]. The cardiovascular scientist defines blood pressure as the measured force upon the blood at some point from within the heart to the vascular tree from arteries to capillaries to veins and back to the pump. Clinicians usually refer to the measurement of pressure in the upper arm (brachial artery pressure). Much of the population may consider blood pressure to overlap with "pressure," meaning mental stress related to the "pressure" of work, family concerns, and various threats. "Blood pressure" alone may not be the optimal term for all these perspectives, so that more precise and meaningful terms are truly needed for an accurate set of definitions that capture current research in this very important area of cardiovascular medicine.

"Hypertension" or "high blood pressure" has been recognized since the nineteenth century as a disorder in which the systemic arterial pressure is persistently increased above a normal or safe level. The effect of hypertension is its association with adverse consequences for those with the disorder [2]. Initially recognized as a manifestation of chronic kidney disease, hypertension was subsequently identified in many without kidney disease, but who had specific causes for their high blood pressure. However, as the epidemiology of high blood pressure progressed, it soon became apparent that the large majority of those with high blood pressure had no other obvious disorder to account for their condition. Thus, the terms "essential hypertension, primary hypertension, and even idiopathic hypertension" entered

L.R. Krakoff, M.D.
Center for Cardiovascular Health, Icahn School of Medicine at Mount Sinai,
New York, NY 10029-6574, USA
e-mail: Lawrence.krakoff@mountsinai.org



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_1

medical language, and secondary hypertension became the label for the far less common diseases, mostly of the kidneys or adrenal glands. Until the 1960s, clinical classification of normal and high blood pressure was binary and depended, with rare exception, on the stethoscope and mercury manometer of the doctor's office or hospital location.

The past 50 years have seen unprecedented growth in technology, physiology, pathology, pharmacology, epidemiology, and clinical care for those with disorders of systemic arterial pressure. It is now certain that the level of arterial pressure and its variability are traits that define phenotypes and that both genetic patterns and various lifestyles and exposures participate in defining that phenotype. The range of classifications and definitions for characterizing systemic arterial pressure and, most importantly, the linkages between these definitions to cardiovascular risk and its management have rapidly expanded. The following section of this introduction will survey the current classifications relevant to the phenotypes that define high and low arterial pressure that will be the detailed subjects of the following chapters of this book.

## 1.2 Which Pressure?

Recording the pressure wave form within arteries discloses several specific characteristics: the peak or *systolic pressure* generated by cardiac stroke volume, the lowest pressure between peaks or *diastolic pressure*, and the difference between systolic and diastolic pressure or *pulse pressure*. The mean arterial pressure is the average pressure for the entire cycle and is near to the diastolic pressure plus one third of the pulse pressure.

Brachial artery pressures have been the basis for past assessment of arterial pressure whether in diagnostic studies or randomized trials of antihypertensive therapy. However, the actual systolic and diastolic pressures "seen" or exposed to the coronary, carotid, cerebral, and renal arteries differ from brachial pressures and may be more closely related to pressure-related pathology. Noninvasive methods for assessing *central aortic pressure* have been developed and explored to define large artery properties more precisely than relying on brachial measurements. Measuring central aortic pressure may be a useful supplement for patient management [3]. Likewise assessing stiffness of large arteries has previously depended on the simple difference between systolic and diastolic brachial pressures, i.e., *pulse pressure*, but more accurate techniques relying on aortic pulse wave velocity and analysis of reflected waves are now available and being implemented in clinical research [4].

## 1.3 Classification of Systemic Arterial Pressure

Table 1.1 displays the definitions for normal and high blood pressure in adults, based on recent guidelines for clinic pressures. The terms isolated systolic hypertension or isolated diastolic hypertension apply when one of the pressures is elevated

**Table 1.1** Classification based on level of clinic pressures

| Definition | Blood pressure range (mmHg) | Comment/source |
|---|---|---|
| Normal-optimal pressure | <120/80 | All guidelines |
| Prehypertension | 120–139/80–89 | JNC-7 [20] |
| High normal pressure | 130–139/85–89 | EHS [21] |
| Hypertension | ≥140/90 | Most guidelines |
| Resistant hypertension | ≥140/90 | On treatment with 3+ antihypertensive drugs, usually including a diuretic [22] |

**Table 1.2** Other definitions. Comparison between systolic and diastolic hypertension

| Definition | Clinic systolic pressure | Clinic diastolic pressure | Comment |
|---|---|---|---|
| Isolated systolic hypertension | ≥140 mmHg | <90 mmHg | In younger (<50) patients associated with high cardiac output. Well-trained athletes |
| | | | Most frequent in patients >50 years related to increased arterial stiffness |
| Isolated diastolic hypertension | <140 mmHg | ≥90 mmHg | Seen in younger patients and associated with increased risk |
| Exercise hypertension [23] | ≥210 mmHg for men ≥190 mmHg for women | ≥90 mmHg or ≥10 mmHg increase | Associated with increased risk factors or left ventricular hypertrophy |

and the other is not, as shown in Table 1.2. During exercise, systolic pressure increases, but the change in diastolic pressure is less consistent. Also shown in Table 1.2 are criteria for exercise-related hypertension.

In routine clinical care, one or a few pressures are measured with uncertain methods despite available guidelines [5]. Improvement in accuracy for office measurement has been recommended, in part by taking more measurements using automated devices, such as the BpTRU [6].

The determinants of arterial pressure are related to age. Elevated systolic pressure, per se, has a somewhat different pathophysiology and significance for age <50 and older populations. For the elderly, arterial fibrosis and calcification contribute to systolic elevations with wide pulse pressures [7]. Age norms for systolic and diastolic pressures for *pediatric* and *adolescent* populations have been derived that define normal pressure, prehypertension, and hypertension in these age groups. These are based on specific age-related cutoffs for upper 90% and 95% percentiles [8]. This age-related definition of hypertension for children from age 10 and upward is significantly correlated with hypertension in adult life based on a long-term tracking study [9].

For accurate diagnosis or classification, useful and reliable methods are crucial. The development of accurate devices for use in both the clinic and out-of-the office settings has radically changed the spectrum for classification of systemic blood pressure [10]. In developed nations, ambulatory blood pressure monitors, home

**Table 1.3** Classification based on comparison between clinic and out-of-office pressures

| Definition | Blood pressure range (mmHg) | Comment/source [24] |
|---|---|---|
| White coat hypertension | Clinic pressures ≥140/90 and 24 h ABP <130/80 or home blood pressures <135/85 | Untreated |
| White coat effect | Clinic pressures ≥140/90 and 24 h ABP <130/80 daytime or home blood pressures <135/85 | Treated patients |
| Masked hypertension | Clinic pressures <140/90 and 24 h ABP >130/80 or home blood pressures >135/85 | Untreated patients |
| Masked resistant or uncontrolled hypertension | Clinic pressures <140/90 and 24 h ABP >130/80 or home blood pressures >135/85 | Treated patients |

blood pressure devices, and improved devices for multiple measurements in the clinic are widely available. Comparison between clinic pressures and out-of-office pressures has led to definition of white coat hypertension and masked hypertension, as described in Table 1.3. The importance of 24 h ambulatory blood pressure monitoring or home blood pressure monitoring has now been widely recognized as reflected in several national and international guidelines [11–15]. The integration of accurate home devices with telemedicine now links measurements to the provider's medical record for ease in comparison between measurements in the unique environment of the clinic/office and the more usual environment of the patient's activity [16].

Hypertension occurs most often without a specific cause and is now generally named essential hypertension in English or its equivalent in other languages. In the past, this condition has been labeled "primary hypertension" or "idiopathic hypertension." The latter term seems, to me, an admission of ignorance, whereas "essential" or "primary" hypertension conveys the implication that a built-in, possibly genetic setting explains why the pressure is increased. When genetic explanations emerge, the term "essential" hypertension may be replaced by such definitions as "polygenic" hypertension in contrast to "monogenic" hypertension that is already in use (see below).

Hypertension caused by or linked to a specific diagnostic entity had been called "secondary" hypertension in past literature. Most often this term referred to rare or infrequent diseases, such as various forms of chronic renal disease, e.g., those with proteinuria nephropathies or adult polycystic kidney disease. The JNC-7 guideline of 2003 introduced an alternate and more inclusive term "identifiable hypertension" that could be applied to such disorders as hypertension associated with obesity or with the sleep apnea syndromes [17]. Table 1.4 lists many of the diagnostic entities considered to be forms of identifiable hypertension. For some the specific pathophysiology causing hypertension is well defined as in the very rare monogenic disorders. The pathophysiologic links are far less clear in many disorders with some having polygenic patterns and others with dominant environmental or acquired traits, e.g., obesity.

**Table 1.4** Identifiable hypertension

| |
|---|
| Prevalent forms of identifiable hypertension |
| Obesity hypertension |
| Sleep apnea syndrome |
| Associated with either type 1 or type 2 diabetes mellitus |
| Renal hypertension |
| Associated with various forms of chronic renal disease |
| Associated with genetic renal disease including polycystic kidney syndrome |
| Associated with monogenic renal tubular genetic disorders: Liddle's syndrome, pseudohypoaldosteronism, etc. |
| Adrenal hypertension |
| Low-renin syndromes |
| Primary aldosteronism |
| Glucocorticoid remediable aldosteronism |
| Congenital adrenal hyperplasia syndrome |
| 11-OHase deficiency, high DOC |
| Apparent mineralocorticoid deficiency |
| Genetic due to deficiency of 11-OH dehydrogenase |
| Acquired due to licorice-like ingestion |
| Excess glucocorticoid syndromes |
| Cushing's syndrome due to pituitary tumors, adrenal adenoma, hyperplasia, or carcinoma |
| Drug related |
| Exogenous glucocorticoid use |
| NSAID use |
| Ephedrine and ephedrine-like sympathomimetic drugs |
| Cocaine |
| Cyclosporine and calcineurin inhibitors |
| Anti-vascular endothelial factor (VEGF) chemotherapeutic drugs: bevacizumab and related agents |

### 1.3.1 Variability of Blood Pressure

Having multiple blood pressure acquired by one of the methods mentioned above, discernable patterns have been recognized that add to the complexity of simple diagnosis, but may add value for prediction of risk, especially for stroke and eventual therapy. At night, the normal expected variation in pressure is a 10–20% fall, the "dipper" pattern. Lack of this fall, "non-dipper" pattern, a nocturnal increase in pressure, the "reverse dipper" pattern, or a greater than normal fall in pressure "extreme dipper" pattern have been studied with relevance to risk of future cardiovascular disease. Seasonal patterns for blood pressure can be detected during the year, most likely due to changes in temperature from warmer to cooler months.

When several pressures are measured, the average and standard deviation can be calculated. Variabilities reflected in the standard deviation (SD) or coefficient of variation (CV) and SD/average have been the subjects of study [18, 19]. From 24-h ABPM or multiple home pressures, the *intraindividual variability* can be calculated. When multiple clinic pressures are available, *intervisit variability* or *visit-to-visit variability* can be assessed. *Interindividual variability* can be derived from population or group studies in which variability can be compared within the cohort to arrive at normal and abnormal values. All of these estimates of variability are now the subject of active research.

## 1.4 Summary

Many terms related to arterial pressure have become regularly used for describing clinically important classifications. Improved methods for accurately measuring pressure repeatedly throughout the spectrum of daily activities including the clinic visit have led to recognition that the clinic visit is a limited and perhaps misleading site for assessing prognosis and the effect of therapy. However, these insights have yet to be fully translated into a practical application for use in many populations, especially when resources are limited. Among the challenges for clinical research in hypertension are the efforts to develop effective and cost-effective strategies that maximize both prediction of individual risk and monitoring treatment.

## References

1. The Lancet (2007) Hypertension: uncontrolled and conquering the world. Lancet 370:539
2. Pickering G (1964) Systemic arterial hypertension. In: Fishman AP, Richards DW (eds) Circulation of the blood: men and ideas. Oxford University Press, New York, pp 487–541
3. Sharman JE, Marwick TH, Gilroy D et al (2013) Randomized trial of guiding hypertension management using central aortic blood pressure compared with best-practice care: principal findings of the BP GUIDE study. Hypertension 62(6):1138–1145
4. Westerhof N, Westerhof BE (2013) A review of methods to determine the functional arterial parameters stiffness and resistance. J Hypertens 31:1769–1775
5. Pickering TG, Hall JE, Appel LJ et al (2005) Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on high blood pressure research. Hypertension 45(1):142–161
6. Myers MG, Valdivieso M, Kiss A (2009) Use of automated office blood pressure measurement to reduce the white coat response. J Hypertens 27(2):280–286
7. McEniery CM, McDonnell BJ, So A et al (2009) Aortic calcification is associated with aortic stiffness and isolated systolic hypertension in healthy individuals. Hypertension 53(3):524–531
8. National High Blood Pressure Education Program Working Group on High Blood Pressure in Childred and Adolescents (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 114(2 Suppl 4th Report):555–576
9. Kelly RK, Thomson R, Smith KJ et al (2015) Factors affecting tracking of blood pressure from childhood to adulthood: the childhood determinants of adult health study. J Pediatr 167(6):1422–1428. e2
10. Krakoff LR (2016) Blood pressure out of the office: its time has finally come. Am J Hypertens 29:289–295
11. Daskalopoulou SS, Rabi DM, Zarnke KB et al (2015) The 2015 Canadian hypertension Education program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol 31(5):549–568
12. Weber MA, Schiffrin EL, White WB et al (2014) Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. J Hypertens 32(1):3–15
13. Piper MA, Evans CV, Burda BU et al (2014) Diagnostic and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: an updated systematic review for the U.S. preventive services task force. Ann Intern Med 162:192–204
14. Head GA, McGrath BP, Mihailidou AS et al (2012) Ambulatory blood pressure monitoring in Australia: 2011 consensus position statement. J Hypertens 30(2):253–266

15. Mayor S (2011) Hypertension diagnosis should be based on ambulatory blood pressure monitoring, NICE recommends. BMJ 343:d5421
16. Omboni S, Gazzola T, Carabelli G, Parati G (2013) Clinical usefulness and cost effectiveness of home blood pressure telemonitoring: meta-analysis of randomized controlled studies. J Hypertens 31(3):455–467. discussion 67–68
17. Chobanian AV, Bakris GL, Black HR et al (2003) Seventh report of the joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 42(6):1206–1252
18. Webb AJ, Rothwell PM (2012) The effect of antihypertensive treatment on headache and blood pressure variability in randomized controlled trials: a systematic review. J Neurol 259:1781–1787
19. Rothwell PM, Howard SC, Dolan E et al (2010) Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 375:895–905
20. Chobanian AV, Bakris GL, Black HR et al (2003) The seventh report of the joint National Committee on prevention, detection, evaluation and treatment of high blood pressure: the JNC 7 report. JAMA 289:2560–2571
21. The Task Force for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology (2013) 2013 ESH/ESC guidelines for the management of arterial hypertension. Eur Heart J 34:2159–2219
22. Ahmed MI, Pisoni R, Calhoun DA (2009) Current options for the treatment of resistant hypertension. Expert Rev Cardiovasc Ther 7(11):1385–1393
23. Fletcher GF, Ades PA, Kligfield P et al (2013) Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation 128(8):873–934
24. Parati G, Stergiou G, O'Brien E et al (2014) European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens 32(7):1359–1366

# Diagnostic and Prognostic Significance of Blood Pressure Indices

2

Stanley S. Franklin, Vanessa Bell, and Gary F. Mitchell

## 2.1 The Physiology of Individual Blood Pressure Indices

The two major physiologic components of blood pressure (BP) are mean arterial pressure (MAP) and pulse pressure (PP) [1, 2]. MAP is the interaction of (a) cardiac output and (b) systemic vascular resistance (SVR): MAP = cardiac output × SVR. PP also depends on two major components: (a) left ventricular ejection characteristics and (b) the stiffness of the aorta. The familiar peak of systolic blood pressure (SBP) and minimum of diastolic blood pressure (DBP) represent a weighted sum and difference of MAP and PP, respectively. Key points to remember: (1) DBP rises with increased SVR but falls with increased arterial stiffness, (2) PP represents a surrogate measurement of central elastic artery stiffness in the presence of a constant cardiac output and heart rate, and (3) central arterial stiffening results in a change in three BP components—(a) a rise in PP leading to (b) a rise in SBP and (c) a fall in DBP.

## 2.2 Age-Related BP Indices

The cross-sectional National Health and Nutrition Examination Survey (NHANES III, 1988–91) [3] and the 1997 longitudinal Framingham Heart Study [4] (Fig. 2.1) have shown that DBP increases with age in young adults but levels off by about 50 years of age and begins to decrease by 60 years of age. SBP also increases in

S.S. Franklin, M.D. (✉)
Division of Cardiology, Department of Medicine, Medical Sciences I, University of California, Irvine, Suite C240, Irvine, CA 92697, USA
e-mail: ssfranklinmd@earthlink.net

V. Bell, B.S. • G.F. Mitchell, M.D.
Cardiovascular Engineering, Inc., Edgewater Drive, Suite 201, Norwood, MA 02062, USA



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_2

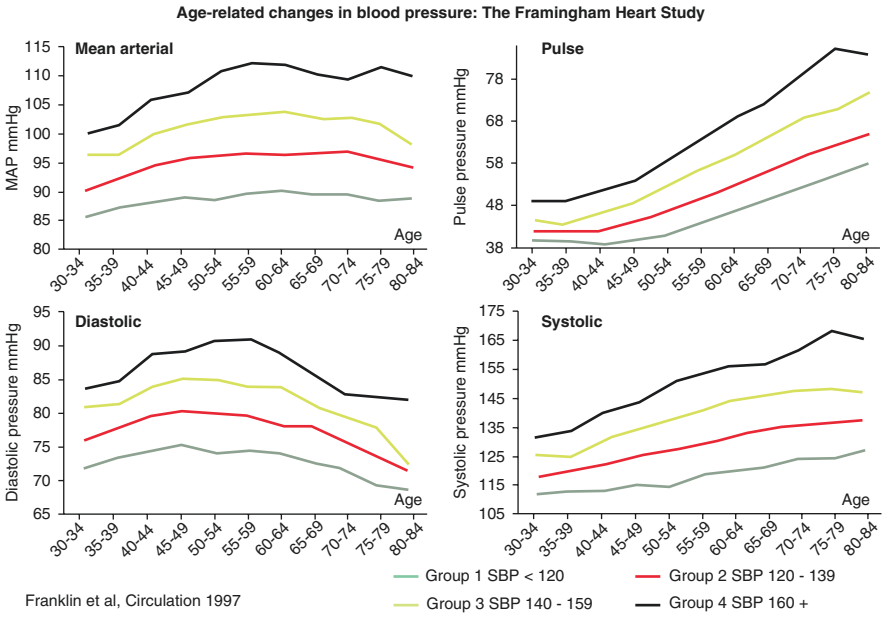



**Fig. 2.1** Arterial pressure components by age: group-averaged data for all subjects and with deaths, MI, and CHF excluded. Averaged blood pressure levels from all available data from each subject within 5-year age intervals (30–34 through 80–84) by SBO groupings 1 through 4 (modified from Franklin SS (1997). Circulation 96:308–315, with permission)

young adults although the rate of increase in SBP is less than DBP, resulting in a modest decrease in PP through midlife. Thereafter, SBP continues to rise, while DBP falls, resulting in widening of PP after midlife as the increase in SBP and fall in DBP accelerate with more vascular aging [4]. Elevated MAP, as a measure of steady-state resistance, is the dominant factor in the almost parallel rise in SBP and DBP during early adulthood. Widening PP, a marker of large artery stiffness, is the dominant change in BP from midlife onward.

## 2.3 BP Indices in the US Population by Age and Sex

The NHANES III, 1988–1991 [5], showed that the predominant forms of hypertension among those age <50 years are isolated diastolic hypertension (IDH, SBP <140 mmHg and DBP ≥90 mmHg) and systolic-diastolic hypertension (SDH, SBP ≥140 mmHg and DBP ≥90 mmHg), which together account for approximately 80% of persons with hypertension from age 18 to 49 years (Fig. 2.2) [5]. Interestingly, the other 20% of the young adults present with isolated systolic hypertension (ISH) and with a male-to-female predominance of 10:1 [6]. This subtype of isolated systolic hypertension was associated with increased cardiac output and stroke volume [6]; although previously labeled spurious by some investigators [7], there is now

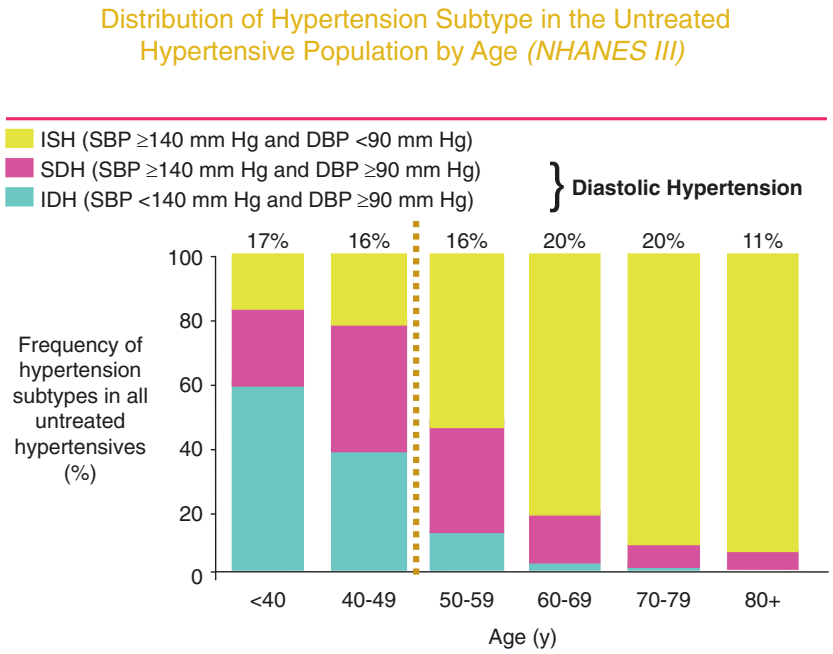



**Fig. 2.2** Frequency distribution of untreated hypertensive individuals by age and hypertension subtype. Numbers at the tops of bars represent the overall percentage distribution of all subtypes of untreated hypertension in the age group (NHANES III, 1988–1994) (from Franklin SS et al (2001). Hypertension 37:869–874, with permission)

evidence of long-term cardiovascular disease (CVD) risk [8]. Chirinos et al. [9], using the NHANES survey population, found obesity to be associated with hypertension in all age groups and both genders, but there was a higher odds of obesity in younger men with IDH and SDH.

By the same token, NHANES showed that three out of four adults with hypertension were aged 50 or older [5]. Moreover, about 80% of untreated or inadequately treated individuals with hypertension from age 50 onward had ISH, which by definition in this age range represents increased arterial stiffness [5].

## 2.4 The Development of Isolated Systolic Hypertension (ISH)

By age of 50 years the predominant form of hypertension is ISH, accounting for more than 75% by the age of 50–59, 80% by the age of 60–69, and 90% by the age 70 years or older [5]. Thus, ISH is the most common subtype of hypertension in the older age population. Furthermore, a 2001 Framingham Heart Study analysis showed that normotensive persons reaching age 65 had a 90% lifetime risk of developing hypertension, almost exclusively of the ISH subtype, if they lived another 20–25 years [10].

Therefore, hypertensives fall into one of two categories: first, a smaller group (26%) of younger (age <50 years) patients, predominantly male (63%) individuals with diastolic hypertension out of proportion to systolic hypertension (primarily IDH and SDH) and, second, a larger group (74%) of older (age ≥50 years) patients, predominantly female (58%) individuals with systolic hypertension out of proportion to diastolic hypertension (primarily ISH).

## 2.5 Two Pathways for the Development of ISH Indices

The NHANES III survey [5] showed that ISH becomes the dominant hypertensive subtype by midlife (50–59 years of age). Importantly, there are two divergent patterns for the development of ISH (Fig. 2.3), as shown in a 2005 Framingham Heart Study analysis. People with untreated or poorly treated diastolic hypertension (often called essential hypertension) at a younger adult age may transition from IDH to SDH and ultimately to ISH as they become older and as their arteries become stiffer; this transition is often called "burned-out diastolic hypertension." Approximately 41% of patients (with a male predominance) convert to ISH from antecedent diastolic hypertension (either or both IDH and SDH) [11]. In contrast, the remaining 59% of people (with a female predominance) developed de novo ISH without going through a stage of diastolic hypertension [11].

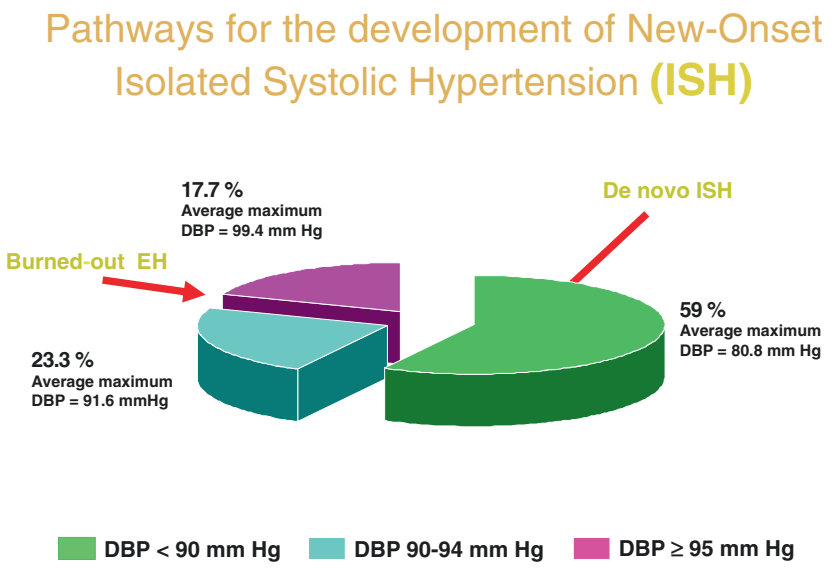



**Fig. 2.3** Of subjects who developed ISH, 59% did not have antecedent diastolic hypertension (de novo ISH) either at baseline or any examination before ISH onset (average maximum DBP of 80.8 mmHg). 23% had a maximum DBP of 90–94 mmHg (average maximum DBP of 91.6 mmHg), and 18% had a maximum DBP of 95 mmHg or higher (average maximum DBP of 99.4 mmHg)—identified as burned-out diastolic hypertension (either IDH and/or SDH) (modified from Franklin SS et al (2005). Circulation 111:1121–1127, with permission)

## 2.6 Value of BP Indices in the Diagnosis of CHD Risk

The potential clinical value of the widening of PP as a CVD risk factor was first introduced in a seminal publication by Darne and associates in 1989 [12]. These findings were confirmed in elderly participants from a 1999 analysis of Framingham Heart Study data, which demonstrated that coronary heart disease (CHD) risk increased with lower DBP at any level of SBP ≥120 mmHg, suggesting that higher PP was an important predictor of CVD risk [13]. Indeed, neither SBP nor DBP was superior to PP in predicting CHD risk [13]. These result supported the conclusion that in older individuals with identical SBP, those with ISH are at greater risk for CHD than those with SDH [13]. Furthermore, age plays an important role in influencing the relation of BP indices to CHD risk. In persons <50 years of age, DBP is a stronger predictor of CHD risk than SBP or PP as shown in a 2001 Framingham Heart Study analysis [14], suggesting that increased SVR and higher MAP play important roles in CHD risk [14]. From age ≥60 years on, there is a shift from DBP to SBP and PP as predictors of CHD risk, suggesting that large artery stiffness becomes the dominant hemodynamic determinant of CVD risk [14].

## 2.7 The Value of Paired BP Indices in Predicting CVD Risk

Despite emerging evidence that persons with ISH and wide PP are at considerable excess CVD risk, the question of which of the BP indices was the best predictor of CVD risk remained somewhat controversial. Indeed, the Prospective Studies Collaboration [15] and Asia-Pacific Cohort Studies Collaboration [16] concluded that MAP was superior to PP, while other studies [17, 18] concluded that SBP was superior to PP in predicting CVD risk. A 2009 Framingham Heart Study reexamined this question by comparing combined versus single BP components [19]. Pooled logistic regression was used within 12 serial 4-year intervals from 1952 to 2000, starting with a new index baseline BP for each 4-year cycle. Continuous and categorical models were compared for prediction of various CVD events (CHD, heart failure, and stroke) [19]. Categorical models in 6 × 6 cross-classification bar graphs were constructed to test for odds of the likelihood of CVD events for the combination of SBP and DBP (Fig. 2.4a) and for PP and MAP (Fig. 2.4b) and adjusted for age, sex, total cholesterol, smoking, body mass index, diabetes, and secular trend [19]. Using the combination of two BP components in Fig. 2.4a, b, respectively, rather than single BP components separately, improved the fit for predicting CVD risk [19]. Introducing the interaction terms in Fig. 2.4a, b further improved the fit over the main effects of the two-component models, indicating that the effect of one BP component on risk varied accordingly to the level of the other [19]. These results confirmed the superiority of combining SBP and DBP as noted in the MRFIT study [20] and extended the findings to older adults and to women [19].

Indeed, both two-component models were superior to any single BP component in predicting CVD risk because they assessed both pulsatile and steady-flow load; a

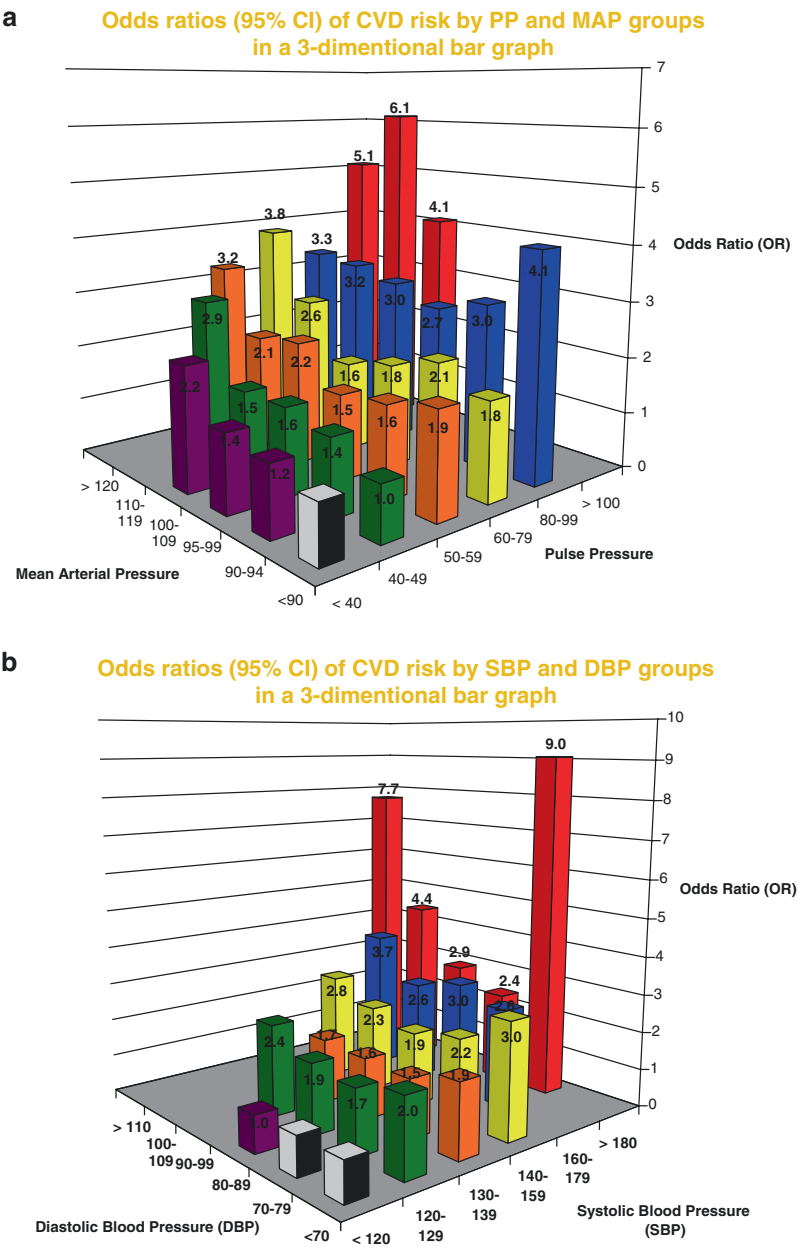



**Fig. 2.4** (**a**) Odds ratios for the likelihood of a cardiovascular event with combined PP and MAP categories in a 6 × 6 cross-classification bar graph, adjusted for age, sex, total cholesterol, smoking, body mass index, diabetes, and secular trend. An interaction term PP × MAP improved the model fit (from Franklin SS et al (2009). Hypertension 119:243–250, with permission). (**b**) Odds ratios for the likelihood of a cardiovascular event with combined SBP and DBP categories in a 6 × 6 cross-classification bar graph, adjusted for age, sex, total cholesterol, smoking, body mass index, diabetes, and secular trend. An interaction term of SBP × DBP improved the model fit (from Franklin SS et al (2009). Hypertension 119:243–250, with permission)

single BP component could not do this. Furthermore, single BP components as predictors of CVD risk in prior studies examined a limited spectrum of the overall hypertensive population by age, sex, and other covariates. When PP, a measure of stiffness, was combined with MAP, a measurement of resistance and steady-flow load, there was a monotonic relation of each BP component to risk. Furthermore, one could relate the two major physiologic components of hydraulic load to clinical outcome [19]. The current 2003 Joint National Committee (JNC-7) guidelines consider both SBP and DBP, whichever is higher, in determining staging of BP; however, they undervalue the CVD risk of increased arterial stiffness, as manifested by a high SBP and a low DBP [21]. Using the Joint National Committee Report (JNC-7) for CVD risk classification, a DBP <70 mmHg as compared to DBP ≥70–89 mmHg is associated with additional risk equivalent to ~20 mmHg higher SBP, i.e., it is equivalent to a shift from prehypertension to stage 1 or from stage 1 to stage 2 hypertension [19, 21]. Moreover, the European Society of Hypertension has recognized widened PP as a distinct risk factor that is separate from elevated SBP in older individuals [22].

## 2.8 Components of PP Associated with Higher CVD Risk

The relation between PP and CVD risk can be further elucidated by studying the components of PP. PP represents the pulsatile portion of BP and can be separated into forward and reflected pressure waves. From these two waveforms, the forward (FWA) and reflected wave amplitude (RWA) can be calculated as well as the global reflection coefficient (RC, the ratio of RWA and FWA).

There is some disagreement on whether the forward or reflected wave is a better correlate of CVD risk. In a multivariable model adjusting for standard CVD risk factors, Framingham Heart Study data showed that greater FWA was associated with a higher risk of CVD, while RC had no relation with events [23]. Other papers have found RWA to be a better predictor of CVD risk than FWA. However, these studies did not measure central aortic flow directly and instead used a single typical flow waveform for all participants or derived pseudo-flow waveforms for analysis [24–26], whereas the Framingham Heart Study measured flow directly for each participant [23]. Additionally, the observed relation between RWA and CVD risk may be due to the strong relation between FWA and RWA. As noted above, RC is not associated with CVD risk [23]. Since RC represents the ratio of RWA and FWA, a CVD risk-related increase in FWA would result in a secondary CVD risk-related increase in RWA at any given level of RC.

The age-related increase in PP is overwhelmingly attributable to an increase in FWA, with modest contributions from RWA and timing of the reflected wave. FWA and PP change in similar fashions throughout age (initially decreasing with age before midlife and then rising dramatically with age after midlife). In contrast, measures of wave reflection, such as augmentation index, increase with age in young adults, when PP is falling, and plateau or fall after midlife, when PP increases markedly. Consistent with the foregoing observations, FWA has been found to account for most of the variability in central and peripheral PP in both younger (<50 years; 80% and 66%, respectively) and older people (≥50 years; 90% and 84%, respectively) [27]. The observed relations between FWA and PP further indicate that FWA

may play a primary role in the pathogenesis of hypertension and CVD. It would be interesting for future studies to investigate the pulsatile hemodynamic effects of hypertensive drugs that reduce MAP but increase peak flow, potentially increasing FWA and PP and thereby limiting beneficial effects of treatment.

## 2.9 Central Pressure and CVD Risk

There is controversy over whether central or peripheral pressure is better at predicting CVD risk. Multiple studies and a meta-analysis have suggested that central pressure is better than peripheral pressure at predicting surrogate end points (LVH, diastolic dysfunction, increased CIMT, etc.) and major CVD events [28–34]. However, these studies may be affected by differing technique, assumptions about a lack of amplification between the brachial and radial artery, and calibration methods [35–37]. In contrast to these studies, Framingham Heart Study data has shown that central systolic and PP are not predictive of CVD events after considering conventional arm SBP. A recent Framingham Heart Study analysis of the SphygmoCor algorithm applied to radial waveforms recorded at the same visit showed no incremental value of central pressure after considering peripheral pressure [38]. Indeed, when brachial systolic pressure was added to a model that already included central aortic systolic pressure, there was an improvement in model fit implying that brachial pressure provided additional prognostic information compared to the central BP obtained from the SphygmoCor algorithm [38]. Additionally, during post-midlife aging when CVD starts to become more common, the difference between central and peripheral pressure diminishes; analysis of data from the Framingham Heart Study, where the average participant age was 62 years, showed that central systolic and PP had a very strong correlation ($R > 0.95$) with the corresponding components of peripheral pressure [38].

Due to the strong correlation between central and peripheral PP in older individuals and the Framingham Heart Study observation that current peripheral BP measurements are as good if not better than current central BP measurements at predicting CVD events, it seems that peripheral pressure provides an adequate estimate of blood pressure-related risk for the time being. If new techniques for measuring central pressure directly, independently of peripheral pressure calibration, are developed, then central BP may prove to be a stronger predictor of future CVD risk. In addition, it is important to note that changes in the central pressure waveform may differ dramatically from change in the peripheral pressure waveform following vasodilator medication [39–41]. Differing effects of BP treatment on central as compared to peripheral blood pressure may have prognostic importance and require further study.

## 2.10 The Role of J-Curve BP Indices in Predicting CVD Risk

Controversy persists regarding the significance of BP J-curves of increased CVD risk as they relate to older people with ISH [42]. The controversy is not about the existence of the DBP J-curve, but rather as to potential causes. One possibility is

that excess risk associated with low DBP could be the result of ISH with widened PP, secondary to a rise in SBP and a fall in DBP—markers of increased arterial stiffness and a proven CVD risk factor [42]. Indeed, the 2009 Framingham Heart Study analysis found that CVD risk increased at both the low and high extremes of DBP when combined with ISH in the two-component model in a sample free of antihypertensive therapy and antecedent CVD events [19]. Therefore, the J-curve relation to CVD risk presumably reflected increased arterial stiffness as manifested by a low DBP and wide PP, rather than adverse effects of excessive DBP lowering with antihypertensive medications. Importantly, data from the NHANES 1999–2006 confirmed that DBP <70 mmHg versus DBP of 70–89 mmHg with a prevalence of 30% among untreated persons with ISH was associated with increased CVD risk; advanced age, female sex, and diabetes mellitus, but not treatment status, were associated with the low DBP value [43].

The second J-curve possibility is that a low DBP and coexisting low SBP may be an epiphenomenon related to an underlying chronic debilitating illness or cardiac dysfunction—so-called reversed causality [44]. As a third possibility, the low DBP J-curve in association with ISH may represent antihypertensive therapy-induced lowering of DBP, which leads to myocardial ischemia and increased risk for an acute coronary event [45]. In the presence of high-grade stenosis of coronary arteries, increased risk of myocardial infarction with antihypertensive therapy-induced decrease in BP may well occur [45], but is by far the least common occurrence of the J-curve phenomenon. Indeed, the risk of plaque disruption that leads to acute coronary syndromes depends more on plaque composition, plaque vulnerability (plaque type), and the degree of pulsatile stress than on the degree of coronary artery stenosis (plaque size) [46]. Not surprisingly, therefore, the majority of myocardial infarctions (>70–85%) occur from plaque rupture in coronary arteries that have <50% stenosis [46]. By the same token, a 2015 Framingham Heart Study analysis showed that persons with an initial CVD event and persistent ISH in combination with a DBP <70 mmHg vs. DBP 70–89 mmHg had increased risk for recurrent CVD events, largely independent of antihypertensive treatment status [47]. Nevertheless, because of the many factors that result in J-curve risks, only a prospective trial with baseline and pre-event BP determinations can establish the presence and frequency of treatment-induced increase risk.

## References

1. Berne RM, Levy MN (1992) Cardiovascular physiology. In: Year book. Mosby, St Louis, MO, pp 135–151
2. Nichols WW, O'Rourke MF, Vlachopoulos C (2011) McDonald's blood flow in arteries, 6th edn. Arnold Hodder Headline Group, London
3. Burt VL, Whelton P, Roccella EJ et al (1995) Prevalence of hypertension in the US adult population: results from the third National Health and nutrition examination survey, 1988-1991. Hypertension 25:305–313
4. Franklin SS, Gustin W, Wong ND et al (1997) Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation 96:308–315
5. Franklin SS, Jacobs MJ, Wong ND et al (2001) Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives. Hypertension 37:869–874

6. McEniery CM, Yasmin WS et al (2005) Increased stroke volume and aortic stiffness contribute to isolated systolic hypertension in young adults. Hypertension 46:221–226
7. Franklin SS, Wilkinson IB, McEniery CM (2012) Unusual hypertension phenotypes. Hypertension 59:173–178
8. Yano Y, Stamler J, Garside DB et al (2015) Isolated systolic hypertension in young adults and 31-year risk of cardiovascular mortality: the Chicago Heart Association Detection Project in Industry study. J Am Coll Cardiol 65:327–335
9. Chirinos JA, Franklin SS, Townsend RR, Raij L (2009) Body mass index and hypertension hemodynamic subtypes in the adult US population. Arch Intern Med 169:580–586
10. Vasan RS, Larson MG, Leip EP et al (2001) Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham heart study: a cohort study. Lancet 358:1682–1686
11. Franklin SS, Pio JR, Wong ND et al (2005) Predictors of new-onset diastolic and systolic hypertension. The Framingham Heart Study. Circulation 111:1121–1127
12. Darne B, Girerd X, Safar M et al (1989) Pulsatile versus steady component of blood pressure: a cross-sectional analysis and a prospective analysis on cardiovascular mortality. Hypertension 13:392–400
13. Franklin SS, Khan SA, Wong ND et al (1999) Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. Circulation 100:354–360
14. Franklin SS, Larson MG, Khan SA et al (2001) Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. Circulation 103:1245–1249
15. Prospective Studies Collaboration (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 360:1903–1913
16. Asia Pacific Cohort Studies Collaboration (2003) Blood pressure indices and cardiovascular disease in the Asia Pacific Region: a pooled analysis. Hypertension 42:69–73
17. Miura K, Dyer AR, Greenland P et al (2001) Pulse pressure compared with other blood pressure indices in the prediction of 25-year cardiovascular and all-cause mortality rates: the Chicago Heart Association Detection Project in Industry Study. Hypertension 38:232–237
18. Mosley WJ, Greenland P, Garside DB, Lloyd-Jones DM (2007) Predictive utility of pulse pressure and other blood pressure measures for cardiovascular outcomes. Hypertension 49:1256–1264
19. Franklin SS, Lopez VA, Wong ND et al (2009) Single versus combined blood pressure components and risk for cardiovascular disease: the Framingham Heart Study. Circulation 119:243–250
20. Domanski M, Mitchell G, Pfeffer M et al (2002) Pulse pressure and cardiovascular disease-related mortality: follow-up study of the multiple risk factor intervention trial (MRFIT). JAMA 287:2677–2683
21. Chobanian AV, Bakris GL, Black HR et al (2003) The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. Hypertension 42:1206–1252
22. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH), The European Society of Cardiology (ESC) (2007) 2007 guidelines for the management of arterial hypertension. Eur Heart J 28:1462–1536
23. Cooper LL, Rong J, Benjamin EJ et al (2015) Components of hemodynamic load and cardiovascular events: the Framingham Heart Study. Circulation 131(4):354–361
24. Chirinos JA, Kips JG, Jacobs DR Jr et al (2012) Arterial wave reflections and incident cardiovascular events and heart failure: MESA (Multiethnic study of atherosclerosis). J Am Coll Cardiol 60(21):2170–2177
25. Wang KL, Cheng HM, Sung SH et al (2010) Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study. Hypertension 55(3):799–805

26. Weber T, Wassertheurer S, Rammer M et al (2012) Wave reflections, assessed with a novel method for pulse wave separation, are associated with end-organ damage and clinical outcomes. Hypertension 60(2):534–541
27. Mitchell GF, Wang N, Palmisano JN et al (2010) Hemodynamic correlates of blood pressure across the adult age spectrum: noninvasive evaluation in the Framingham Heart Study. Circulation 122(14):1379–1386
28. Agabiti-Rosei E, Mancia G, O'Rourke MF et al (2007) Central blood pressure measurements and antihypertensive therapy: a consensus document. Hypertension 50(1):154–160
29. Jankowski P, Kawecka-Jaszcz K, Czarnecka D et al (2008) Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. Hypertension 51(4):848–855
30. Laurent S, Cockcroft J, Van BL et al (2006) Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 27(21):2588–2605
31. Roman MJ, Devereux RB, Kizer JR et al (2007) Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the strong heart study. Hypertension 50(1):197–203
32. Safar ME, Blacher J, Pannier B et al (2002) Central pulse pressure and mortality in end-stage renal disease. Hypertension 39(3):735–738
33. Vlachopoulos C, Aznaouridis K, O'Rourke MF et al (2010) Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J 31(15):1865–1871
34. Williams B, Lacy PS, Thom SM et al (2006) Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the conduit artery function evaluation (CAFE) study. Circulation 113(9):1213–1225
35. Mitchell GF, Hwang SJ, Vasan RS et al (2010) Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation 121(4):505–511
36. Mitchell GF (2015) Does measurement of central blood pressure have treatment consequences in the clinical praxis? Curr Hypertens Rep 17(8):66
37. Segers P, Mahieu D, Kips J et al (2009) Amplification of the pressure pulse in the upper limb in healthy, middle-aged men and women. Hypertension 54(2):414–420
38. Mitchell GF, Hwang SJ, Larson MG et al (2016) Transfer function-derived central pressure and cardiovascular disease events: the Framingham Heart Study. J Hypertens 34:1528–1534
39. Kelly R, Daley J, Avolio A, O'Rourke M (1989) Arterial dilation and reduced wave reflection. Benefit of dilevalol in hypertension. Hypertension 14(1):14–21
40. Kelly RP, Gibbs HH, O'Rourke MF et al (1990) Nitroglycerin has more favourable effects on left ventricular afterload than apparent from measurement of pressure in a peripheral artery. Eur Heart J 11(2):138–144
41. Mitchell GF, Lacourciere Y, Arnold JM et al (2005) Changes in aortic stiffness and augmentation index after acute converting enzyme or vasopeptidase inhibition. Hypertension 46(5):1111–1117
42. Franklin SS (2010) Isolated systolic hypertension and the j-curve of cardiovascular disease risk. Artery Res 4:1–6
43. Franklin SS, Chow VH, Mori AD, Wong ND (2011) The significance of low DBP in US adults with isolated systolic hypertension. J Hypertens 29:1101–1108
44. Marschner IC, Simes RJ, Keech A (2007) Biases in the identification of risk factor threshholds and J-curves. Am J Epidemiol 166:824–831
45. Messerli FH, Mancia G, Conti CR et al (2006) Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? Ann Intern Med 144:884–893
46. Falk E, Shah PK, Fuster V (1995) Coronary plaque disruption. Circulation 92:657–671
47. Franklin SS, Gokhale SS, Chow VH et al (2015) Does low diastolic blood pressure contribute to the risk of recurrent hypertensive cardiovascular disease events?: the Framingham Heart Study. Hypertension 65:299–305

# Role of Circadian Rhythms and Seasonal Variation in BP Levels

# 3

Pietro Amedeo Modesti and Danilo Malandrino

## 3.1 Introduction

High blood pressure (BP) causes more deaths than any other risk factors, including diabetes and cigarette smoking [1], so the diagnosis of hypertension is a key element for clinical practice. To reach the diagnosis, blood pressure values higher than the ideal maximum limits have to be registered in repeated occasions. This point is the first implication of the inherent biological BP short- and long-term variability [2]. In general, when observing repeated measurements in the same subject, relatively high (or relatively low) observations are likely to be followed by less extreme ones nearer the subject's true mean, a phenomenon defined as "regression to the mean." Taking multiple measurements across several weeks is thus the first measure to attenuate the influence of within-person BP variability, and this procedure is consistently recommended by guidelines for the diagnosis of hypertension in the clinical setting [3].

The problem arises whenever baseline measurements taken at a single visit are used both for selection of participants and for comparisons with pressures obtained later. The limited possibility to have the diagnosis confirmed at repeated visits is a common bias in epidemiological studies [4]. A regression to the mean is also observed in intervention studies, the studies with higher starting baseline blood pressures usually demonstrating greater responses in the placebo group [5]. When the goal is to estimate the risk of developing a future hypertension, the incidence in studies that have diagnosed hypertension based on more visits is usually less than that detected in the studies that have made the diagnosis on the basis of a single visit [6]. Finally some patients may be receiving unnecessary antihypertensive drug therapy leading to wasted resources and the potential for adverse drug effects.

P.A. Modesti (✉) • D. Malandrino
Department of Experimental and Clinical Medicine, Universita' degli Studi di Firenze, Largo Brambilla 3, 50134 Florence, Italy
e-mail: pamodesti@unifi.it



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_3

The 24 h pattern typical of diurnally active normotensive and uncomplicated hypertensive persons displays small BP increase before the termination of nighttime sleep, striking rise upon morning awakening, and decline by 10–20% in SBP and of lesser amount in DBP, during sleep relative to wake-time means. Individuals with this normal nighttime reduction are known as dippers (extreme dipping >20% nocturnal BP fall). Nondipping are usually defined for nocturnal BP fall <10% and reverse dipping being defined for increased nocturnal BP [2]. The introduction of ambulatory blood pressure monitoring (ABPM) in clinical practice offered a useful tool to avoid misdiagnosis and overtreatment [6]. The value of ABPM is superior to office BP measurement for predicting clinical outcomes. According to a recent meta-analysis [6], each 10 mmHg increment in 24 h systolic ABPM, adjusted for OBPM, was consistently and statistically significantly associated with an increased risk for fatal and nonfatal stroke (hazard ratios ranging from 1.28 to 1.40 and fatal and nonfatal cardiovascular event hazard ratios ranging from 1.11 to 1.42).

The knowledge of the main physiological factors involved in the timing and amplitude of BP fluctuations may improve the accuracy of diagnosis and monitoring of hypertension.

## 3.2 Factors Influencing Circadian Rhythm

The BP decrease during sleep time is associated to the reduction in physical and mental activity, change in body position, and lower activity of the autonomic nervous system. BP is lowest during deep (stages 3/4) sleep and highest, although on average not to the level when fully awake, during less deep (stages 1/2 and rapid eye movement [REM]) sleep. Blunted or absent reductions in nighttime BP have been reported in subjects working during the night [7] and in those who have poorer sleep quality as a result of more waking episodes determined by actigraphic data [8, 9]. Although the mechanisms underlying the loss of the nocturnal reduction in BP are not completely understood [10], individuals with a nondipping BP pattern have been found to have increased sympathetic nervous system activity [11], decreased parasympathetic nervous system activity [12], and higher levels of epinephrine and norepinephrine when compared to individuals with a normal reduction in nighttime BP [11]. In addition to physiological factors such as sleep and physical activity, environmental factors such as climate or seasonality may also significantly affect the variability of blood pressure. The influence of seasonality on blood pressure has implications for clinical practice. CV risk assessment in the single patient might give different results when performed in hot months (summer) or in cold months (winter), with blood pressure measurement being a key element for risk stratification. Likewise estimation of mean BP levels in population studies may vary according to the period of the year [13]. Different behavioral factors, such as diet and physical activity, also vary with seasonality. The influence of seasonality should thus be separated from environmental (climate, pollution) or behavioral (physical activity, diet) variations.

## 3.3 Seasonal BP Variations

Among the different environmental variables known to affect blood pressure, seasonality has relevant implications either in clinics or in research. The influence of the season on blood pressure measurements performed in the clinics was first described by Rose [14]. In clinical trials, seasonality can be associated with larger BP variations than those induced by drugs [15]. The standardization for room temperature largely removed the effect of the season on BP in the UK Heart Disease Prevention Project [16]. Therefore, guidelines consistently recommend the importance of a standardized room temperature in hypertension clinics. However, also when BP measurements are made in comfortably warm rooms, a negative relationship between outdoor temperature and BP values was observed (Table 3.1) [13].

These environmentally related BP variations may indeed influence results of epidemiological studies as revealed in a large-scale population-based study where office, home, and 24 h ambulatory systolic and diastolic BPs were lower in summer and higher in winter both in normotensive and in hypertensive individuals [24].

Seasonal adaptation of antihypertensive drugs is not specifically considered in hypertension guidelines because treatment targets are defined by BP values. However, in the daily clinical practice, physicians are often faced with the effects of warm temperature which may cause BP to reduce during summer with the potential implications of falls or acute renal failure especially in the elderly.

Likewise the absolute increase in BP values observed during winter could potentially contribute to increase the risk for cardiovascular (CV) events during the cold season. The general tendency of blood pressure (casual and ambulatory measures) to be higher in winter than in summer may contribute to the higher cardiovascular mortality observed in winter [25]. On the other hand, a nonrandom distribution of enrollments over the year can bias results of clinical trials aimed at assessing the antihypertensive effect of a drug and of epidemiological surveys aimed at assessing hypertension burden.

Fluctuations in temperature are therefore usually considered as a major independent determinant for seasonal BP variations. However, the relationship between seasonality

**Table 3.1** Average increase in office systolic blood pressure per 1 °C reduction in environmental temperature

| Author (ref.) | Population | Age (years) | Temperature | mmHg/−1 °C |
|---|---|---|---|---|
| Madsen et al. [17] | 18,770 | 30–77 | Outdoor[a] | 0.15 |
| Modesti et al. [18] | 6404 | 30–80 | Outdoor[a] | 0.13 |
| Barnett et al. [19] | 115,434 | 35–64 | Outdoor[a] | 0.19 |
| | – | – | Indoor | 0.31 |
| Alpérovitch et al. [20] | 8801 | >65 | Outdoor[b] | 0.15 |
| Kent et al. [21] | 26,018 | >45 | Outdoor[c] | 0.21 |
| Lewington et al. [22] | 510,000 | 35–74 | Outdoor[d] | 0.57 (>5 °C) |
| Modesti et al. [23] | 1847 | 21–90 | Outdoor[a] | 0.19 |
| | – | – | PET | 0.34 |

*PET* mean 24 h environmental temperature measured at personal level
[a]Mean 24 h outdoor temperature measured by the local meteorological office
[b]Temperature measured at 11 a.m. by the local meteorological office
[c]Daily maximum temperature provided by National Aeronautics and Space Administration's (NASA's) Marshall Space Flight Center
[d]Mean monthly outdoor temperature

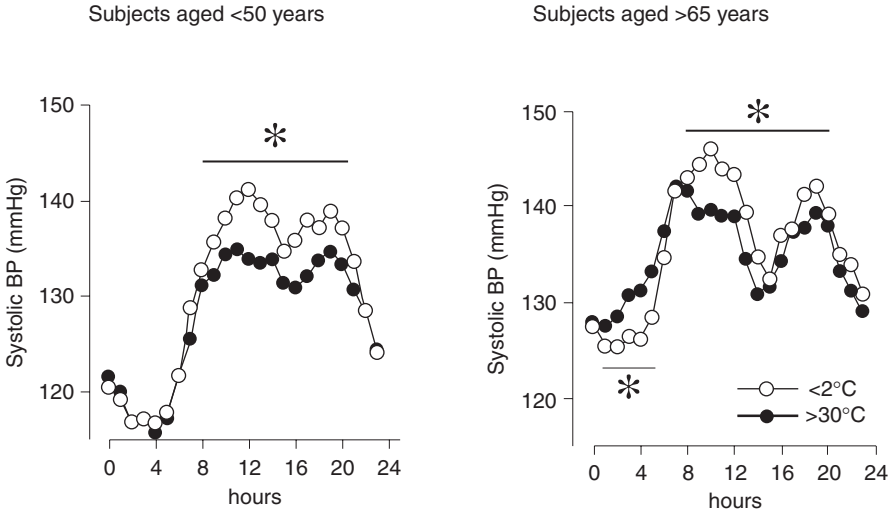



**Fig. 3.1** Systolic BP in subjects aged <50 years and >65 years during days with low and high outdoor temperature (*$p$ <0.05) (modified from [18])

and outdoor temperature is more complex, involving both long-term regulatory factors and acute responses to environmental temperatures. Although the short- and long-term BP response to climate may overlap, they may not be identical. Average 24 h ambulatory blood pressure is indeed higher on cold days (outdoor temperature <10th percentile) than in warm days (outdoor temperature >90th percentile) [18]. In the long term (during summer), the reduction in daytime BP values during hot weather is however also associated with a significant increase in nighttime BP values [18, 26] (Fig. 3.1).

Conversely, when the short-/medium-term response to climate change is specifically investigated, a different pattern of response is observed because the onset of a cold weather front is followed within 2 days by a concordant increase of 24 h, daytime, and nighttime ambulatory BP. More precisely, changes observed in nighttime and 24 h ABP values following climate acute changes were concordant [27]. These observations suggest that although the short-/medium-term and long-term BP response to climate and season may partially overlap, when considering temperature only, we cannot disentangle the short-term from the long-term BP response at nighttime.

Some methodological issues have to be considered. Firstly, it is likely that other components (diet, exercise) potentially contribute in the relationship between season and BP. As an example, milder sleep problems associated with hot weather or an enhanced physical activity in summer time might contribute to nighttime BP increase. Seasonal diet changes have been observed. In a large (38,037 participants) population-based cohort prospective study performed from 1979 to 2008 [28], highly statistically significant seasonal patterns were observed with increases in traditional CVD risk factors in colder or darker periods. However, the magnitude of the seasonal differences was likely too small to contribute to acute CVD events. The relatively small changes are probably because the population of Tromsø is well adapted to a harsh climate, as better protection to seasonal influences may prevent winter excess of in CVD events. In Israel, 94 male industrial employees were screened twice in 1 year,

and the seasonal increase in fat and cholesterol intake at winter time was found to be associated with changes in BMI and serum cholesterol [29]. A significant trend for change in the values of cholesterol, LDL-C, and HDL-C in different seasons, with higher cholesterol and LDL-C values in winter than in summer, was also observed in a cross-sectional study including 2890 men and 4004 women 20–64 years old from the participants of Tehran Lipid and Glucose Study (TLGS) performed between 1999 and 2001 [30]. Seasonal variation in amplitude, type, and intensity of physical activity was also observed, with total activity increasing in summer in comparison to winter [31–33]. Secondly, the inclusion of a single meteorological variable in data analysis has limitations. Usually, only temperature is considered although humidity level and high ground-level wind turbulence may enhance the thermal perception of cold discomfort notwithstanding relatively high air temperature. Wind speed increase was observed to induce the same BP increase at different air temperatures [27]. Therefore, the relationship between skin temperature and air temperature is significantly affected by other weather variables. Finally, from a methodological point of view, obtaining true measurements of exposition is the main problem when investigating the effects of climate on human health especially when the aim is to disentangle the effects of climate from those of seasonality. As an example, a reduced intensity in ultraviolet light during winter might also reduce epidermal photosynthesis of vitamin D3 and parathyroid hormone, which was shown in turn to be associated with elevated BP levels [34]. However, direct sunlight exposition can be hardly estimated both in the single subject and in population studies. As regards measurement of temperature, important exposure misclassification also exists. During winter, people generally spend most of their time indoors in regulated environments where the temperature is held constant and the exposition to outdoor temperature is usually limited. In Europe, both thermal efficiency of housing and the behavioral capability to cope with cold weather were indeed found to increase with latitude [35]. In England and Wales, the association of year-to-year variation in excess winter mortality with the number of cold days in winter (<5 °C), evident until the mid-1970, has recently disappeared [36], and the link between winter temperature and excess winter mortality is no longer as strong as before. Historical trends in excess winter mortality are also showing a gradual reduction for deaths between 1980 and 2011 [37]. In the reanalysis of BP data collected within the WHO MONICA Project [19] (collection period ranging from 1979 to 1997), the random effects for season on the main risk factor for CV events (BP) were latitude dependent (left panel, Fig. 3.2). In a more recent analysis [6], where the large majority of studies were performed after 1997 (only seven studies were started before 1977), no association between the estimated amplitude of seasonal BP variations and latitude was observed (right panel, Fig. 3.2).

Those changes might be probably linked to the improved energy efficiency of homes and housing quality [36]. The measurement of temperature at the personal level (PET) by using portable thermometers [39] may importantly reduce exposure misclassification. In a recent study, aimed at disentangling the effects of temperature [23] from those of seasonality, temperature was measured at the personal level in patients undergoing ambulatory BP monitoring. In addition, the number of hours between sunrise and sunset was also included in multiple regression analysis as a continuous measure of seasonality. The study for the first time provided evidence that temperature and seasonality independently affect blood pressure. More

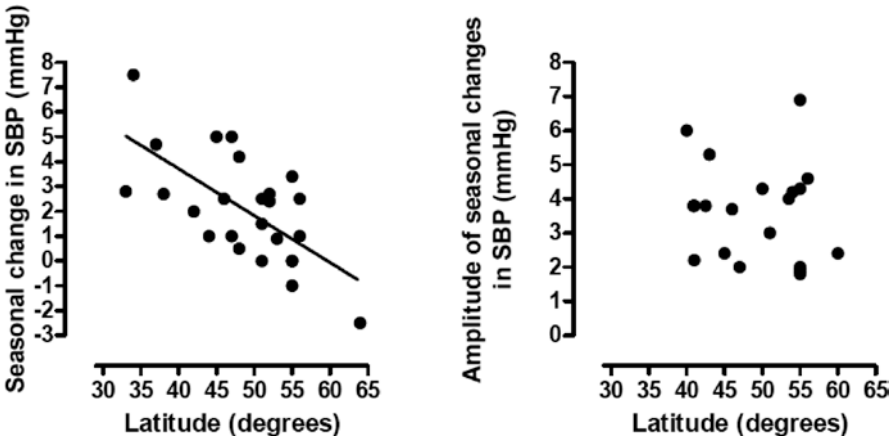



**Fig. 3.2** *Left panel*: Population-specific seasonal change in systolic blood pressure against latitude in the WHO MONICA Project [19] (collection period ranging from 1979 to 1997). *Right panel*: Estimated amplitude of seasonal changes in blood pressure by latitude in a more recent analysis [38] where the large majority of studies were performed after 1997

**Table 3.2** Independent predictors of systolic blood pressure at multivariate linear regression analysis

| | | | 95% CI | | |
|---|---|---|---|---|---|
| Systolic BP | Variables | B | Lower | Upper | *p* |
| Daytime | Daytime heart rate (bpm) | 0.03 | 0.01 | 0.06 | 0.003 |
| | Daytime relative humidity (%) | 0.00 | −0.02 | 0.02 | 0.714 |
| | Daytime AP (hPa) | 0.00 | −0.04 | 0.04 | 0.966 |
| | Daylight (h) | −0.05 | −0.21 | 0.11 | 0.531 |
| | Daytime PET (°C) | −0.14 | −0.25 | −0.02 | 0.023 |
| *Multiple r = 0.914; n = 1802* | | | | | |
| Nighttime | Nighttime heart rate (bpm) | 0.15 | 0.09 | 0.21 | 0.001 |
| | Nighttime relative humidity (%) | 0.03 | −0.01 | 0.08 | 0.150 |
| | Nighttime AP (hPa) | −0.01 | −0.09 | 0.06 | 0.718 |
| | Daylight (h) | 0.63 | 0.37 | 0.90 | 0.001 |
| | Nighttime PET (°C) | −0.01 | −0.12 | 0.11 | 0.931 |
| *Multiple r = 0.668; n = 1787* | | | | | |
| Morning surge | 24-h heart rate (bpm) | −0.05 | −0.11 | 0.02 | 0.148 |
| | 24-h relative humidity (%) | −0.01 | −0.06 | 0.04 | 0.690 |
| | 24-h AP (hPa) | 0.04 | −0.05 | 0.12 | 0.381 |
| | Daylight (h) | −0.54 | −0.87 | −0.21 | 0.001 |
| | Δ PET (°C) | 0.01 | −0.13 | 0.15 | 0.892 |
| *Multiple r = 0.473; n = 1700* | | | | | |

*PET* personal-level environmental temperature, *AP* atmospheric pressure. Δ PET = Morning PET minus the lowest nighttime PET. Data are adjusted for office systolic BP, age, gender, BMI, and drug treatment (adapted from [23])

precisely, daytime systolic blood pressure was independently affected by air temperature, whereas nighttime SBP and morning BP surge were mainly affected by seasonality [23]. The direct effect of PET on 24 h SBP was evident in subjects aged more than 65 years, thus indicating that temperature-associated 24 h ambulatory BP changes are more pronounced with aging (Table 3.2) [23].

## 3.4 Clinical Implications

Cross-sectional and observation surveys indicate that health interventions targeted at better protection against cold weather (e.g., improved home heating and reduced exposition to cold climate) may be particularly effective in the elderly [40–42].

Nighttime BP seems to be mainly related with seasonality, with temperature mainly affecting daytime BP values. In addition to air temperature, any seasonal diet changes (alcohol, vegetable, and salt intake), adiposity, or physical activity could potentially also lead to changes in blood pressure.

Coupled with reduced fluid intake, with advancing age, there is a decrease in total body water. Because of their low water reserves, the elderly are suggested to learn to drink regularly when not thirsty and to moderately increase their salt intake when they sweat [42]. The independent association between blood pressure increase at nighttime in the elderly and daylight hours might stay against this simplistic explanation. The large majority of experimental studies are indeed confined to short-term (up to few days) exposition of aged subjects to high temperature, whereas no information is available on blood volume adaptation in the long term. It might thus be hypothesized that blood volume adaptation, resulting in BP increase at nighttime, might occur in the long term in the elderly. This response might be modulated between spring and summer because the night BP levels are highest in spring, although the daily hours of light show the highest level in summer.

The importance of seasonal BP variations is now considered in most clinical trials. Conversely although the possibility of a higher prevalence of hypertension during winter compared with summer was recently reported, only one population study specifically investigated the possible bias introduced by environmental temperature on hypertension burden assessment in a large survey [43]. According to the HYDY study [43], the odds ratio for hypertension diagnosis was 0.98 (95% Cl 0.96–0.99) per 1 °C of temperature measured at home (logistic regression analyses adjusted for age, gender, education, and average air temperature at the two survey visits).

Seasonal BP variations have relevant implication in the clinical practice especially regarding antihypertensive treatments. Retrospective analyses of published trial data have concluded that antihypertensive drug classes may differ in their effects on intersession visit-to-visit blood pressure variability and associated risk of stroke [44, 45]. However, these post hoc analyses lacked actual intersession information for individual trial participants, adherence to drugs, duration of drug action, or adjustment for climate or seasonality. According to previous evidence, antihypertensive drugs do not prevent seasonal variation in BP [46]. Likewise antihypertensive drugs (metoprolol, carvedilol, lisinopril, eprosartan, amlodipine, and HCTZ) did not markedly affect the size of the cold-induced rise of BP compared to placebo or no drug in normo- and hypertensive subjects. However, it is possible that heat-exposed subjects need lower dosages or at least less frequently combination therapy because of lower BP in warm conditions. Most importantly, subjects exposed to extreme temperature changes must have a more careful follow-up.

Addressing the importance of the environment on BP during hypertension management and diagnosis, and the possible interactions with patient features, may have relevant implications in clinical and research settings.

**Conclusions**

The control for concurrent environmental changes is to be considered both in clinical practice and in research studies. In the daily clinical practice, ABPM is important in monitoring the antihypertensive treatment in elderly patients under conditions of unstable and often "extreme" temperature exposures. Short-term temperature changes mainly affect BP during daytime (temperature as a negative predictor), whereas seasonality mainly affects nighttime SBP (with daylight hours as positive predictor) and morning BP surge (with daylight hours as negative predictor). The design of clinical trials should consider the months for enrollments, with long-term seasonal BP variations being especially relevant in the elderly. PET is to be considered as the gold standard to reduce exposure misclassification in research studies. The number of daylight hours can be considered as a continuous measure of seasonality to be included in multivariate analysis. Although potentially important, the measurement of sunshine exposition is more critical.

Population surveys in general should routinely factor in the seasonal variation in blood pressure. Epidemiological surveys aimed at estimating hypertension burden in a community may include environmental temperature measured indoor as a variable potentially affecting results rather than considering outdoor temperature only. Awareness of this phenomenon will result in more personalized, tailored dosages of antihypertensive medications.

## References

1. Lim SS, Vos T, Flaxman AD et al (2012) A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380:2224–2260
2. Modesti PA, Rapi S (2015) From the epidemiologist to the physician: a complex issue for a labile risk. J Clin Hypertens 17:428–430
3. Mancia G, Fagard R, Narkiewicz K et al (2013) 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 31:1281–1357
4. Modesti PA, Rapi S, Bamoshmoosh M et al (2012) Impact of one or two visits strategy on hypertension burden estimation in HYDY, a population-based cross-sectional study: implications for healthcare resource allocation decision making. BMJ Open 2:e001062
5. Patel HC, Hayward C, Ozdemir BA et al (2015) Magnitude of blood pressure reduction in the placebo arms of modern hypertension trials implications for trials of renal denervation. Hypertension 65:401–U321
6. Piper MA, Evans CV, Burda BU et al (2015) Diagnostic and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 162:192–204
7. Yamasaki F, Schwartz JE, Gerber LM et al (1998) Impact of shift work and race/ethnicity on the diurnal rhythm of blood pressure and catecholamines. Hypertension 32:417–423
8. Mansoor GA (2002) Sleep actigraphy in hypertensive patients with the 'non-dipper' blood pressure profile. J Hum Hypertens 16:237–242

9. Kario K, Schwartz JE, Pickering TG (1999) Ambulatory physical activity as a determinant of diurnal blood pressure variation. Hypertension 34:685–691
10. Kario K, Matsuo T, Kobayashi H et al (1996) Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients—advanced silent cerebrovascular damage in extreme dippers. Hypertension 27:130–135
11. Sherwood A, Steffen PR, Blumenthal JA et al (2002) Nighttime blood pressure dipping: the role of the sympathetic nervous system. Am J Hypertens 15:111–118
12. Nakano Y, Oshima T, Ozono R et al (2001) Non-dipper phenomenon in essential hypertension is related to blunted nocturnal rise and fall of sympatho-vagal nervous activity and progress in retinopathy. Auton Neurosci 88:181–186
13. Modesti PA (2013) Season, temperature and blood pressure: a complex interaction. Eur J Intern Med 24:604–607
14. Rose G (1961) Seasonal variation in blood pressure in man. Nature 189:235
15. Brennan PJ, Greenberg G, Miall WE, Thompson SG (1982) Seasonal variation in arterial blood pressure. Br Med J (Clin Res Ed) 285:919–923
16. Heller RF, Rose G, Pedoe HD, Christie DG (1978) Blood pressure measurement in the United Kingdom Heart Disease Prevention Project. J Epidemiol Community Health 32:235–238
17. Madsen C, Nafstad P (2006) Associations between environmental exposure and blood pressure among participants in the Oslo Health Study (HUBRO). Eur J Epidemiol 21:485–491
18. Modesti PA, Morabito M, Bertolozzi I et al (2006) Weather-related changes in 24-hour blood pressure profile: effects of age and implications for hypertension management. Hypertension 47:155–161
19. Barnett AG, Sans S, Salomaa V et al (2007) The effect of temperature on systolic blood pressure. Blood Press Monit 12:195–203
20. Alperovitch A, Lacombe JM, Hanon O et al (2009) Relationship between blood pressure and outdoor temperature in a large sample of elderly individuals: the Three-City study. Arch Intern Med 169:75–80
21. Kent ST, Howard G, Crosson WL, Prineas RJ, McClure LA (2011) The association of remotely-sensed outdoor temperature with blood pressure levels in REGARDS: a cross-sectional study of a large, national cohort of African-American and White participants. Environ Health 10(1):7
22. Lewington S, Li LM, Sherliker P et al (2012) Seasonal variation in blood pressure and its relationship with outdoor temperature in 10 diverse regions of China: the China Kadoorie Biobank. J Hypertens 30:1383–1391
23. Modesti PA, Morabito M, Massetti L et al (2013) Seasonal blood pressure changes: an independent relationship with temperature and daylight hours. Hypertension 61:908–914
24. Sega R, Cesana G, Bombelli M et al (1998) Seasonal variations in home and ambulatory blood pressure in the PAMELA population. Pressione Arteriose Monitorate E Loro Associazioni. J Hypertens 16:1585–1592
25. Baker-Blocker A (1982) Winter weather and cardiovascular mortality in Minneapolis-St. Paul. Am J Public Health 72:261–265
26. Fedecostante M, Barbatelli P, Guerra F et al (2012) Summer does not always mean lower: seasonality of 24 h, daytime, and night-time blood pressure. J Hypertens 30:1392–1398
27. Morabito M, Crisci A, Orlandini S et al (2008) A synoptic approach to weather conditions discloses a relationship with ambulatory blood pressure in hypertensives. Am J Hypertens 21:748–752
28. Hopstock LA, Barnett AG, Bonaa KH et al (2013) Seasonal variation in cardiovascular disease risk factors in a subarctic population: the Tromso study 1979-2008. J Epidemiol Community Health 67:113–118
29. Shahar DR, Froom P, Harari G et al (1999) Changes in dietary intake account for seasonal changes in cardiovascular disease risk factors. Eur J Clin Nutr 53:395–400
30. Hadaegh F, Harati H, Zabetian A, Azizi F (2006) Seasonal variability of serum lipids in adults: Tehran Lipid and Glucose Study. Med J Malaysia 61:332–338
31. Matthews CE, Freedson PS, Hebert JR et al (2001) Seasonal variation in household, occupational, and leisure time physical activity: longitudinal analyses from the seasonal variation of blood cholesterol study. Am J Epidemiol 153:172–183

32. Wuerzner G, Bochud M, Zweiacker C et al (2013) Step count is associated with lower nighttime systolic blood pressure and increased dipping. Am J Hypertens 26:527–534
33. O'Connell SE, Griffiths PL, Clemes SA (2014) Seasonal variation in physical activity, sedentary behaviour and sleep in a sample of UK adults. Ann Hum Biol 41:1–8
34. Rostand SG (1997) Ultraviolet light may contribute to geographic and racial blood pressure differences. Hypertension 30:150–156
35. The Eurowinter Group (1997) Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. Lancet 349:1341–1346
36. Staddon PL, Montgomery HE, Depledge MH (2014) Climate warming will not decrease winter mortality. Nat Clim Change 4:190–194
37. Modesti PA (2014) The hazard of rounding Cape Horn: is it changing? Heart 100:1489–1490
38. Marti-Soler H, Gubelmann C, Aeschbacher S et al (2014) Seasonality of cardiovascular risk factors: an analysis including over 230 000 participants in 15 countries. Heart 100:1517–1523
39. Brook RD, Shin HH, Bard RL et al (2011) Can personal exposures to higher Nighttime and early-morning temperatures increase blood pressure? J Clin Hypertens 13:881–888
40. Morabito M, Crisci A, Vallorani R et al (2011) Innovative approaches helpful to enhance knowledge on weather-related stroke events over a wide geographical area and a large population. Stroke 42:593–600
41. Morabito M, Modesti PA, Cecchi L et al (2005) Relationships between weather and myocardial infarction: a biometeorological approach. Int J Cardiol 105:288–293
42. Brook RD, Weder AB, Rajagopalan S (2011) "Environmental hypertensionology" the effects of environmental factors on blood pressure in clinical practice and research. J Clin Hypertens (Greenwich) 13:836–842
43. Modesti PA, Bamoshmoosh M, Rapi S et al (2013) Epidemiology of hypertension in Yemen: effects of urbanization and geographical area. Hypertens Res 36:711–717
44. Rothwell PM, Howard SC, Dolan E et al (2010) Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. Lancet Neurol 9:469–480
45. Webb AJ, Fischer U, Mehta Z, Rothwell PM (2010) Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. Lancet 375:906–915
46. Seguro C, Siddi PP, Sau F et al (1992) The effect of antihypertensive therapy on the seasonal variations in arterial pressure in hypertensive patients. Cardiologia 37:51–58

# Natural History of Treated and Untreated Hypertension

# 4

Massimo Volpe and Carmine Savoia

## 4.1 Hypertension and Target Organ Damage

Elevated blood pressure is the most prevalent and relevant risk factor for death and disability worldwide. Hypertension occurs in more than one billion individuals causing an estimated 9.4 million deaths every year [1]. Overall the prevalence of hypertension appears to be around 40% of the general population, with a steep increase with aging from 7% in individuals age 18–39 to 65% in individuals over age 59 [2]. There are clear differences in the average blood pressure levels across countries, with no systematic trends toward blood pressure changes in the past decade [3]. During middle and older age, blood pressure is strongly and directly related to cardiovascular and overall mortality [4]. This association seems to exist across large and diverse population groups aged 40–89 years, including men and women from different ethnicities, with and without established vascular disease [4–6].

Prospective cohort studies have reported a continuous log-linear association between blood pressure and vascular events over a wide range, apparently beginning at values of 115 mmHg for systolic and 75 mmHg for diastolic with no apparent threshold [4]. Notably, taking into account the continuous and direct relationship between blood pressure and cardiovascular disease, most blood pressure-associated cardiovascular complications occur in individuals with prehypertension. In the Framingham Heart Study, compared with the subjects with optimal blood pressure, those with high-normal blood pressure showed a significantly increased risk of cardiovascular disease independent of other risk factors, and a nonsignificant trend toward an increased incidence of events was also shown in the group with normal blood pressure [7].

M. Volpe, M.D., F.A.H.A., F.E.S.C. (✉) • C. Savoia, M.D., F.A.H.A.
Division of Cardiology, Clinical and Molecular Medicine Department, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy
e-mail: massimo.volpe@uniroma1.it



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_4

About half of hypertensive patients develop related end-organ damage if blood pressure is left untreated over 7–10 years. The remaining patients exhibit a less impactful course with hypertensive complications occurring slowly. Fewer than 5% of people with hypertension enter a very rapid, sometimes malignant course with rapid deterioration in cardiac, renal, and neurologic function.

Tissue- and organ-deteriorating and remodeling processes induced by the hypertensive status may impair the physiology and the structure of the heart, large- and medium-sized arteries, kidneys, and brain. Thus, the presentation of the target organ complications in hypertensive patients may reflect different pathophysiological abnormalities including diastolic and systolic dysfunction, left ventricular hypertrophy, endocardial scarring, congestive heart failure (39% of cases in men and 59% in women), and coronary disease; accelerated atherosclerosis and aneurysm formation (with or without dissection); stroke (both hemorrhagic and thrombotic infarction); and nephrosclerosis (with and without renal failure) [8].

Stroke mortality is often viewed as a surrogate of hypertension consequences, because hypertension is regarded as the most important cause of this event. A close relationship between prevalence of hypertension and mortality for stroke has been reported [9]. Nowadays, Western European countries exhibit a downward trend, in contrast to Eastern European countries which show an increase in death rates from stroke [10].

It should be noted that only a small fraction of the hypertensive population presents with an elevation of blood pressure alone, whereas the majority of the patients have additional cardiovascular risk factors. Population studies have clearly shown that the total cardiovascular risk exceed the sum of its individual components when blood pressure elevation is concomitantly associated with other cardiovascular risk factors. Therefore, international guidelines emphasize that prevention of coronary heart disease should be related to quantification and target of global cardiovascular risk [3, 11–16]. Several methods and tools have been developed for estimating total cardiovascular risk, although all currently available models for cardiovascular risk assessment have some methodological and conceptual limitations [3, 17–25].

Based on those methods, for more than a decade, international guidelines for the management of hypertension have stratified cardiovascular risk in different categories, based on blood pressure values, the presence of other cardiovascular risk factors, diabetes or asymptomatic organ damage, as well as symptomatic cardiovascular disease or chronic kidney disease or cardiovascular events [3, 11–16]. The large number of patients with hypertension is identified at low, moderate, high, or very high risk. The estimation of total cardiovascular risk may be easy to evaluate in specific subgroups of patients, especially those at high or very high cardiovascular risk, such as patients with diabetes or with severely elevated single risk factors or with established cardiovascular disease. Those are the patients that require intensive cardiovascular risk-reducing measures.

It should be emphasized that for the management of hypertensive patients, the recognition of target organ damage is crucial, even when asymptomatic, in view of the fact that the presence of target organ damage is the expression of organ abnormalities promoted by hypertension (i.e., heart, kidney, brain) which markedly increases the cardiovascular risk in the cardiovascular continuum.

If the blood pressure elevation is identified and properly managed early in the natural history of hypertension and adequate antihypertensive strategies (i.e., lifestyle changes, drugs) are timely initiated together with the control of the other cardiovascular risk factors, the reduction of cardiovascular risk and/or normalization of target organ damage may be achieved and the prognosis obviously improved [3, 17–25].

## 4.2 Pathophysiology of Vascular Changes in Hypertension and Hypertensive (Pheno)Types

Hypertension commonly produces structural changes in arteries, arterioles, and target organs in several patterns as a consequence of the mechanical effects of blood pressure and shear stress, as well as of the action of neurohormonal systems including the renin-angiotensin-aldosterone system, endothelins, catecholamines, as well as agents generated in perivascular fat and inflammatory mediators (i.e., different cytokines and chemokines and immune mediators, such as lymphocytes and macrophages and their products). Resistance arteries may play an important role in the development of hypertension and may also contribute to the pathogenesis of cardiovascular complications. Chronically elevated blood pressure induces vascular stretch that initiates complex signal transduction cascades leading to vascular remodeling [26–28]. Angiotensin II, one of the final products of the renin-angiotensin-aldosterone system, may induce vascular remodeling and injury by several mechanisms including vasoconstriction, cell growth, generation of reactive oxygen species (ROS), and inflammation. Also the endothelium is a crucial regulator of vascular tone. Its function is impaired in patients with hypertension, with reduced nitric oxide-mediated vasodilation, and with increased vascular tone that is associated with a proinflammatory and prothrombotic state, as well as vascular remodeling [29, 30].

Experimental and clinical data support the notion that the hypertension subtypes defined by isolated or combined elevations of systolic and diastolic blood pressure reflect distinct pathophysiological mechanisms in the vasculature, have different prognostic implications, and may require a different therapeutic approach [31, 32].

During the prehypertension phase which could be defined as the combination of normal plus high-normal blood pressure categories (blood pressure values ranged 120–139 for systolic or 80–89 for diastolic), repetitive perturbations of cardiovascular homeostasis occur, reflecting an array of hereditary and environmental factors. With the course of time, these small changes accumulate and yield larger pathophysiologic changes that are recognizable as early hypertension. In the setting of cardiovascular disease prevention, this condition recognizes individuals at increased risk of developing progressive vasculopathy with stiffening of the aorta and elastic arteries over time [33]. Early vascular remodeling and endothelial dysfunction usually evolve to increased peripheral vascular resistance, reflecting an array of genetic, environmental, and homeostatic factors. Early functional perturbations may be slight and reversible, whereas subsequent chronic large changes tend to be larger, slower, and irreversible.

The vascular phenotype of hypertension differs according to the age of subjects. Essential hypertension is characterized by increased peripheral vascular resistance to blood flow, which occurs generally as a result of energy dissipation in small arteries and arterioles, particularly in younger individuals, whereas late in life, large artery stiffening results in raised systolic blood pressure. Enhanced constriction of resistance arteries in hypertension may increase peripheral resistance by reducing lumen diameter [34, 35]. In younger individuals with elevated blood pressure, vascular remodeling occurs in small arteries and arterioles. It is usually eutrophic with a reduced lumen diameter and normal media cross section, reduced or enhanced stiffness, and increased extracellular matrix deposition and associated with endothelial dysfunction. In severe or advanced stage of hypertension, as well as in secondary forms and refractory hypertension, hypertrophic vascular remodeling of small arteries and arterioles may be found. A predominant rise in arteriolar resistance may lead to isolated diastolic hypertension if arterial stiffness is normal or low or combined systo-diastolic hypertension if large artery stiffness also increases.

Arterial hypertension as well as aging and the concomitant intervention of other cardiovascular risk factors may increase arterial stiffness in large conduit arteries. Thus, systolic blood pressure tends to increase with age leading to an elevated frequency of isolated systolic hypertension in the elderly associated with a large pulse pressure [36]. This type of hypertension may reflect diffuse atherosclerotic processes and therefore is considered an important determinant of cardiovascular risk. As blood pressure remains elevated for a prolonged time, particularly in subjects older than 55 years of age, vascular changes occur predominantly in large, conduit arteries (i.e., aorta), which become stiffer as arteriosclerosis develops, resulting in increased pulse pressure. The increase in the stiffness of the aorta and large elastic arteries, not accompanied by a rise in arteriolar resistance, may lead to isolated systolic hypertension. This occurs in a degree that depends on associated cardiovascular risk factors, progression of atherosclerosis, and inflammatory accumulation of lipids in the intima, triggered in part by endothelial dysfunction, dyslipidemia, age, smoking, and diabetes. Low-grade inflammation localized in vascular and perivascular tissue, including fat, is recognized as an important contributor to the pathophysiology of hypertension [37], to the initiation and progression of atherosclerosis, and to the development of cardiovascular disease [28, 38]. Inflammation of large arteries exerts its effects in part by contributing to endothelial dysfunction and increasing vascular stiffness.

Vascular stiffness can be evaluated by carotid-femoral pulse wave velocity (PWV) and, at some degree, by pulse pressure which is increased with aging and in hypertensive patients and is significantly and independently associated with both target organ damage and increased risk for cardiovascular morbidity and mortality [39]. In view of the progressive stiffening of the conduit arteries, the progressive amplification of the pressure wave during transmission from the aorta to peripheral arteries is attenuated with aging particularly in hypertensive patients. This can represent a confounding factor in the assessment of hypertension subtypes [31, 32] since brachial diastolic blood pressure may overestimate aortic blood pressure, particularly in young subjects. Hence, among patients younger than age 65, pulse

pressure and systolic blood pressure predict outcomes better than diastolic blood pressure [40]; this is even more striking in patients aging over 65. In those people only elevated systolic blood pressure and pulse pressure predict risk of adverse cardiovascular events and total mortality [41].

Major intervention trials showed that drug therapy generally produces a greater degree of diastolic than systolic blood pressure control, so that it is currently reported that elevated systolic blood pressure is more difficult to control, especially in the elderly. For example, in the Hypertension Optimal Treatment (HOT) study [42], more than 90% of subjects achieved diastolic blood pressure normalization, whereas less than 50% achieved systolic blood pressure normalization. In the Antihypertensive and Lipid-Lowering Trial to Prevent Heart Attack (ALLHAT) [43] and the Controlled Onset Verapamil Investigation of Cardiovascular Events (CONVINCE) trials [44], approximately 90% of participants had their diastolic blood pressure normalized after 2 years of treatment, whereas about 50% achieved systolic blood pressure normalization. In treated hypertensive subjects, those with uncontrolled systolic blood pressure were at higher risk of cardiovascular disease than those with uncontrolled diastolic blood pressure after adjustment for confounding factors [45]. Thus, effective systolic blood pressure control is the real challenge and the main focus of treatment.

The vascular disease of hypertension, by promoting tissue under perfusion and progression of atherosclerosis, contributes to myocardial ischemia and cardiovascular events, heart failure, stroke, nephrosclerosis and chronic kidney disease, and peripheral vascular disease.

Target organ damage in hypertension results from blood pressure load and the activity of neurohormonal effects and is in large measure a consequence of vascular injury that occurs in hypertension. Vascular complications of hypertension include changes in the structure and function of large and small arteries, as well as accelerating the progression of atherosclerosis [34, 35]. Endothelial dysfunction is recognized as a key early determinant in the progression to atherosclerosis and is now well established to be independently associated with increased cardiovascular risk [30]. An activated renin-angiotensin system plays a key role in the pathophysiology of endothelial dysfunction in hypertension [46] since it is in part responsible for triggering vascular inflammation by inducing oxidative stress, resulting in upregulation of inflammatory mediators.

## 4.3 Defining the Targets in Hypertension Management

Extensive evidence from randomized controlled trials has demonstrated benefit of blood pressure-lowering strategies in reducing cardiovascular events in individuals with hypertension [47–49] even at high-normal blood pressure levels, since about half of the total blood pressure-attributable disease burden occurs in people with systolic blood pressure lower than 140 mmHg [50]. The best approach to reduce blood pressure remains subject to controversy [13, 51, 52]. Patients with sustained elevations of blood pressure most often progress to established hypertension as well

as to target organ damage development. Preventing end-organ damage by controlling hypertension and the other risk factors is more effective than trying to reverse the changes once established. Nevertheless, controlling blood pressure after end-organ damage has developed also carries proven benefit. The therapeutic approach should consider total cardiovascular risk in addition to blood pressure levels in order to maximize cost-effectiveness of the management of hypertension and related cardiovascular risk.

Nonpharmacologic therapy may be sufficient for mild elevations in blood pressure in patients without other risk factors. For instance, reducing sodium intake, alcohol intake, and obesity lowered the incidence of hypertension from a 5-year trial in patients with high-normal blood pressure [53]. In high-risk individuals, antihypertensive treatment strategies, initiation and intensity of treatment, and particularly the use of drug combinations, as well as other treatments for controlling other cardiovascular risk factors and/or subclinical target organ damage, may be different from those to be implemented in lower-risk individuals. Indeed, there is evidence that, in high-risk individuals, blood pressure control is more difficult and more frequently requires the combination of different antihypertensive drugs also with other therapies, such as aggressive lipid-lowering treatments.

The large variety of antihypertensive drug options requires individualization for particular patients and a careful and thoughtful balance of antihypertensive efficacy, cost-effectiveness, and compelling indications and contraindications. However, whether blood pressure-lowering treatment reduces the risk of cardiovascular disease in all types of patient populations remains unclear.

Successful reductions in blood pressure and other cardiovascular risk factors can dramatically reduce the incidence of cerebrovascular and coronary morbidity and mortality, especially for individuals with the highest elevations of blood pressure, those with multiple risk factors, and the elderly. Effective therapy lowers the overall relative risk of congestive heart failure in randomized controlled trials [3]. In patients with chronic renal failure, tight blood pressure control slows decline in renal function [54]. Among patients with prior stroke or transient ischemic attack, blood pressure lowering reduces the risk of dementia and cognitive decline [55].

However, evidence for the protective effects of pharmacologically induced blood pressure reduction in individuals with lower blood pressure or with comorbidities is less solid [56–59].

Modern drug-based therapeutic approach has the capacity to reduce blood pressure in a high percentage of patients with hypertension [60, 61]. Nevertheless, over the past decade, observational clinical studies and surveys have shown that the prevalence of hypertension increased by about 10%. Nearly one third of patients were unaware of their condition. Although two thirds were told to adopt lifestyle changes or take medications, the percentage of hypertensives consistently controlled with medications has remained low (only 30% achieved blood pressure control $\leq$140/90 mmHg) [62], being this related to a number of factors including poor adherence and physician's inertia. Over the past 30 years, data from different surveys suggest that 30–40% of treated hypertensive patients reached the suggested target [2]. Also in Italy, in a large population of treated hypertensive patients

followed in outpatient clinics, hypertension centers, or general practice, through one decade of observation, ~60% of hypertensive patients were treated, and among these only 33% achieved effective blood pressure control. Therefore, more effective interventions to improve management of hypertension are needed [63].

In this regard, interventional trials consistently showed that it is possible to achieve effective blood pressure targets in about 70% of treated hypertensive patients with different cardiovascular risk profiles, especially through the use of rational, effective, and well-tolerated combination therapies. Since about 70–80% of treated hypertensive patients require a combination therapy based on at least two classes of drugs in order to achieve the recommended blood pressure goals, it is of great importance to implement this strategy in routine clinical practice [64]. Among the various combination therapies currently available for hypertension treatment and control, the use of those strategies based on drugs that antagonize the renin-angiotensin system, such as angiotensin II type 1 receptor antagonists (angiotensin receptor blockers) and ACE inhibitors, in combination with diuretics and/or calcium channel blockers, has been shown to significantly reduce the risk of major cardiovascular events and to improve patient compliance to treatment, resulting in a greater antihypertensive efficacy and better tolerability compared with monotherapy [65].

Effective and well-tolerated single-pill combination therapies are now available. This type of therapeutic approach may improve adherence and simplify treatment. The combination of a renin-angiotensin system blocker with a calcium channel blocker and a diuretic improves adherence to therapy [65].

A better control of blood pressure in hypertensive patients may largely contribute to modifying the natural course of the disease which is still characterized by high level of morbidity and mortality.

The actual blood pressure thresholds at which treatment should be initiated and the target levels at which blood pressure should be maintained still remain a topic of debate. In particular what has been less clear is whether there is further cardiovascular benefit when blood pressure is treated more intensively to a goal lower than 140/90 mmHg.

Most major hypertension treatment guidelines still suggest that clinicians should try to treat adults to a blood pressure target of $\leq$140/90 mmHg [3, 11–16]. However, after years of recommendations for a low target blood pressure in hypertensive patients, particularly those with diabetes or previous cardiovascular or renal disease, major guidelines on hypertension management have reevaluated the concept of the "lower the better." Hence, they have reversed a trend toward lower blood pressure thresholds and targets, recommending targets below 140/90 mmHg in most patients, particularly for those at high risk [3, 11–16]. In the elderly patients, a target of blood pressure <150/90 mmHg was recommended.

Several publications in recent years (most derived from non-randomized clinical trial) have supported this notion suggested by the hypothesized "J-curve" effect of blood pressure treatment, defined as the occurrence of additional cardiovascular events when the blood pressure is lowered beyond the level required to maintain tissue perfusion [66]. This concept has led to the concern that excessive lowering of blood pressure could increase the risk of cardiovascular events, although the notion

of the J-curve should be referred primarily to diastolic and not systolic blood pressure reduction, in terms of additional harm for the reduction of diastolic blood pressure <65 mmHg [67–69]. Thus, targets for diastolic blood pressure <90 mmHg seem safe in the J-curve phenomenon. Moreover, in diabetic patients, previous guidelines recommended target blood pressure levels of around 130/85 mmHg. After the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [70], this statement was challenged since in a population of 4733 patients with type 2 diabetes, an intensive blood pressure-lowering therapy (systolic blood pressure <120 mmHg) did not report a significant difference in overall cardiovascular event rates as compared to standard target of systolic blood pressure <140 mmHg. Therefore, the last European guidelines recommend target blood pressure levels of <140/85 mmHg in diabetic patients. By contrast, a systematic review of trials of more versus less blood pressure-lowering regimen reported a significant reduction in major vascular events [71].

Nevertheless recent evidence has challenged again this orientation in the management of hypertension. The Systolic Blood Pressure Intervention Trial (SPRINT) has recently shown that intensive systolic blood pressure control (to <120 mmHg) reduced the incidence of cardiovascular events and mortality by 25% (5.2% vs. 6.8%; hazard ratio 0.75; 95% confidence interval 0.64–0.89) compared with standard systolic blood pressure control (135–139 mmHg) in a population of 9361 subjects aged ≥50 years at increased risk for cardiovascular events, not including patients with diabetes and previous stroke. This may imply the need to reevaluate again blood pressure targets in hypertensive patients at high risk for cardiovascular events [72]. However, uncertainty remains as to whether such benefits hold for high-risk individuals excluded from the trial, especially those with diabetes or cerebrovascular disease [59]. Very recently two meta-analyses further support the notion of the implementation of intensive blood pressure control in high-risk hypertensive patients. A meta-analysis of 19 treat-to-target trials (in about 45,000 subjects) and a 7 mmHg mean systolic blood pressure reduction (from 140 to 133 mmHg) led to a 14% (95% confidence interval 0.78–0.96) reduction in major cardiovascular events [73]. These beneficial effects were consistent across major patient subgroups and types of interventions, and significant gains could be achieved from further lowering of systolic blood pressure to lower than 140 mmHg. Although an increase in hypotension occurred as a result of more intensive blood pressure lowering, including serious hypotensive events, there was no suggestion that these adverse effects would outweigh the benefits of treatment in high-risk patient populations.

In a second meta-analysis of 129 studies (over 600,000 subjects included) in various populations of hypertensive patients including those at relatively low blood pressure levels at baseline, those at high risk, and those presenting previous cardiovascular and cerebrovascular events, blood pressure-lowering treatment significantly reduced the risk of cardiovascular disease and death realized from a 10 mmHg systolic blood pressure reduction similarly across different quintiles of baseline systolic blood pressure (<130, 130–139, 140–149, 150–159, ≥160 mmHg) [74]. No significant trend toward increased risk was reported for any outcome (major cardiovascular events, coronary heart disease, stroke, heart failure, renal failure, and

all-cause mortality). Thus, a J-shaped relationship could not be substantiated, and the treatment effects were unlikely to be attenuated in trials that included participants with low systolic blood pressures at baseline, particularly those with less than 130 mmHg. However, it remains unclear whether a concomitant reduction in diastolic blood pressure (which is more directly related to the J-curve phenomenon) could also result in a reduced rate of cardiovascular events.

Although the SPRINT trial and the two meta-analyses included studies with heterogeneous cohorts, as well as the focus of intensive therapy was only on systolic blood pressure, the impact for the clinical practice appears dramatic in terms of the need of redefining blood pressure thresholds and targets. Therefore, expert consensus and guideline implementation will be probably required in order to properly address the issue of management of hypertensive patients.

## References

1. WHO (2013) A global brief on hypertension. World Health Organization, Geneva
2. Hajjar I, Kotchen TA (2003) Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. JAMA 290:199–206
3. Mancia G, Fagard R, Narkiewicz K et al (2013) 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 34:2159–2219
4. Lewington S, Clarke R, Qizilbash N et al (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 360:1903–1913
5. Lawes CMM, Rodgers A, Bennett DA et al (2003) Blood pressure and cardiovascular disease in the Asia Pacific region. J Hypertens 21:707–716
6. Rapsomaniki E, Timmis A, George J et al (2014) Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. Lancet 383:1899–1911
7. Vasan RS, Larson MG, Leip EP et al (2001) Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med 345:1291–1297
8. Neutel JM, Smith DH, Weber MA (1999) Is high blood pressure a late manifestation of the hypertension syndrome? Am J Hypertens 12:215S–223S
9. Wolf-Maier K, Cooper RS, Banegas JR et al (2003) Hypertension prevalence and blood pressure levels in 6 European countries, Canada and the United States. JAMA 289:2363–2369
10. Redon J, Olsen MH, Cooper RS et al (2011) Stroke mortality trends from 1990 to 2006 in 39 countries from Europe and Central Asia: implications for control of high blood pressure. Eur Heart J 32:1424–1431
11. Weber MA, Schiffrin EL, White WB et al (2014) Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. J Hypertens 32:3–15
12. McManus RJ, Caulfield M, Williams B, National Institute for Health and Clinical Excellence (2012) NICE hypertension guideline 2011: evidence based evolution. BMJ 344:e181
13. James PA, Oparil S, Carter BL et al (2014) 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 311:507–520
14. Stephan D, Gaertner S, Cordeanu EM (2015) A critical appraisal of the guidelines from France, the UK, Europe and the USA for the management of hypertension in adults. Arch Cardiovasc Dis 108:453–459

15. Daskalopoulou SS, Rabi DM, Zarnke KB et al (2015) The 2015 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol 31:549–568
16. Blacher J, Halimi JM, Hanon O et al (2014) Management of hypertension in adults: the 2013 French Society of Hypertension guidelines. Fundam Clin Pharmacol 28:1–9
17. Pyorala K, De Backer G, Graham I et al (1994) Prevention of coronary heart disease in clinical practice. Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. Eur Heart J 15:1300–1331
18. D'Agostino RB Sr, Vasan RS, Pencina MJ et al (2008) General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 117:743–753
19. Conroy RM, Pyorala K, Fitzgerald AP et al (2003) Estimation often-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 24:987–1003
20. Woodward M, Brindle P, Tunstall-Pedoe H (2007) Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). Heart 93:172–176
21. Hippisley-Cox J, Coupland C, Vinogradova Y et al (2008) Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ 336:1475–1482
22. Assmann G, Cullen P, Schulte H (2002) Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. Circulation 105:310–315
23. Ridker PM, Buring JE, Rifai N, Cook NR (2007) Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA 297:611–619
24. Ridker PM, Paynter NP, Rifai N et al (2008) C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. Circulation 118:2243–2251
25. Cooney MT, Dudina AL, Graham IM (2009) Value and limitations of existing scores for the assessment of cardiovascular risk: a review for physicians. J Am Coll Cardiol 54: 1209–1227
26. Callera G, Tostes R, Savoia C et al (2007) Vasoactive peptides in cardiovascular (patho)physiology. Expert Rev Cardiovasc Ther 5(3):531–552
27. Savoia C, Schiffrin EL (2006) Inflammation in hypertension. Curr Opin Nephrol Hypertens 15(2):152–158
28. Savoia C, Schiffrin EL (2007) Reduction of C-reactive protein and the use of anti-hypertensives. Vasc Health Risk Manag 3(6):975–983
29. Cosentino F, Rubattu S, Savoia C et al (2011) Endothelial dysfunction and stroke. J Cardiovasc Pharmacol 38(Suppl 2):S75–S78
30. Savoia C, Sada L, Zezza L et al (2011) Vascular inflammation and endothelial dysfunction in experimental hypertension. Int J Hypertens 2011:281240
31. Verdecchia P, Angeli F (2005) Natural history of hypertension subtypes. Circulation 111:1094–1096
32. Smulyan H, Safar ME (1997) Systolic blood pressure revisited. J Am Coll Cardiol 29:1407–1413
33. Franklin SS, Pio JR, Wong ND et al (2005) Predictors of new-onset diastolic and systolic hypertension: the Framingham Heart Study. Circulation 111:1121–1127
34. Schiffrin EL (2004) Remodeling of resistance arteries inessential hypertension and effects of antihypertensive treatment. Am J Hypertens 17:1192–1200
35. Schiffrin EL, Touyz RM (2004) From bedside to bench to bedside: role of renin angiotensin aldosterone system in remodeling of resistance arteries in hypertension. Am J Physiol Heart Circ Physiol 287:H435–H446
36. Franklin SS, Gustin W IV, Wong ND et al (1997) Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation 96:308–315
37. Caillon A, Schiffrin EL (2016) Role of inflammation and immunity in hypertension: recent epidemiological, laboratory, and clinical evidence. Curr Hypertens Rep 18(3):21

38. Savoia C, Schiffrin EL (2007) Vascular inflammation in hypertension and diabetes: molecular mechanisms and therapeutic interventions. Clin Sci (Lond) 112(7):375–384
39. Schiffrin EL (2004) Vascular stiffening and arterial compliance. Implications for systolic blood pressure. Am J Hypertens 17:S39–S48
40. Haider AW, Larson MG, Franklin SS et al (2003) Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. Ann Intern Med 138:10–16
41. Cushman WC (1998) The clinical significance of systolic hypertension. Am J Hypertens 11:182S–185S
42. Hansson L, Zanchetti A, Carruthers G et al (1998) Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 351:1755–1762
43. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (2002) Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 288:2981–2897
44. Black HR, Elliott WJ, Grandits G et al (2003) Principal results of the Controlled ONset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) Trial. JAMA 289:2073–2082
45. Benetos A, Bean TK, Gaurier S et al (2002) Prognostic value of systolic and diastolic blood pressure in treated hypertensive men. Arch Intern Med 102:577–581
46. Savoia C, Schiffrin EL (2006) Inhibition of the renin angiotensin system: implications for the endothelium. Curr Diab Rep 6(4):274–278
47. Staessen JA, Fagard R, Thijs L et al (1997) Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet 350:757–764
48. Beckett NS, Peters R, Fletcher AE et al (2008) Treatment of hypertension in patients 80 years of age or older. N Engl J Med 358:1887–1898
49. SHEP Cooperative Research Group (1991) Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 265:3255–3264
50. Rodgers A, Ezzati M, Vander Hoorn S et al (2004) Distribution of major health risks: findings from the Global Burden of Disease Study. PLoS Med 1:e27
51. Wright JT Jr, Fine LJ, Lackland DT et al (2014) Evidence supporting a systolic blood pressure goal of less than 150 mmHg in patients aged 60 years or older: the minority view. Ann Intern Med 160:499–503
52. Law MR, Morris JK, Wald NJ (2009) Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 338:b1665
53. Stamler R, Stamler J, Gosch FC et al (1989) Primary prevention of hypertension by nutritional-hygienic means. Final report of a randomized, controlled trial. JAMA 262:1801–1807
54. Bakris GL, Weir MR, Shanifar S et al (2003) Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. Arch Intern Med 163:1555–1565
55. Tzourio C, Anderson C, Chapman N et al (2003) Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med 163:1069–1075
56. Patel A, MacMahon S, Chalmers J et al (2007) Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 370:829–840
57. PROGRESS Collaborative Group (2001) Randomised trial of a perindopril- based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet 358:1033–1041
58. Yusuf S, Sleight P, Pogue J et al (2000) Effects of an angiotensin-converting-enzyme inhibitor, Ramipril, on cardiovascular events in high-risk patients. N Engl J Med 342:145–153

59. Wright JTJ, Williamson JD, Whelton PK et al (2015) A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 373:2103–2116
60. Chobanian AV (2009) Shattuck Lecture. The hypertension paradox–more uncontrolled disease despite improved therapy. N Engl J Med 361:878–887
61. Chobanian AV (2015) Time to reassess blood-pressure goals. N Engl J Med 373:2093–2095
62. Wang Y, Wang QJ (2004) The prevalence of prehypertension and hypertension among US adults according to the new joint national committee guidelines: new challenges of the old problem. Arch Intern Med 164:2126–2134
63. Tocci G, Ferrucci A, Pontremoli R et al (2015) Blood pressure levels and control in Italy: comprehensive analysis of clinical data from 2000-2005 and 2005-2011 hypertension surveys. J Hum Hypertens 29(11):696–701
64. Volpe M, Rosei EA, Ambrosioni E et al (2013) 2012 consensus document of the Italian Society of Hypertension (SIIA): strategies to improve blood pressure control in Italy: from global cardiovascular risk stratification to combination therapy. High Blood Press Cardiovasc Prev 20(1):45–52
65. Volpe M, de la Sierra A, Kreutz R et al (2014) ARB-based single-pill platform to guide a practical therapeutic approach to hypertensive patients. High Blood Press Cardiovasc Prev 21(2):137–147
66. Chalmers J (2011) Is a blood pressure target of <130/80 mmHg still appropriate for high-risk patients? Circulation 124:1700–1702
67. Kaplan NM (2011) The diastolic J curve: alive and threatening. Hypertension 58:751–753
68. Williams B (2009) Hypertension and the "J-curve". J Am Coll Cardiol 54:1835–1836
69. Boutitie F, Gueyffier F, Pocock S et al (2002) J-shaped relationship between blood pressure and mortality in hypertensive patients: new insights from a meta-analysis of individual patient data. Ann Intern Med 136:438–448
70. ACCORD Study Group (2010) Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 362:1575
71. Lv JC, Neal B, Ehteshami P et al (2012) Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: a systematic review and meta-analysis. PLoS Med 9:e1001293
72. The SPRINT Research Group (2015) A randomized trial of intensive versus standard blood pressure control. N Engl J Med 373:2103–2116
73. Xie X, Atkins E, Lv J et al (2016) Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet 387:435–443
74. Ettehad D, Emdin CA, Kiran A et al (2016) Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 387:957–967

# Part II

# Mechanisms of Hypertension Development

# The Kidneys, Volume and Blood Pressure Regulation, and Hypertension

# 5

Joey P. Granger and Frank T. Spradley

## 5.1 Introduction

Control of blood pressure is important in that it is a critical determinant of blood flow and oxygen and nutrient delivery to all tissues of the body. The control of blood pressure is complex and time-dependent and involves the integration of neural, hormonal, physical, and autacoid factors. While short-term blood pressure regulation is achieved through rapid alterations in cardiac output and/or total peripheral resistance, long-term control of blood pressure involves more slowly acting systems and is intimately linked to the regulation of extracellular fluid volume. Extracellular fluid volume is determined by the balance of intake and excretion of sodium and water by the kidneys.

Several decades ago, Guyton and Coleman [1] proposed that if an increase in blood pressure could produce sustained increases in sodium and water excretion through a renal-pressure natriuresis and diuresis mechanism, then this system would have a near infinite gain for the long-term control of arterial pressure by regulating blood volume. In addition, they proposed that elevation in blood pressure above the normal the set point for blood pressure control only occurs when factors impair the sodium and fluid excretory ability of the kidney and shifts the relation between sodium excretion and arterial pressure toward higher levels [1–3]. While there is strong theoretical and experimental evidence that the kidney is a major determinant of the long-term control of arterial pressure, the initial cause of abnormal pressure natriuresis and hypertension need not be intrinsic to the kidney [1–4]. The focus of this chapter is to review the importance of the kidneys in the long-term regulation of

J.P. Granger, Ph.D. (✉) • F.T. Spradley
Department of Physiology and Biophysics, School of Graduate Studies in the Health Sciences, Cardiovascular-Renal Research Center, University of Mississippi Medical Center, 2500 N. State St, Jackson, MS 39216, USA
e-mail: jgranger@umc.edu



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_5

extracellular volume and blood pressure and briefly summarize the various intra- and extrarenal factors that contribute to abnormal pressure natriuresis in hypertension.

## 5.2 Long-Term Regulation of Extracellular Volume and Blood Pressure

Extracellular fluid volume is controlled by various neural, hormonal, autacoid, and physical factors that regulate the excretion of salt and water by the kidneys. The renal-body fluid system concept predicts that a higher sodium and fluid intake than output would lead to an increase in extracellular volume and arterial pressure (see Fig. 5.1). If the excretory ability of the kidney is not impaired, the increase in arterial pressure raises sodium excretion and extracellular fluid volume would then decrease, thereby reducing venous return and cardiac output until blood pressure returns to normal and fluid intake and output are reestablished. Conversely, when

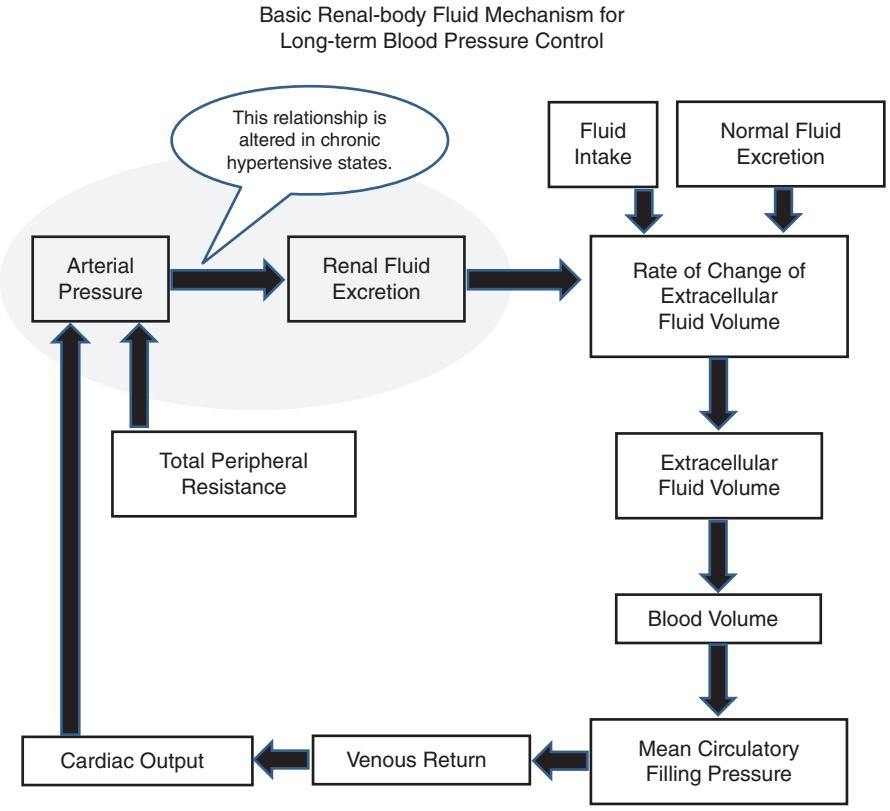



**Fig. 5.1** Basic renal-body fluid feedback mechanism for long-term regulation of blood pressure and body fluid volumes (redrawn from [1])

sodium and fluid output exceeds intake, extracellular fluid volume, blood volume, venous return, and cardiac output fall, which ultimately leads to a decrease in blood pressure below normal. This decrease in arterial pressure causes the kidneys to retain sodium and water until fluid balance is achieved and blood pressure is restored to the normal set point. Thus, according to the renal-body fluid feedback mechanism concept, the set point for long-term blood pressure control is the arterial pressure at which sodium and water intake and output are at equilibrium (see Fig. 5.2) [1–3].

A key component of this mechanism for regulating salt and water balance is pressure natriuresis/diuresis, which is the effect of increased arterial pressure to raise sodium and water excretion. An important feature of pressure natriuresis is that various hormonal and neural control systems can amplify or blunt the pressure natriuresis mechanism [1–3, 5–8]. For example, in most individuals, chronic increases in sodium intake are associated with only small changes in arterial pressure. The lack of significant increases in arterial pressure in response to elevations in sodium intake is due to a number of very effective volume control systems that are activated by extracellular volume expansion. For example, in response to increases in sodium intake, decreased formation of antinatriuretic hormones and/or increased formation of natriuretic factors enhance the effectiveness of pressure natriuresis and allow sodium balance to be maintained with little or no increase in arterial pressure. On the other hand, excessive activation of antinatriuretic systems or abnormalities in natriuretic systems can reduce the effectiveness of pressure natriuresis, thereby necessitating greater increases in arterial pressure to maintain

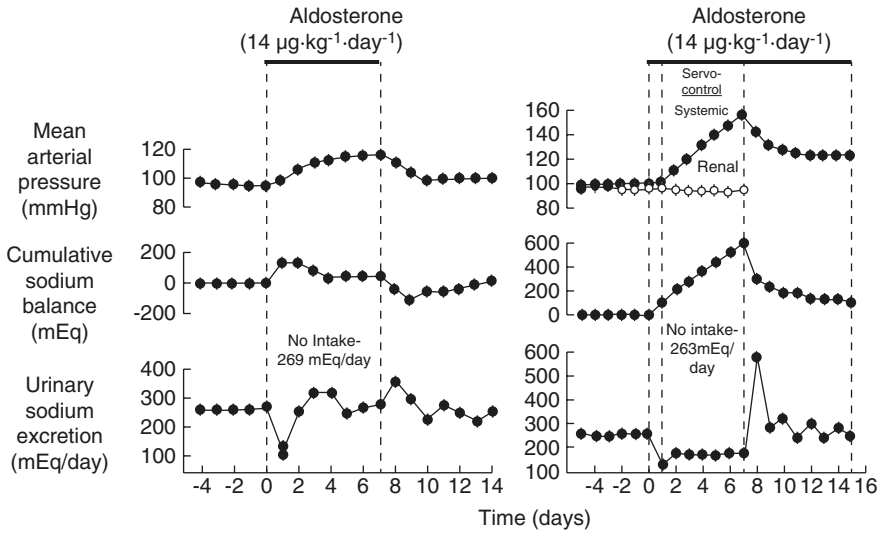



**Fig. 5.2** Effects of chronic aldosterone infusion on sodium excretion when renal perfusion pressure was allowed to increase (*left panel*) or was servo-controlled (*right panel*). Notice that when renal perfusion pressure was prevented from increasing, "escape" from sodium retention did not occur, and cumulative sodium balance and systemic arterial pressure continued to increase (redrawn from [12])

sodium and water balance. Thus, excessive activation of antinatriuretic systems or abnormalities in natriuretic systems impairs the excretory ability of the kidney and shifts the relation between sodium excretion and arterial pressure toward higher levels and resets the set point for long-term blood pressure control (see Fig. 5.2).

While total peripheral resistance and cardiac output are determinants of arterial pressure, one prediction of the renal-body fluid feedback mechanism is that if the pressure natriuresis mechanism is not impaired, a primary increase in total peripheral resistance or increases in cardiac pumping ability would not result in long-term alterations in arterial pressure [1, 2, 5–8]. For instance, an increase in total peripheral resistance would result in an immediate elevation in arterial pressure (see Fig. 5.1). The increase in arterial pressure would increase sodium and water excretion, via pressure natriuresis. As long as fluid excretion exceeds fluid intake, extracellular fluid volume will continue to decrease, reducing venous return and cardiac output, until blood pressure returns to normal and fluid balance is reestablished. Thus, primary increases in total peripheral resistance or increases in cardiac pumping do not result in long-term alterations in arterial pressure; thus, hypertension can develop only when physiological and/or pathophysiological factors impair the excretory ability of the kidney and shifts the relation between sodium excretion and arterial pressure toward higher levels [1–3, 5–8].

## 5.3 Pressure Natriuresis: A Key Factor in Maintaining Sodium Balance in Hypertension

Another important prediction of the renal-body fluid feedback control system concept is that an increase in blood pressure in hypertensive states is an essential compensatory mechanism that allows sodium balance to be maintained in the face of an underlying sodium-retaining defect [5–8]. To determine the importance of the pressure natriuresis mechanism in achieving sodium balance caused by aldosterone excess, Hall and colleagues [6] examined the long-term effects of aldosterone on sodium excretion and arterial pressure in normal dogs and in dogs where renal artery pressure was prevented from increasing with an electronically servo-controlled aortic occluder. In dogs in which renal artery pressure was permitted to increase during chronic aldosterone infusion, sodium excretion decreased markedly on the first day and then returned to control levels on days 2–3 of aldosterone infusion as arterial pressure increased (see Fig. 5.3). In contrast, in dogs in which renal artery pressure was prevented from increasing, sodium excretion decreased on the first day and remained below sodium intake for the 7 days of aldosterone infusion. The sustained sodium retention resulted in dramatic increases in cumulative sodium balance and systemic arterial pressure. The results from this study clearly demonstrated that an increase in renal arterial pressure is essential in allowing the kidneys to override the chronic sodium-retaining actions of aldosterone and to achieve normal sodium balance. Similar findings were reported from the same group during chronic administration of other sodium-retaining hormones, such as angiotensin (ang) II and norepinephrine [7, 8].

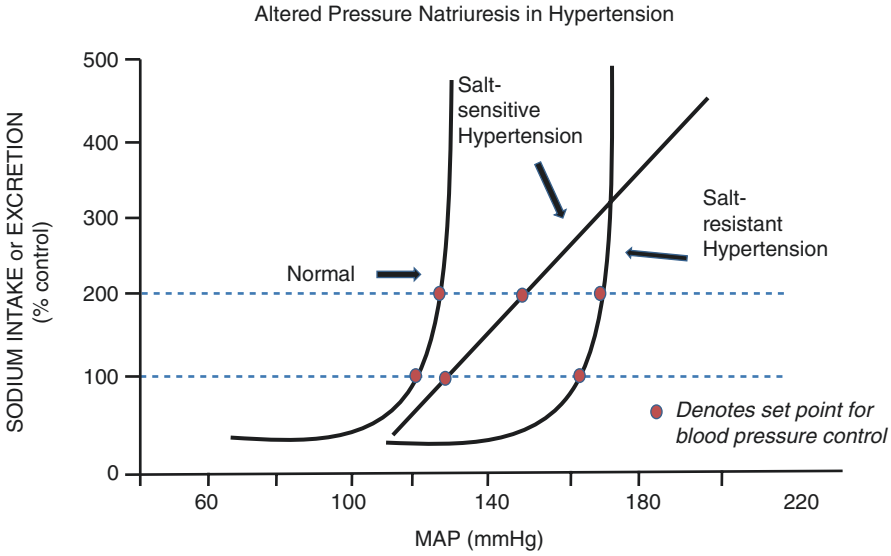



**Fig. 5.3** Steady-state relationships between arterial pressure and urinary sodium excretion and sodium intake for control dogs with normal kidneys and for dogs with a rightward hypertensive shift in the pressure natriuresis relationship in salt-sensitive and salt-resistant hypertension [6]

## 5.4 Impaired Renal-Pressure Natriuresis in Hypertension Caused by Intra- and Extrarenal Factors

An important observation that points toward abnormal kidney function as a key factor in causing hypertension is that almost all forms of experimental hypertension are caused by perturbations to the kidneys that alter renal hemodynamics or tubular reabsorption and reduce the kidney's ability to excrete sodium and water. For example, constriction of the renal arteries, compression of the kidneys, and administration of sodium-retaining hormones such as ang II or aldosterone are all associated with either decreases in renal blood flow and GFR and/or increases in renal tubular reabsorption prior to development of hypertension [5–8]. Further evidence supporting an important role for the kidneys in the development and maintenance of hypertension is that in all known monogenic forms of human hypertension, the common pathway to hypertension appears to be increased renal tubular reabsorption caused by mutations that directly increase renal electrolyte transport (e.g., Liddle's or Gordon's syndromes) or the synthesis and/or activity of antinatriuretic hormones (e.g., glucocorticoid-remediable aldosteronism) [4–8].

A shift in the pressure natriuresis relationship can occur as a result of *intrarenal* abnormalities such as excess formation of ang II, reactive oxygen species, inflammatory cytokines and endothelin-1 (via $ET_A$ receptor activation) or decreased synthesis of nitric oxide and natriuretic prostanoids, decreased renal medullary production of ET-1 (and decreased $ET_B$ receptor activation), or even genetic defects

**Table 5.1** Partial list of factors affecting renal pressure natriuresis in hypertension

| |
|---|
| *Prohypertensive—antinatriuretic factors* |
| Angiotensin II |
| Aldosterone |
| Renal sympathetic nerve activity |
| Endothelin (via ETa receptor activation) |
| Vascular 20-HETE (hydroxyeicosatetraenoic acid) |
| Immune factors and inflammatory cytokines |
| Reactive oxygen species |
| Renal vascular stenosis |
| Glomerular disease |
| Genetic defects in renal sodium transporters |
| *Deficiency of antihypertensive—natriuretic factors* |
| Nitric oxide |
| Prostaglandins |
| Renal tubular 20-HETE |
| EETS |
| Atrial natriuretic peptide |
| Renal medullary endothelin (via loss of ETb receptor activation) |

that enhance renal sodium transport systems. In other instances, the altered kidney function is caused by *extrarenal* disturbances, such as increased renal sympathetic nervous activity (RSNA) or excessive formation of antinatriuretic hormones such as aldosterone. The remaining portion of this chapter will discuss how these and other intra- and extrarenal factors impair renal-pressure natriuresis and lead to the development of chronic hypertension (see Table 5.1).

*Angiotensin II, the kidney, and hypertension*. The renin-angiotensin system (RAS) plays a critical role in the long-term regulation of extracellular fluid volume and blood pressure and is involved in the pathogenesis of various forms of hypertension, including renovascular hypertension and human essential hypertension [7, 10]. The RAS, via AT1 receptor, plays an important role in maintaining sodium balance and a relatively normal pressure as sodium intake is altered from low to high levels [5].

The effect of ang II to reduce renal-pressure natriuresis and cause hypertension is the result of its effects to directly or indirectly stimulate sodium transport [9–11]. While AT1 receptors are prominently expressed in the kidney, they are also expressed in the heart, blood vessels, adrenal glands, and the brain [11–14]. Because AT1 receptors are ubiquitously expressed, dissecting the quantitative importance of each individual organ system, including the kidney, in the long-term regulation of blood pressure has been difficult. Utilizing a combined gene targeting with renal cross transplantation approach, Coffman and colleagues examined the role of AT1 receptors in the kidney and their contribution to the development of ang II-induced hypertension [11–14]. They found that ang II causes hypertension primarily through effects on AT1 receptors in the kidney associated with reduced urinary sodium excretion, independent of actions of the sympathetic nervous system or aldosterone. When AT1 receptors are eliminated from the kidney, the extrarenal AT1 receptors are not sufficient to induce hypertension (see Fig. 5.4). Coffman and colleagues also reported that deletion of AT1 receptors in the proximal tubule alone reduces

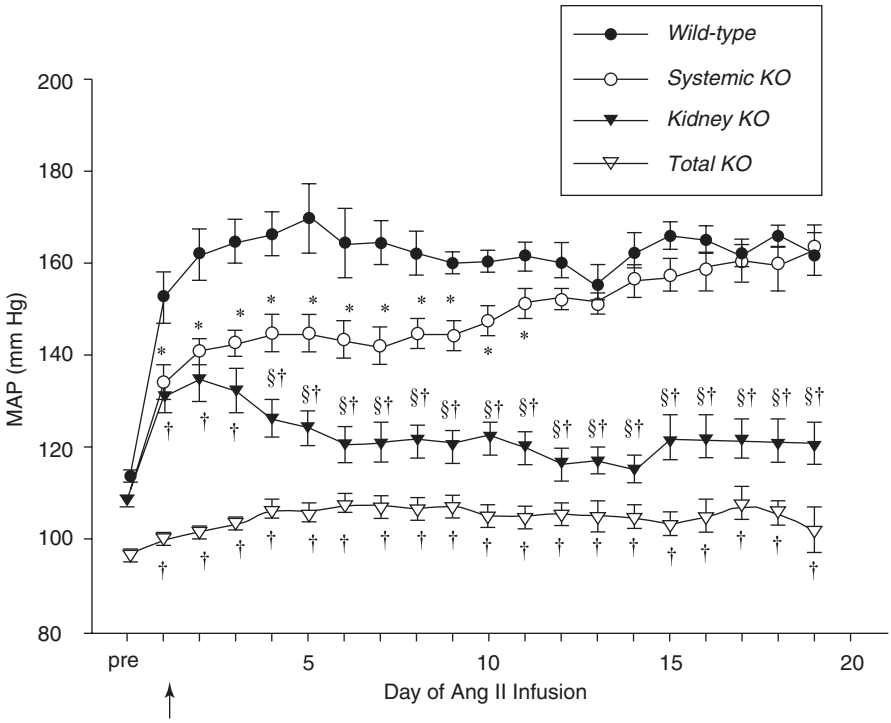



**Fig. 5.4** A dominant role for renal $AT_{1A}$ receptors in blood pressure control was demonstrated using four groups of cross-kidney transplanted mice, namely, whole-body $AT_{1A}$ expressing (wild type), $AT_{1A}$ expressing systemically but not in the kidney (systemic $AT_{1A}$), $AT_{1A}$ expressing only in the kidney (kidney KO), and no $AT_{1A}$ in either location (total KO). Mice then received 21 days of ang II infusion. Blood pressure response to ang II in the systemic KO recapitulated that of the wild-type group by day 12 of ang II infusion. Absence of renal $AT_{1A}$ receptors in the kidney KO animals ameliorated ang II-induced hypertension. Total KO blood pressure shows minimal response to ang II infusion [44]

proximal fluid reabsorption, alters expression of key sodium transporters, improves pressure natriuresis, and significantly attenuates ang II-induced hypertension [11–14]. Collectively, these findings highlight the critical role of the kidney in the pathogenesis of ang II-dependent hypertension. In addition, they suggest that the major mechanism of action of RAS blockade in hypertension is attenuation of ang II signaling in the kidney.

*Aldosterone, the kidney, and hypertension*. In addition to primary hyperaldosteronism, excess activation of mineralocorticoid receptor by aldosterone has also been implicated in several forms of human hypertension, including renovascular hypertension, patients with resistant hypertension, and obesity-related hypertension [15–20]. Aldosterone plays an important role in the chronic regulation of blood pressure via its sodium-retaining actions on the kidney. Aldosterone alters the renal-pressure natriuresis relationship by enhancing sodium transport in the distal tubules and cortical collecting ducts. The sodium-retaining effect of aldosterone is due to

binding of aldosterone to intracellular mineralocorticoid receptor and activation of transcription by target genes. These target genes, in turn, stimulate synthesis or activation of the sodium-potassium ATPase pump on the basolateral epithelial membrane and activation of amiloride-sensitive sodium channels on the luminal side of the epithelial membrane [18].

As sodium intake is increased to high levels, aldosterone levels are suppressed, allowing sodium excretion to increase to match sodium intake. Conversely, when sodium intake is restricted, aldosterone levels increase, and sodium excretion is reduced to match the low sodium intake. Thus, a change in aldosterone production in response to changes in sodium intake is another important hormone in the maintenance of sodium balance. An inability to suppress aldosterone production in response to increases in sodium intake therefore is another potential mechanism for salt-sensitive hypertension in humans.

*The renal sympathetic nervous system*. Another system that can reduce the renal-pressure natriuresis relationship and cause chronic hypertension is the renal sympathetic nervous system [21, 22]. The kidneys receive extensive sympathetic innervation, and increases in RSNA reduce sodium excretion by increasing tubular reabsorption or decreasing the filtered load of sodium via α-adrenergic receptor activation [21, 22]. Renal nerves can act directly on the tubule to increase sodium reabsorption or indirectly by increasing renal vascular resistance and reducing medullary blood flow and renal interstitial pressure. In addition, increases in RSNA can enhance tubule reabsorption by activating the RAS.

Excessive activation of the renal sympathetic nervous system has been implicated in the pathogenesis of several experimental and genetic forms of hypertension [21, 22]. Evidence for a role of the renal nerves in hypertension derives from animal studies showing that renal denervation attenuates or delays the development of hypertension in several forms of experimental hypertension [21, 22]. One particular experimental form of hypertension that is mediated via enhanced RSNA is obesity-related hypertension [21, 22]. Obesity is often associated with increased sympathetic activity [21, 22]. To determine the role of renal nerves in mediating the sodium retention and hypertension associated with obesity, Kassab and colleagues [23] examined the hemodynamic and renal excretory responses to a high-fat diet in control and bilaterally renal-denervated dogs (see Fig. 5.5). In response to a high-fat diet, body weight increased similarly in the control and bilaterally renal-denervated groups. Arterial pressure increased by 15% in the control group but, in sharp contrast, 5 weeks of a high-fat diet in the bilaterally renal-denervated group did not significantly increase arterial pressure. Furthermore, after 5 weeks of a high-fat diet, cumulative sodium retention was 455 ± 85 mmol in the control group and only 252 ± 47 mmol in the bilaterally renal-denervated group. Similar increases in glomerular filtration rate and renal plasma flow occurred in both groups in response to the high-fat diet, indicating that the sodium retention in response to a high-fat diet was due to enhanced sodium reabsorption [23]. The results of this study indicate that the renal nerves play an important role in mediating the sodium retention and hypertension associated with obesity.

While there is growing evidence for a role of the renal sympathetic nervous system in the development of several animal models of hypertension, the importance of

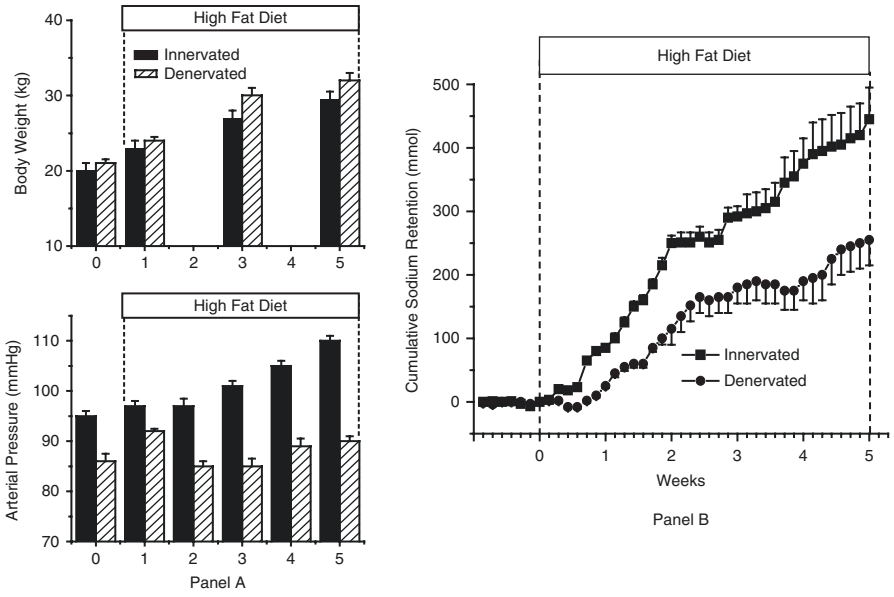



**Fig. 5.5** Changes in body weight and arterial pressure (*Panel A*) and cumulative sodium balance (*Panel B*) in response to a high-fat diet in dogs with innervated and denervated kidneys (redrawn from [58])

renal nerves in the pathogenesis of human hypertension has yet to be fully elucidated [21, 22]. Application of the norepinephrine spillover methodology in humans has demonstrated activation of the sympathetic nervous outflow to the kidneys in humans with essential hypertension [21, 22]. Renal norepinephrine spillover, on average, is elevated two- to threefold in both normal weight patients with essential hypertension and in those with obesity-related hypertension [21, 22].

Evidence for a potential role of renal nerves in human hypertension are the findings that ablation of the renal sympathetic nerves with a radiofrequency-emitting catheter inserted percutaneously significantly reduces blood pressure in patients with resistant hypertension [24–26]. Symplicity HTN-1 and HTN-2 demonstrated significant reductions of blood pressure within 6 months of the procedure. In contrast, the Symplicity HTN-3 trial, which controlled for factors believed to influence the outcome, including the addition of a sham arm, yielded a much lower blood pressure reduction compared with the Symplicity HTN-1 and HTN-2 trials [24–26]. The exact reasons for the variable findings with the renal ablation procedure may be multiple including inadequate renal denervation. While some studies support a potential role for renal nerves in patients with resistant hypertension, it also remains unclear as to the relative importance of destruction of renal afferent versus efferent nerves in the antihypertensive effect achieved by the radiofrequency ablation procedure [26].

*The renal endothelin system*. Endothelin-1 (ET-1) is derived from preproendothelin, which is cleaved after translation to form proendothelin [27–29]. Proendothelin is cleaved in the presence of a converting enzyme to produce the 21

amino acid peptide, ET-1. ET-1 receptor binding sites have been identified throughout the body with the greatest numbers of receptors in the kidneys. ET-1 can either elicit a prohypertensive, antinatriuretic effect by activating endothelin type A ($ET_{A)}$ receptors and causing renal vasoconstriction or an antihypertensive, natriuretic effect via endothelin type B ($ET_B$) receptor activation (see Fig. 5.6). Thus, the ability of ET-1 to influence blood pressure regulation and renal-pressure natriuresis is highly dependent on where ET-1 is produced in the kidney and which renal ET receptor type is activated [27–29].

ET-1, via $ET_A$ receptor activation, exerts a variety of actions within the kidney that, if sustained chronically, could contribute to the development of hypertension and progressive renal injury [27–29]. ET-1 decreases GFR and renal plasma flow [27–29]. Long-term effects of ET-1 on the kidney include stimulation of mesangial cell proliferation and extracellular matrix deposition as well as stimulation of vascular smooth muscle hypertrophy in renal resistance vessels [27–29]. Previous

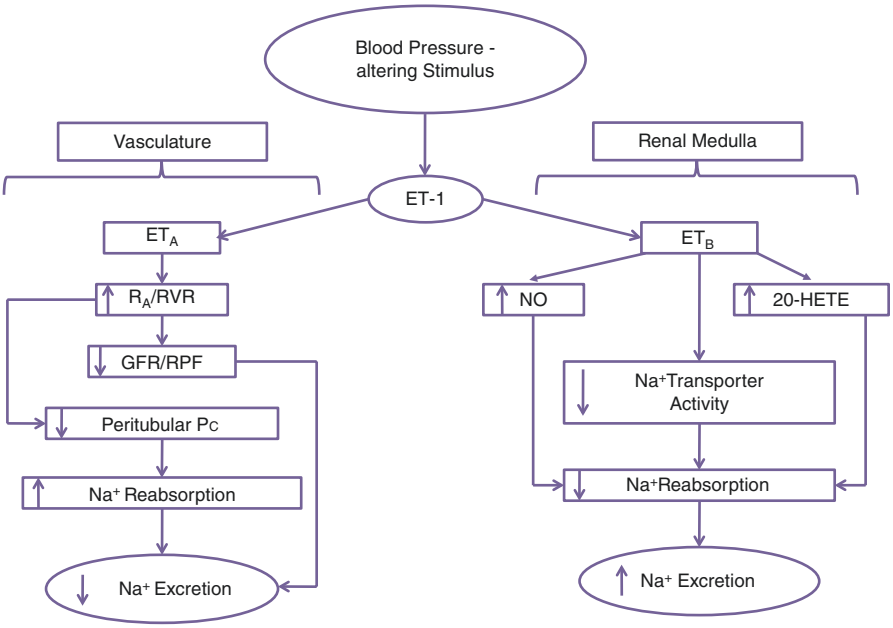



**Fig. 5.6** Pro- and antihypertensive actions of endothelin-1 (ET-1). The ability of ET-1 to influence blood pressure regulation and renal-pressure natriuresis is highly dependent on where ET-1 is produced and which renal ET receptor type is activated. ET-1 can elicit a prohypertensive, antinatriuretic effect by activating $ET_A$ receptors in the kidneys. Activation of renal $ET_A$ receptors increases renal vascular resistance (RVR), which decreases renal plasma flow (RPF) and glomerular filtration rate (GFR) and enhances sodium reabsorption by decreasing peritubular capillary hydrostatic pressure (Pc). The net effect of renal $ET_A$ receptor activation would be increased in sodium retention and blood pressure. Conversely, ET-1 can elicit an antihypertensive, natriuretic effect via $ET_B$ receptor activation. Activation of the renal $ET_B$ receptor leads to enhanced synthesis of nitric oxide (NO) and prostaglandin $E_2$ (PG) and suppression of the renin-angiotensin system. The net effect of renal $ET_B$ receptor activation would be decreases in sodium retention and blood pressure

studies have indicated that expression of ET-1 is greatly enhanced in animal models of severe hypertension with renal vascular hypertrophy and in models of progressive renal injury [27–29]. In addition, treatment with endothelin receptor antagonists attenuated the hypertension and small artery morphologic changes and improved kidney function in these models [30, 31]. An interesting unanswered question that emerges is whether the beneficial effect of the $ET_A$ blockade in reducing renal injury is mediated through reducing blood pressure or through direct renal mechanisms. Moreover, the importance of selective $ET_A$ blockade in human hypertension remains unknown [32–34].

While much attention has been given to the role of ET-1 in the pathophysiology of cardiovascular and renal disease acting via an $ET_A$ receptor, recent studies indicate an important physiological role for ET-1 in the regulation of sodium balance and arterial pressure via $ET_B$ receptor activation. The most compelling evidence that the endothelin system may play a significant role in the regulation of sodium balance and arterial pressure are the reports that transgenic animals deficient in $ET_B$ receptors develop a severe form of salt-sensitive hypertension [35]. Additional evidence comes from studies indicating that pharmacological antagonism of $ET_B$ receptors produces significant hypertension in rats [35–38].

The collecting duct $ET_B$ receptor appears to be an important physiologic regulator of renal sodium excretion and blood pressure. Ge and colleagues [39, 40] reported that disruption of $ET_B$ receptors in the collecting duct cells of mice was found to produce significant hypertension that was salt-sensitive. Collecting duct $ET_B$ KO mice on a normal sodium diet were hypertensive. Collecting duct $ET_B$ knockout mice on a high-sodium diet had worsened hypertension, reduced urinary sodium excretion, and excessive weight gain [39]. Similar findings were found in mice with combined $ET_B$ and $ET_A$ receptor KO in the collecting duct cells [40] These findings provide strong evidence that the collecting duct $ET_B$ receptor is an important physiologic regulator of renal sodium excretion and blood pressure.

*Nitric oxide (NO) deficiency and hypertension*. All components of the NO system are located within the kidney, and pharmacological or genetic disruption of this system results in a sustained hypertension associated with reductions in renal hemodynamics and pressure natriuresis [41–44]. The magnitude of the increase in blood pressure is also dependent on dietary sodium intake. These findings have led to the concept that NO is not only important in the long-term regulation of sodium balance and blood pressure but also to the notion that abnormalities in NO production results in altered pressure natriuresis and a salt-sensitive form of hypertension. Several lines of evidence suggest that NO may play an important role in the regulation of sodium balance and in pathogenesis of salt-sensitive hypertension [41–45]. An increase in renal NO production or release, as evidence by increased urinary excretion of NO metabolites or the NO second messenger, cyclic GMP, has been reported to be essential for the maintenance of normotension during a dietary salt challenge. Prevention of this increase in renal NO production results in salt-sensitive hypertension [41–45].

Reductions in NO synthesis also reduce sodium excretory function either through direct effects on tubular transport or through changes in intrarenal physical factors, such as renal interstitial hydrostatic pressure or medullary blood flow [46, 47].

Consistent with this concept are observations that the acute infusion of an NO synthase inhibitor directly into the renal medulla significantly reduces papillary blood flow, renal interstitial hydrostatic pressure, and decreases urinary sodium and water excretion without affecting glomerular filtration rate or systemic pressure [41, 46, 47]. Chronic medullary interstitial infusion of nitric oxide synthase inhibitors into conscious rats results in sustained reductions in medullary blood flow, sustained sodium and water retention, and hypertension, which are reversed when the infusion is discontinued (see Fig. 5.7). These findings demonstrate that reductions in medullary blood flow may be another important mechanism whereby inhibition of NO in the kidney leads to a hypertensive shift in pressure natriuresis [46].

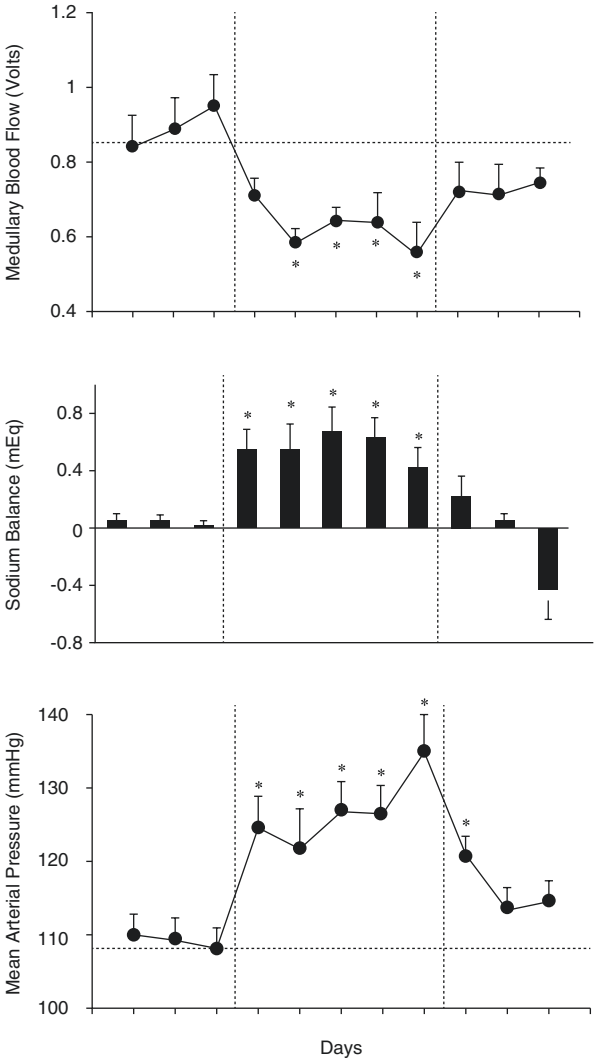



**Fig. 5.7** Effects of chronic renal medullary interstitial infusion of the nonselective nitric oxide synthase inhibitor L-NAME (8.6 mg/kg/day) on renal medullary blood flow (*top*), daily sodium balance (*middle*), and mean arterial blood pressure (*bottom*) in conscious male Sprague-Dawley rats. The space between the vertical dashed lines indicates the L-NAME infusion period whereby the left line is the beginning and the right line is when infusion was halted. *Significant difference from control ($P < 0.05$) (redrawn from [46])

*Atrial natriuretic peptide*. Atrial natriuretic peptide (ANP) elicits an antihypertensive, natriuretic effect via its receptors (NPR). ANP is 28 amino acid peptide synthesized and released from atrial cardiocytes in response to stretch [48]. Once ANP is released from the atria, it enhances sodium excretion through extrarenal and intrarenal mechanisms [48]. A deficiency in ANP production or a defect in its receptors may reduce pressure natriuresis and lead to hypertension by enhancing tubular sodium reabsorption either directly by enhancing the active tubular transport of sodium or indirectly via alterations in medullary blood flow, physical factors, and intrarenal hormones.

Plasma levels of ANP are elevated in numerous physiological conditions associated with enhanced sodium excretion [48]. Acute saline load to induce blood volume expansion consistently elevates circulating levels of ANP. Some, but not all, investigators have reported that chronic increases in dietary sodium intake raise circulating levels of ANP. Several studies have reported that infusions of exogenous ANP at rates that result in physiologically relevant plasma concentrations, comparable to those observed during volume expansion, have significant renal and cardiovascular effects [49]. Infusion of ANP at a rate that causes a twofold increase in plasma ANP elicits significant natriuresis, especially in the presence of other natriuretic stimuli, such as high renal perfusion pressure [49]. Long-term physiological elevations in plasma ANP also shift the renal-pressure natriuresis relationship and reduce arterial pressure [49].

The development of genetic mouse models that exhibit chronic alterations in expression of the genes for ANP or its receptors (NPR-A, NPR-C) has also provided compelling evidence for a role of ANP in chronic regulation of renal-pressure natriuresis and blood pressure [50, 51]. Transgenic mice overexpressing the ANP gene are hypotensive relative to the non-transgenic littermates, whereas mice harboring functional disruptions of the ANP or NPR-A genes are hypertensive. The ANP gene "KO" mice develop a salt-sensitive form of hypertension in association with failure to adequately suppress the RAS [50, 51]. These findings suggest that genetic deficiencies in ANP or natriuretic receptor activity could play a role in the pathogenesis of salt-sensitive hypertension.

*Arachidonic acid metabolites*. Cyclooxygenase metabolizes arachidonic acid into prostaglandin (PG) $G_2$ and subsequently to $PGH_2$, which is then further metabolized by tissue-specific isomerases to PGs and thromboxane [52, 53]. Although the kidney produces many types of PGs with multiple functions, the major renal prostaglandin controlling sodium excretion is $PGE_2$ [52, 53]. However, production of other arachidonic acid metabolites, such as prostacyclin, thromboxane, and 20-HETE (hydroxyeicosatetraenoic acid), may also influence renal-pressure natriuresis and blood pressure regulation. The largest production of $PGE_2$ occurs in the medulla with decreasing synthesis in the cortex. $PGE_2$ is synthesized and rapidly inactivated and, once synthesized, is released and not stored. Once released, $PGE_2$ influences sodium transport by several intrarenal mechanisms.

Inhibition of PG synthesis with nonselective or selective inhibitors of cyclooxygenase-2 (COX-2) activity induces or exacerbates salt-sensitive hypertension, an effect that has been attributed to inhibition of renal COX-2 activity and subsequent

increase in renal sodium transport. Zhang et al. recently reported that macrophages isolated from kidneys of high-salt-treated mice have increased levels of COX-2 and microsomal PGE synthase-1 (mPGES-1) [54]. Furthermore, they showed that bone marrow transplantation from either COX-2-deficient or mPGES-1-deficient mice into WT mice or macrophage-specific deletion of the $PGE_2$ type 4 (EP4) receptor induced salt-sensitive hypertension and increased phosphorylation of the renal sodium chloride cotransporter (NCC). These studies suggest that COX-2-derived $PGE_2$ in hematopoietic cells plays an important role in response to chronically increased dietary sodium intake and also indicate that inhibiting COX-2 expression or activity in hematopoietic cells can result in a predisposition to salt-sensitive hypertension [54].

In addition to renal PGs generated via the COX pathway, other eicosanoids that inhibit tubular sodium transport are produced by cytochrome P450 (CYP) monooxygenase metabolism of arachidonic acid [53]. CYP enzymes metabolize arachidonic acid primarily to 20-HETE and EETs. It is known that 20-HETE is a potent constrictor of the renal vasculature, but interestingly, 20-HETE and EETS inhibit sodium reabsorption in the proximal tubule and TALH.

The renal production of CYP metabolites of arachidonic acid is altered in genetic and experimental models of hypertension, and this system contributes to the resetting of pressure natriuresis and the development of hypertension. In the SHR, the renal production of 20-HETE is increased, and inhibitors of the formation of 20-HETE decrease arterial pressure [53]. Blockade of 20-HETE synthesis also reduces blood pressure or improves renal function in deoxycorticosterone acetate (DOCA)-salt, ang II-infused, and Lyon hypertensive rats [53]. In contrast, 20-HETE formation is reduced in the TALH of Dahl salt-sensitive rats, and this contributes to elevated sodium reabsorption [53]. Enhanced 20-HETE synthesis improves pressure natriuresis and lowers blood pressure in Dahl salt-sensitive rats, whereas inhibitors of 20-HETE production promote the development of hypertension in Lewis rats [53].

*Oxidative stress*. Recent studies suggest that reactive oxygen species (ROS) may play a role in the initiation and progression of cardiovascular dysfunction associated with diseases, such as hyperlipidemia, diabetes mellitus, and hypertension [54–56]. In many forms of hypertension, the increased ROS are derived from NAD(P)H oxidases, which could serve as a triggering mechanism for uncoupling endothelial NOS by oxidants, resulting in reduced bioavailability of NO [54–56].

ROS produced by migrating inflammatory cells and/or vascular cells have distinct functional effects on each cell type [54]. These effects include endothelial dysfunction, renal tubule sodium transport, cell growth, migration, inflammatory gene expression, and matrix regulation. ROS, by renal hemodynamics and renal tubule cell function, can play a role in altering renal-pressure natriuresis and blood pressure regulation [54, 57].

Growing experimental evidence supports a role for ROS in various animal models of sodium-sensitive hypertension [58, 59]. The Dahl salt-sensitive rat has increased vascular and renal superoxide production and increased levels of $H_2O_2$. The renal protein expression of superoxide dismutase (SOD) is decreased in the

kidney of Dahl salt-sensitive rats, and long-term administration of tempol, an SOD mimetic, significantly decreases arterial pressure and renal damage. Another salt-sensitive model, the stroke-prone spontaneously hypertensive rat (SHRSP), has elevated levels of superoxide and decreased total plasma antioxidant capacity. Superoxide production is also increased in the DOCA-salt hypertensive rat [58, 59]. Treatment of the DOCA-salt rats with apocynin, an NADPH oxidase inhibitor/ROS scavenger, decreases aortic superoxide production and arterial pressure [58, 59].

The importance of oxidative stress in human hypertension is unclear. An imbalance between total oxidant production and the antioxidant capacity in human hypertension has been reported to occur in some but not all studies. The equivocal findings in human studies are most likely due to difficulty of assessing oxidative stress in humans. Moreover, most of recent human studies have found that vitamin E and C supplementation has little or no effect on blood pressure. However, it should be noted that these are relatively weak antioxidants, and further studies are needed to assess the role of ROS in human hypertension.

*Inflammatory cytokines and the immune system in hypertension and renal injury*. Growing evidence over the last 5 years supports the concept that both innate and adaptive immunity contribute to the development of hypertension and hypertensive renal injury [60–66]. Macrophages and T cells accumulate in the kidney of hypertensive animals and are thought to contribute to altered renal hemodynamics and tubular function in hypertension [60–66]. Findings that plasma levels of pro-inflammatory cytokines correlate with increased blood pressure in human hypertension and in some experimental animal models of hypertension also provide additional support for a role for cytokines in hypertension [60–66]. Moreover, several studies have demonstrated that chronic increases in plasma cytokines, comparable to concentrations observed in the hypertension associated with hypertension preeclampsia, cause significant and sustained increases in blood pressure [64].

Animal studies utilizing genetic deletion of cytokines or its receptors support a role of cytokines in hypertension. For example, mice with knockout of IL-6 have significantly lower blood pressure than wild-type mice during 2 weeks of ang II infusion [65]. Although these findings demonstrate a significant role for IL-6 in mediating the chronic hypertensive response to ang II in mice, the importance of inflammatory cytokines in the pathogenesis and progression of the various forms of human hypertension is unclear and is currently an area of active investigation.

Results from several recent studies also suggest that T cells play a role in the progression of hypertension [66–70]. Harrison and colleagues proposed that hypertensive stimuli lead to renal injury, neoantigen formation, and eventual T-cell activation within the kidney [66]. T-cell-derived signals promote entry of other inflammatory cells such as macrophages, which results in renal vasoconstriction and increased sodium reabsorption, thereby increasing the severity of the hypertension (see Fig. 5.8). Supporting this concept are results from studies in RAG-1$^{-/-}$ mice, which lack T cells and B cells [66–68]. These mice do not develop the degree of hypertension in response to ang II infusion as wild-type mice, an observation that was attributed to lack of T cells [66–68]. Moreover, chronic ang II infusion was associated with a greater number of activated T cells as well as increased RANTES,

a chemotactic protein, in the vasculature and perivascular fat. These observations were confirmed by Crowley et al. using a model very similar to the RAG-1$^{-/-}$ mice [66–68]. They reported that ang II hypertension, renal injury, left ventricular hypertrophy, and cardiac fibrosis were prevented in SCID mice lacking T cells [66].

Although there is growing evidence suggesting that the immune system plays a role in the progression of hypertension, the mechanisms by which hypertension stimulates an immune response remain unclear but might involve the formation of neoantigens that activate adaptive immunity [66, 70]. Moreover, while findings in experimental models of hypertension are intriguing, the importance of the immune system in the pathogenesis of hypertension in humans remains to be determined., However, in a very interesting recent study, Itani and colleagues used a humanized mouse model in which the murine immune system was replaced by the human immune system to determine whether human T cells are activated in hypertension [69]. They reported that a hypertensive stimulus of ang II promoted accumulation of human T cells in the kidney, aorta, and lymph nodes of these humanized mice. The

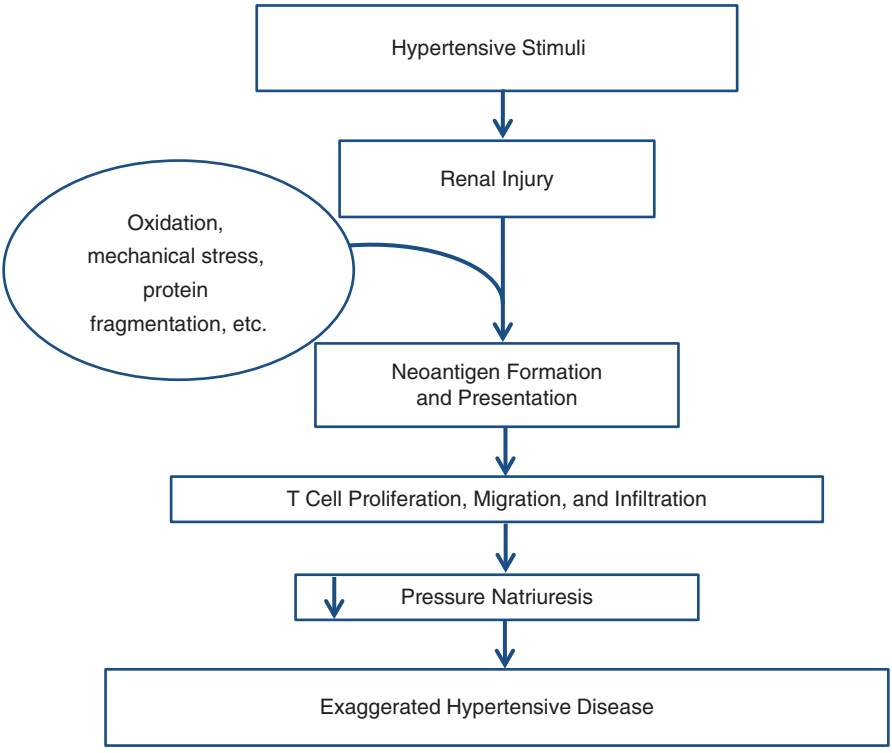



**Fig. 5.8** Proposed role of T cells and inflammation in progression of chronic hypertension. Initial hypertensive stimuli leads to renal injury, neoantigen formation, and eventual T-cell activation within the kidney. T-cell-derived signals promote entry of other inflammatory cells, such as macrophages, which result in renal vasoconstriction and sodium reabsorption, thereby increasing the severity of hypertension and cardiovascular-renal disease (redrawn from [20])

cells exhibited an increase in the memory cell marker CD45RO. In addition, $CD3^{-}$ $CD45^{+}$ cells were increased in lymph nodes of ang II-infused mice. They also demonstrated that circulating T cells of humans with hypertension exhibit evidence of activation, as indicated by an increased percent of memory T cells and an increase in production of IL-17A and IFN-γ [69]. Thus, human T cells become activated and invade critical end-organ tissues in response to ang tempol, a superoxide dismutase mimetic II hypertension in the humanized mouse model.

## References


1. Guyton AC, Coleman TG, Cowley AW et al (1972) Arterial pressure regulation: overriding dominance of the kidneys in long-term regulation and in hypertension. Am J Med 52:584–594
2. Hall JE (2016) Renal dysfunction, rather than nonrenal vascular dysfunction, mediates salt induced hypertension. Circulation 133(9):894–906
3. Hall JE, Granger JP (2005) Regulation of fluid and electrolyte balance in hypertension: role of hormones and peptides. In: Battegay EJ, Lip GHY, Bakris GL (eds) Hypertension: principles and practice. Taylor & Francis, Boca Raton, pp 121–142
4. Lifton RP (1996) Molecular genetics of human blood pressure variation. Science 272:676–680
5. Hall JE, Guyton AC, Smith MJ Jr et al (1980) Blood pressure and renal function during chronic changes in sodium intake: role of angiotensin. Am J Physiol 239:F271–F280
6. Hall JE, Granger JP, Smith MJ et al (1984) Role of renal hemodynamics and arterial pressure in aldosterone "escape". Hypertension 6(suppl I):I183–I192
7. Hall JE, Mizelle HL, Hildebrandt DA et al (1990) Abnormal pressure natriuresis: a cause or a consequence of hypertension? Hypertension 15(6 pt 1):547–559
8. Hall JE, Granger JP, Hester RL et al (1986) Mechanisms of sodium balance in hypertension: role of pressure natriuresis. J Hypertens 4(suppl 4):S57–S65
9. Te Riet L, van Esch JH, Roks AJ et al (2015) Hypertension: renin-angiotensin-aldosterone system alterations. Circ Res 116(6):960–975
10. Navar LG, Harrison-Bernard LM, Nishiyama A et al (2002) Regulation of intrarenal angiotensin II in hypertension. Hypertension 39:316–322
11. Coffman TM (2011) Renin angiotensin system under pressure: the search for the essential mechanisms of hypertension. Nat Med 17(11):1402–1409
12. Crowley SD, Zhang J, Herrera M et al (2011) Role of AT1 receptor-mediated salt retention in angiotensin II-dependent hypertension. Am J Physiol Renal Physiol 301(5):F1124–F1130
13. Gurley SB, Riquier-Brison AD, Schnermann J et al (2011) AT1A angiotensin receptors in the renal proximal tubule regulate blood pressure. Cell Metab 13(4):469–475
14. Coffman TM, Crowley SD (2008) Kidney in hypertension: Guyton Redux. Hypertension 51(4):811–816
15. Luther JM (2016) Aldosterone in vascular and metabolic dysfunction. Curr Opin Nephrol Hypertens 25(1):16–21
16. Epstein M, Calhoun DA (2011) Aldosterone blockers (mineralocorticoid receptor antagonism) and potassium-sparing diuretics. J Clin Hypertens (Greenwich) 13(9):644–648
17. Shibata S, Fujita T (2011) The kidneys and aldosterone/mineralocorticoid receptor system in salt-sensitive hypertension. Curr Hypertens Rep 13(2):109–115
18. Arroyo JP, Lagnaz D, Ronzaud C et al (2011) Nedd4-2 modulates renal Na+-Cl- cotransporter via the aldosterone-SGK1-Nedd4-2 pathway. J Am Soc Nephrol 22(9):1707–1719
19. de Paula RB, da Silva AA, Hall JE (2004) Aldosterone antagonism attenuates obesity induced hypertension and glomerular hyperfiltration. Hypertension 43:41–47
20. Calhoun DA, Nishizaka MK, Zaman MA et al (2002) Hyperaldosteronism among black and white subjects with resistant hypertension. Hypertension 40:892–896

21. DiBona GF (2003) Neural control of the kidney: past, present, and future. Hypertension 4:621–624
22. DiBona GF, Esler M (2010) Translational medicine: the antihypertensive effect of renal denervation. Am J Physiol Regul Integr Comp Physiol 298(2):R245–R253
23. Kassab S, Kato T, Wilkins FC et al (1995) Renal denervation attenuates the sodium retention and hypertension associated with obesity. Hypertension 25:893–897
24. Krum H, Whitbourn R, Sobotka P et al (2009) Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof- of-principle cohort study. Lancet 373:1275–1281
25. Esler MD, Krum H, Sobotka PA et al (2010) Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet 376(9756):1903–1909
26. Iliescu R, Lohmeier TE, Tudorancea I et al (2015) Renal denervation for the treatment of resistant hypertension: review and clinical perspective. Am J Physiol Renal Physiol 309(7):F583–F594
27. De Miguel C, Speed JS, Kasztan M et al (2016) Endothelin-1 and the kidney: new perspectives and recent findings. Curr Opin Nephrol Hypertens 25(1):35–41
28. Nasser SA, El-Mas MM (2014) Endothelin ETA receptor antagonism in cardiovascular disease. Eur J Pharmacol 737:210–213
29. Kohan DE, Rossi NF, Inscho EW et al (2011) Regulation of blood pressure and salt homeostasis by endothelin. Physiol Rev 91:1–77
30. Kassab S, Novak J, Miller T et al (1997) Role of endothelin in mediating the attenuated renal hemodynamics in Dahl salt-sensitive hypertension. Hypertension 30:682–686
31. Kassab S, Miller M, Novak J et al (1998) Endothelin-A receptor antagonism attenuates the hypertension and renal injury in Dahl salt-sensitive rats. Hypertension 31:397–402
32. Krum H, Viskoper RJ, Lacourciere Y et al (1998) The effect of an endothelin receptor antagonist, Bosentan, on blood pressure in patients with essential hypertension. N Engl J Med 338:784–790
33. Prasad VS, Palaniswamy C, Frishman WH (2009) Endothelin as a clinical target in the treatment of systemic hypertension. Cardiol Rev 17:181–191
34. Goddard J, Kohan D, Pollock D et al (2008) Role of endothelin-1 in clinical hypertension: 20 years on. Hypertension 52:452–459
35. Gariepy CE, Ohuchi T, Williams SC et al (2000) Salt-sensitive hypertension in endothelin-B receptor-deficient rats. J Clin Invest 105:925–933
36. Pollock DM, Pollock JS (2001) Evidence for endothelin involvement in the response to high salt. Am J Physiol Renal Physiol 281:F144–F150
37. Bagnall AJ, Kelland NF, Gulliver-Sloan F et al (2006) Deletion of endothelial cell endothelin B receptors does not affect blood pressure or sensitivity to salt. Hypertension 48:286–293
38. Ohuchi T, Kuwaki T, Ling G et al (1999) Elevation of blood pressure by genetic and pharmacological disruption of the ETB receptor in mice. Am J Physiol Regul Integr Comp Physiol 276:R1071–R1077
39. Ge Y, Bagnall A, Stricklett P, Strait K et al (2006) Collecting duct-specific knockout of the endothelin B receptor causes hypertension and sodium retention. Am J Physiol Renal Physiol 291(6):F1274–F1280
40. Ge Y, Bagnall A, Stricklett PK et al (2008) Combined knockout of collecting duct endothelin A and B receptors causes hypertension and sodium retention. Am J Physiol Renal Physiol 295(6):F1635–F1640
41. Schnackenberg CG, Kirchner K, Patel A et al (1997) Nitric oxide, the kidney, and hypertension. Clin Exp Pharmacol Physiol 24:600–606
42. Granger JP, Alexander BT (2000) Abnormal pressure natriuresis in hypertension: role of nitric oxide. Acta Physiol Scand 168:161–168
43. Schnackenberg C, Wilkins C, Granger JP (1995) Role of nitric oxide in modulating the vasoconstrictor actions of angiotensin II in preglomerular and postglomerular vessels in dogs. Hypertension 26:1024–1029

44. Granger JP, Alberola A, Salazer F et al (1992) Control of renal hemodynamics during intrarenal systemic EDNO synthesis blockade. J Cardiovasc Pharmacol 20:S160–S162
45. Granger JP, Novak J, Schnackenberg C et al (1996) Role of renal nerves in mediating the hypertensive effects of nitric oxide synthesis inhibition. Hypertension 27:613–618
46. Mattson DL, Lu SH, Nakanishi K et al (1994) Effect of chronic renal medullary nitric oxide inhibition on blood pressure. Am J Physiol Heart Circ Physiol 266:H1918–H1926
47. Cowley AW Jr, Mori T, Mattson D et al (2003) Role of renal NO production in the regulation of medullary blood flow. Am J Physiol Regul Integr Comp Physiol 284:R1355–R1369
48. Knox FG, Granger JP (1992) Control of sodium excretion: an integrative approach. In: Windhager E (ed) Handbook of renal physiology. Oxford University Press, New York, pp 927–967
49. Granger JP, Opgenorth TJ, Salazar J et al (1986) Long-term hypotensive and renal effects of chronic infusions of atrial natriuretic peptide in conscious dogs. Hypertension 8:II112–II116
50. Melo LG, Steinhelper ME, Pang SC et al (2000) ANP in regulation of arterial pressure and fluid-electrolyte balance: lessons from genetic mouse models. Physiol Genomics 3:45–58
51. Melo LG, Veress AT, Chong CK et al (1998) Salt-sensitive hypertension in ANP knockout mice: potential role of abnormal plasma renin activity. Am J Physiol 274:R255–R261
52. Cheng HF, Harris RC (2004) Cyclooxygenases, the kidney, and hypertension. Hypertension 43:525–530
53. Roman RJ (2002) P-450 metabolites of arachidonic acid in the control of cardiovascular function. Physiol Rev 82:131–185
54. Zhang MZ, Yao B, Wang Y et al (2015) Inhibition of cyclooxygenase-2 in hematopoietic cells results in salt-sensitive hypertension. J Clin Invest 125(11):4281–4294
55. Taniyama Y, Griendling KK (2003) Reactive oxygen species in the vasculature: molecular and cellular mechanisms. Hypertension 42:1075–1081
56. Wilcox CS (2002) Reactive oxygen species: roles in blood pressure and kidney function. Curr Hypertens Rep 4:160–166
57. Schreck C, O'Connor PM (2011) NAD(P)H oxidase and renal epithelial ion transport. Am J Physiol Regul Integr Comp Physiol 300(5):R1023–R1029
58. Manning RD Jr, Meng S, Tian N (2003) Renal and vascular oxidative stress and salt-sensitivity of arterial pressure. Acta Physiol Scand 179:243–250
59. Garvin JL, Ortiz PA (2003) The role of reactive oxygen species in the regulation of tubular function. Acta Physiol Scand 179:225–232
60. Sanz-Rosa D, Oubina MP, Cediel E et al (2005) Effect of AT1 receptor antagonism on vascular and circulating inflammatory mediators in SHR: role of NF{kappa}B/I{kappa}B system. Am J Physiol Heart Circ Physiol 288:H111–H115
61. De Miguel C, Guo C, Lund H et al (2011) Infiltrating T lymphocytes in the kidney increase oxidative stress and participate in the development of hypertension and renal disease. Am J Physiol Renal Physiol 300(3):F734–F742
62. Mattson DL (2010) Effector memory T lymphocytes in renal disease. Am J Physiol Renal Physiol 299(6):F1257
63. De Miguel C, Das S, Lund H et al (2010) T lymphocytes mediate hypertension and kidney damage in Dahl salt-sensitive rats. Am J Physiol Regul Integr Comp Physiol 2010 298(4):R1136–R1142
64. Granger JP, Alexander BT, Llinas MT et al (2002) Pathophysiology of preeclampsia: linking placental ischemia/hypoxia with microvascular dysfunction. Microcirculation 9:147–160
65. Lee DL, Sturgis LC, Labazi H et al (2006) Angiotensin II hypertension is attenuated in interleukin-6 knockout mice. Am J Physiol Heart Circ Physiol 290:H935–H940
66. Harrison DG, Guzik TJ, Lob HE et al (2011) Inflammation, immunity, and hypertension. Hypertension 57:132–140
67. Guzik TJ, Hoch NE, Brown KA et al (2007) Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. J Exp Med 204:2449–2460

68. Crowley SD, Song YS, Lin EE et al (2010) Lymphocyte responses exacerbate angiotensin II-dependent hypertension. Am J Physiol Regul Integr Comp Physiol 298:R1089–R1097
69. Itani HA, McMaster WG Jr, Saleh MA et al (2016) Activation of human T cells in hypertension: studies of humanized mice and hypertensive humans. Hypertension 68(1):123–132
70. Wenzel U, Turner JE, Krebs C et al (2016) Immune mechanisms in arterial hypertension. J Am Soc Nephrol 27(3):677–686

# Nervous System

# 6

Gino Seravalle, Gianmaria Brambilla, Daniela Prata Pizzala, and Guido Grassi

## 6.1 Methods of Investigating Sympathetic Activity

A growing interest in the role of the sympathetic nervous system in the pathogenesis of hypertension and cardiovascular disease is mainly driven by developments in methods used to investigate adrenergic activity [1, 2]. The most commonly used techniques include (a) measurements of plasma catecholamines, (b) regional noradrenaline spillover, (c) assessment of baroreceptor function, (d) spectral analysis of heart rate variability, (e) microneurography, and (f) imaging techniques.

### 6.1.1 Catecholamines

For many years, the only way to measure sympathetic activity was to assess catecholamines and their metabolites in urine. Further progress came with the introduction of high-performance liquid chromatography (HPLC) to measure catecholamine levels in the plasma of venous and subsequently also arterial blood samples. The interpretation of studies based on blood catecholamine measurements is, however, confounded by many factors [3]: (a) Only 5–10% of the noradrenaline released is ultimately found in the circulation; (b) plasma and urinary levels depend not only on catecholamine release but also on their reuptake and further metabolism; (c) renal function has a major effect on urinary catecholamine excretion; (d) there is large regional variation in sympathetic activity in various organs and organ systems affecting cardiovascular regulation, such as resistance

G. Seravalle
Cardiologia, Ospedale San Luca, IRCCS Istituto Auxologico Italiano, Milan, Italy

G. Brambilla • D.P. Pizzala • G. Grassi (✉)
Clinica Medica, Università Milano-Bicocca, Milan, Italy
e-mail: guido.grassi@unimib.it



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_6

vessels, the heart, the kidneys, and the central nervous system; thus catecholamine levels may reflect "overall" sympathetic activity; (e) catecholamine level measurements are poorly reproducible; (f) this is a static method of assessing sympathetic activity which is, in fact, dynamically regulated.

Plasma and urine catecholamine levels are an indirect indicator of sympathetic activity and thus have only a limited use in research applications.

### 6.1.2 Regional Catecholamine Spillover

In the 1980s, a technique of radioisotope-based measurements of regional catecholamine spillover has been introduced [1, 4]. This method has several advantages over measuring catecholamine levels: (a) it is possible to distinguish the contribution of increased release and reduced reuptake to the overall increased noradrenaline level and (b) more precise evaluation of sympathetic activity in selected organs such as the heart or kidneys is possible by comparing noradrenaline levels in arterial and venous blood samples drawn from specific vessels.

The potential role of impaired neuronal noradrenaline reuptake can be directly assessed by infusion of the noradrenaline transport inhibitor desipramine [5]. Noradrenaline stores in the human heart could be estimated by quantifying the processing inside sympathetic nerves of tritiated noradrenaline to its intraneuronal metabolite, tritiated dihydroxyphenylglycol (DHPG), coupled with measurement of the specific activity of DHPG in coronary sinus plasma.

Because of its invasiveness and thus the need for arterial and venous catheterization, this method is used only for research purposes.

### 6.1.3 Baroreceptor Function Testing

The most commonly used method of evaluating baroreceptor function is the phenylephrine test. Intravenous phenylephrine bolus or infusion results in increased blood pressure and reflex bradycardia as reflected by an increased R-R interval. The measure of baroreceptor function is R-R interval prolongation (in ms) related to a 1 mmHg increase in blood pressure. Baroreflex sensitivity can also be assessed by the sequence technique [6, 7], in which the slope of the regression line between the spontaneous increases or reductions in systolic blood pressure and the related lengthening or shortening in the pulse interval is calculated over spontaneous sequences of three or more consecutive beats.

Recently, a new method for quantifying the spontaneous baroreflex activity of the adrenergic tone has been developed [8, 9]. Briefly, sympathetic baroreflex sensitivity was assessed by using the slope of the linear portion of the relationship between muscle sympathetic nerve activity and diastolic blood pressure. For this analysis, sympathetic nerve activity values were combined into 3 mmHg bins that have been shown to reduce the statistical impact of the non-baroreflex beat-to-beat variability in muscle sympathetic nerve activity.

### 6.1.4 Spectral Analysis of Heart Rate Variability

Spectral analysis of heart rate variability allows noninvasive testing of the autonomic function [10, 11]. This is based on a cyclic variation of a series of R-R intervals. Sinus rhythm variability is largerly related to autonomic activity. The analysis is performed using a fast Fourier transform or the autoregression method. Power spectrum analysis reveals low-frequency (0.04–0.15 Hz; LF) and high-frequency (0.15–0.4 Hz; HF) components. The respiratory-related HF component is attributed mainly to vagal mechanisms. By contrast, different hypotheses have been proposed for the LF oscillation of R-R variability. In several studies, the LF component was not related to rates of noradrenaline spillover from the heart and/or muscle sympathetic nerve traffic [12]. Thus, while the LF/HF ratio may be considered as a marker of sympathovagal balance, it is unjustified to consider the low-frequency power a surrogate measure of sympathetic nerve firing.

### 6.1.5 Microneurography

Microneurography is the only method allowing direct measurements of adrenergic activity in humans [1, 12, 13]. The testing is usually done in the peroneal nerve using microelectrodes with a diameter of approx. 100 μm and an electrode tip diameter of 1–5 μm.

Microneurography allows the activity of postganglionic sympathetic fibers innervating either skeletal muscle (muscle sympathetic nerve activity, MSNA) [1, 12, 13] or skin (skin sympathetic nerve activity, SSNA) to be recorded [1, 12].

The activity of sympathetic fibers innervating resistance vessels in skeletal muscle is the major factor affecting peripheral flow and resistance. Sympathetic traffic in skeletal muscle sympathetic nerves is synchronized with the heart rate, so the firing rate in impulses per minute cannot exceed the heart rate. The so-called resting sympathetic activity is thus defined as the mean number of impulses per minute or 100 heartbeats. This allows comparisons of sympathetic activity to be made between groups.

A major advantage of microneurography is that it is an opportunity not only to assess precisely resting sympathetic activity but also to track changes in cardiovascular regulation in response to various stimuli. These changes in sympathetic activity are extremely dynamic in nature, with a significant increase or reduction in firing rate seen within seconds. There are some methods to evaluate sympathetic reactivity (mental “arithmetic” test, mirror drawing test, hand grip test, “cold pressor” test).

An important tool for evaluating sympathetic reactivity is the combination of microneurography with baroreceptor and chemoreceptor function testing. Baroreceptor function may be assessed using both mechanical and pharmacological methods. A collar-shaped pressure chamber modulating transmural pressure in the carotid sinuses is used to decompress baroreceptors. Baroreceptor function may be assessed by evaluating changes in sympathetic activity following administration of sodium nitroprusside and phenylephrine. Adrenergic activity increases when blood

pressure is reduced and decreases when blood pressure rises. The measure of baroreceptor function is the change in sympathetic activity related to lowering or increasing blood pressure by 1 mmHg.

Not only firing rate but also amplitude is used to evaluate changes in sympathetic activity in response to stress. Total activity is defined as the sum of the amplitudes of all impulses. Assuming that resting total activity is 100%, relative changes in activity during testing may be measured.

A tilt test is an important diagnostic method in cardiovascular disease. The use of microneurography during tilt testing is limited by the risk of microelectrode reposition during tilting. A special chamber involving the lower part of the body is therefore used to simulate tilting. A gradual increase in lower body negative pressure results in a reduction of central venous pressure and decompression of cardiopulmonary mechanoreceptors and arterial baroreceptors. In contrast to the activity of sympathetic fibers innervating resistance vessels, SSNA does not depend on changes in blood pressure, and sympathetic nerve traffic is not synchronized with the heart rate, with some impulses extending for several heartbeats. SSNA is largely related to thermogenesis. In addition, it is affected by emotional stress and auditory stimuli. Complete silence is thus required to record SSNA. Simultaneous recording of MSNA and SSNA makes it possible to determine whether the increase in sympathetic activity occurs only in the cardiovascular system (increased MSNA but not SSNA) or is more generalized (both MSNA and SSNA are increased).

Microneurographic studies are characterized by excellent reproducibility [14], both when comparing same-day recording and recordings performed several months and even years apart. The safety of microneurography is an important issue. This was confirmed in a prospective follow-up study involving hundreds of subjects [15].

Microneurographic findings should not be analyzed apart from hemodynamic data. Microneurography is thus particularly useful when used together with other research techniques such as the following: (a) continuous blood pressure measurements (either invasive or noninvasive using the Finapres device), (b) central venous pressure measurement, (c) peripheral flow and resistance measurement using plethysmography, and (d) assessment of metabolic parameters.

### 6.1.6 Imaging Techniques

Several imaging methods have recently been introduced to assess sympathetic activity in humans. These techniques, utilizing both positron emission tomography and single photon emission computed tomography scanning, have been used to evaluate the anatomy of sympathetic innervations. The most widely used scanning agents include [$^{123}$I]meta-iodobenzylguanidine (MIBG), 6-[$^{18}$F]fluorodopamine, and [$^{11}$C] hydroxyephedrine [12]. These methods have demonstrated sympathetic denervation in patients with pure autonomic failure.

## 6.2 Sympathetic Influences in the Blood Pressure Regulation

The sympathetic nervous system is a major regulatory element of cardiac output and systemic vascular resistance, i.e., the major effector components of neural blood pressure regulation. Tonic sympathetic activity is mainly generated by neurons located in the rostral ventrolateral medulla (RVLM) and regulated by arterial baroreceptors, cardiopulmonary mechanoreceptors, and chemoreceptors. Sympathetic activity is also modulated by neurons in the limbic system, the hypothalamus, and the cortex [16]. Neurotransmitters involved are epinephrine that is released from adrenal medulla, whereas norepinephrine is released mainly from the nerve terminals where it is stored as subcellular granules [17]. Stimulus induces norepinephrine release into the synaptic clefts where it exerts its effects (vasoconstriction and increase in blood pressure); the large part is inactivated by reuptake by storage granules, and the remainder escapes into systemic circulation. Because only 20% of norepinephrine appears in the circulation, plasma levels are merely a rough indicator of sympathetic tone [2]. Adrenergic and dopaminergic receptors are the main target sites through which neurotransmitters exert their vasomotor action (Table 6.1). Activation of the α-receptors leads to vasoconstriction, whereas activation of the β-receptors increases cardiac output. The precise physiological activity of the dopaminergic receptors in blood pressure regulation is not completely understood. Animal models deficient of $\alpha_1$-receptors are resistant to vasopressor stimuli [18]. Stimulation of $\alpha_1$-receptors may favor cardiovascular hypertrophy, while stimulation of $\alpha_2$-receptors leads to vasodilation. Both $\beta_1$- and $\beta_2$-receptors have an influence on the heart rate and cardiac output, and less on vascular resistance. All the subtypes of dopamine receptors play a role in cardiovascular and renal function and in particular on hormonal signaling, renal sodium, and blood flow [19]. A large body of evidences has also shown that blood pressure and blood volume regulation closely depends on the interactions between sympathetic nervous system, the renin-angiotensin system, and renal sodium excretion [20–22]. Electrical stimulation of renal sympathetic nerves increases renin release from juxtaglomerular cells, both through changes in renal blood flow and direct stimulation of β-adrenergic receptors, and exerts anti-natriuretic effects by a direct action on tubular renal sodium reabsorption.

### 6.2.1 Effect of Sympathetic Activation on Cardiovascular Regulation

Sympathetic activation leads to increased heart rate (through $\beta_1$-receptor activation) and peripheral vasoconstriction (through $\alpha_1$-receptor activation). Thus, sympathetic activity exerts a direct effect on the two major parameters determining blood pressure, namely, peripheral resistance and cardiac output. When discussing the effect of the sympathetic nervous system on blood pressure level, the counteracting effect of

**Table 6.1** Sites and effect of activation of adrenergic receptors

| Receptor | Sites | Effect of activation |
|---|---|---|
| $\alpha_{1,A,B,C}$ | Smooth muscle: blood vessel, iris, circular muscle of the ureter, uterus, bladder, rectal sphincter | Constriction |
| | Intestine | Relaxation |
| | Heart | Positive inotropic, trophic |
| | Salivary glands | Salivation |
| | Adipose tissue | Glycogenolysis |
| | Sweat glands | Sweating |
| | Proximal renal tubules | Sodium absorption, gluconeogenesis |
| $\alpha_{2,A,B,C}$ | Presynaptic nerve ending | Inhibition of noradrenaline release |
| | Platelets | Aggregation, degranulation |
| | Pancreas | Inhibition of insulin secretion |
| | Adipose tissue | Inhibition of lipolysis |
| | Blood vessel smooth muscle | Constriction |
| | Kidney | Inhibition of renin secretion |
| $\beta_1$ | Heart | Positive inotropic and chronotropic, trophic |
| | Adipose tissue | Lipolysis |
| | Kidney | Renin secretion |
| $\beta_2$ | Liver | Glycogenolysis, gluconeogenesis |
| | Skeletal muscle | Glycogenolysis, lactate release |
| | Smooth muscle: bronchi, uterus, intestine, skeletal muscle blood vessels, bladder detrusor | Relaxation |
| | Pancreas | Amylase secretion |
| | Salivary glands | Salivation |
| $\beta_3$ | Adipose tissue | Lipolysis |
| | Skeletal muscle | Thermogenesis |
| $I_1$ | Medulla | Blood pressure elevation |
| | Kidney | Tubular sodium absorption |
| $I_2$ | Monoamine oxidase | ? |
| $I_3$ | Pancreas | Insulin secretion |

the parasympathetic system should also be considered. The regulatory effect of the sympathetic system involves both the heart and the resistance vessels, while the parasympathetic system affects mainly the heart. Increased sympathetic tone in hypertension is associated with reduced parasympathetic tone. Physiologically, elevated blood pressure caused by increased sympathetic activity leads to baroreflex activation, in turn resulting in inhibition of the sympathetic activity and the return of blood pressure to baseline values. It appears now well established that baroreceptor contributes not only to short- but also long-term regulation of blood pressure levels [23, 24]. It is likely that the anteroventral region of the third ventricle plays an important role in the long-term regulation of blood pressure, sympathetic activity, and fluid/volume homeostasis. This region of the brain is sensitive to circulating hormones, blood pressure, and fluid/volume changes. These pathways are synchronized and routed to the paraventricular nucleus of the hypothalamus which is the transmitter of excitatory and inhibitory signals for long-term blood pressure control.

## 6.3 Increased Adrenergic Tone in the Development of the Hypertensive State

Increased adrenergic activity in patients with hypertension is supported by various lines of evidence, including measurements of heart rate and catecholamine levels, and data obtained using microneurographic approach. The simplest indicator of adrenergic activation is tachycardia [2, 25]. Tachycardia related to hyperkinetic circulation is often seen in subjects with borderline hypertension, particularly among young men, and is accompanied by increased plasma noradrenaline levels. Tachycardia and increased cardiac output are thought to be hemodynamic hallmarks of early hypertension; this condition is not usually associated with increased peripheral resistance.

The presence of hyperkinetic circulation is associated with disturbed autonomic balance as assessed by heart rate variability [26]. Decreased total heart rate variability, attenuation of the high-frequency spectral component dependent on parasympathetic activity, and an increased LF/HF ratio, suggesting sympathetic activation, have been found in patients with hypertension. Norepinephrine spillover from the neuroeffector junctions is increased in young subjects with borderline blood pressure elevation. This enhanced release takes place particularly in the kidney and in the heart, that is, two organs with a key role in blood pressure homeostatic control [27]. An increase in central sympathetic outflow in young borderline hypertensive subjects has been also obtained by microneurographic studies [28]. The complex borderline hypertension syndrome, however, is characterized by other abnormalities involving the hemodynamic state, the metabolic and hormonal profile, as well as the hemorheological condition. Several of these abnormalities are triggered and reinforced by autonomic alterations. This appears to be particularly the case for metabolic disarray, which is frequently detected in the early hypertensive phases and includes hyperinsulinemia, insulin resistance, dyslipidemia, and hypercholesterolemia. Most of these alterations, with visceral obesity, represent the main features of the metabolic syndrome and are characterized by a hyperadrenergic tone [29, 30].

### 6.3.1 Increased Adrenergic Tone in the Progression of Hypertensive State

Several evidences have clearly shown that in man although parasympathetic dysfunction remains stable in the hypertensive state, the sympathetic activation undergoes a progressive potentiation [1, 2]. Microneurographic approach performed in subjects with normal blood flow, with moderate essential hypertension, and with essential hypertension of a more severe degree, has clearly shown (Fig. 6.1) a paralleled progressive increase in blood pressure values and sympathetic nerve traffic in these three conditions, suggesting a key role of adrenergic neural factors not only in the development but also in the progression of the hypertensive state [31].

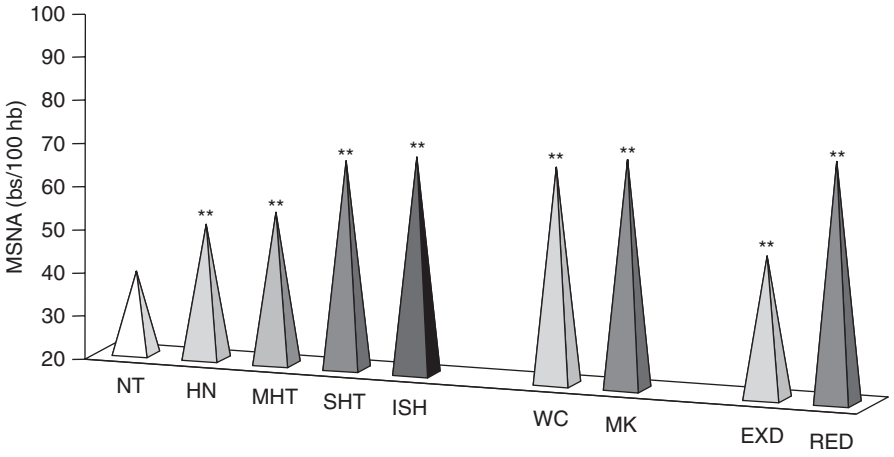



**Fig. 6.1** Mean values of muscle sympathetic nerve traffic (MSNA) expressed as burst incidence corrected for heart rate values (bursts/100 heartbeats), in normotensive subjects (NT, BP 120–129/80–84 mmHg) and in patients with high-normal blood pressure (HN, BP 130–139/85–89 mmHg), moderate (M, BP 140–145/90–95 mmHg) and severe (S, BP >145/>95 mmHg) hypertension (HT), and isolated systolic hypertension (ISH, BP >160/<90 mmHg), white-coat (WC, elevated office BP/normal 24-h BP) and masked (MK, normal office BP/elevated 24-h BP) hypertension, extreme dippers (EXD, nighttime BP reduction >20%), and reverse (RED, nighttime BP increased) dippers. Asterisk (**$p$ <0.01) refers to the level of statistical significance vs NT. Figure based on data from [31, 32, 36, 39, 40]

A few other issues related to the autonomic alterations characterizing essential hypertension deserve to be mentioned. First, the sympathetic overactivity is not only a feature of the established condition. The prehypertensive state, that is, the category of patients characterized by blood pressure values ranging from 135 to 140 mmHg for systolic and 85–90 mmHg for diastolic and with a high risk of developing a "true" hypertensive state [32], shows sympathetic nerve traffic values greater for magnitude than the ones detected in the true normotensive state (Fig. 6.1), and this is independent on the presence of a family history of hypertension [33, 34]. In these subjects the sympathetic activation does not seem to be confined to peripheral circulation, but it rather occurs also at cardiac level as suggested by the increase in low-frequency component of heart rate variability [35]. The presence of an early sympathetic activation may concur together with other factors to the development of the target organ damage and may also represent a mechanism which participates at the progression of the high-normal blood pressure to the established hypertensive state.

Second, the sympathetic overactivity is not only a feature of young and middle-age hypertensives, but it also occurs in elderly hypertensives, even when the blood pressure elevation selectively affects systolic values (Fig. 6.1) [36]. Third, the hypertension-related increase in adrenergic outflow appears to be specific for some cardiovascular districts, such as the heart, the kidneys, and the skeletal muscle vasculature, and peculiar to the hypertensive state of essential nature [27, 31, 37].

Fourth, independently from the measurement (in- or out-of-office), sympathetic activity is increased both in "white-coat" hypertension (elevated clinic but normal ambulatory blood pressure) and in "masked" hypertension (normal clinic but elevated ambulatory blood pressure) (Fig. 6.1) [38, 39]. An important observation comes from the 24-h blood pressure recording and in particular from the day/night blood pressure difference. Hypertensive patients with the so-called reverse dipping pattern profile (i.e., those patients in whom blood pressure values do not undergo any reduction during nighttime but rather show a tendency to increase) are characterized by a more pronounced sympathetic activation than that seen in dipper hypertensives (Fig. 6.1) [40].

The increase in sympathetic cardiovascular influences is involved not only in favoring the progression of blood pressure elevation but also in promoting hypertension-related target organ damage [1, 2]. A marked increase in sympathetic nerve traffic and in cardiac norepinephrine spillover has been observed in left ventricular hypertrophy, in left ventricular dysfunction, and in congestive heart failure [41–43]. This is also the case for the hypertension-related deterioration in renal function that may promote the occurrence of an overt renal insufficiency [44]. In this case sympathetic activity appears to be involved in the pathogenesis of the disease, given the evidence that adrenergic activation is detectable in the initial stages of the renal dysfunction [45].

## 6.4 Mechanisms Leading to Sympathetic Activation and New Hypothesis

What triggers sympathetic neural activation in causing the blood pressure elevation is not fully understood. Mechanisms such as psychological stress, exaggerated renin-angiotensin system activity, baroreceptor and chemoreceptor dysfunction, and brainstem activation have been proposed as possible causes, but none is clearly demonstrated in human hypertension [1, 2]. As far as reflex mechanisms are concerned, there is evidence that arterial baroreceptors reflexes, cardiopulmonary reflexes, and chemoreceptor reflexes are impaired in human hypertension [2]. In hypertension, however, baroreceptor impairment has been documented for the parasympathetic but not for the sympathetic component of the reflex, unless congestive heart failure or left ventricular dysfunction is concomitantly detected [2, 43]. Indeed, although the arterial baroreceptor regulation of heart rate has been shown to be reset and blunted, the modulation of both blood pressure and sympathetic nerve traffic exerted by this reflexogenic area does not appear to undergo any impairment, both in mild and severe hypertension [31]. However, reflex influences from other reflexogenic areas appear to be altered in hypertension. This is the case for the cardiopulmonary reflex, whose control of vascular resistance and renin release from the kidney is markedly reduced, especially in hypertensive subjects with left ventricular hypertrophy [2]. This is also the case for the arterial chemoreflex, whose reflex restraint on adrenergic drive is blunted in hypertension, particularly when obesity, metabolic syndrome, or sleep apnea is concomitantly present [2]. Other hypotheses

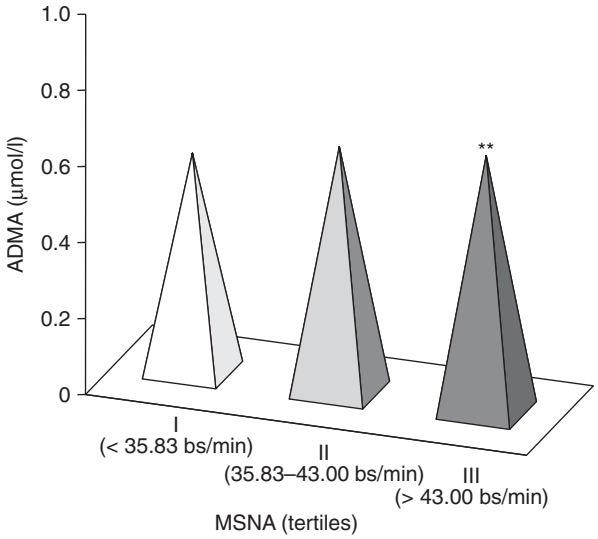



**Fig. 6.2** Values of asymmetric dimethylarginine (ADMA) in hypertensive patients with renal failure subdivided in three groups according to muscle sympathetic nerve traffic (MSNA) tertile values. Data are shown as means ± standard errors. Figure based on data from [47]

to explain the autonomic dysfunction in hypertension are as follows: (a) the metabolic hypothesis takes into account the role of hyperinsulinemia and the related insulin resistance frequently accompanying the hypertensive state [2]; (b) the activation of humoral systems (such as nitric oxide, endothelins, vasopressin, leptin-melanocortin system, atrial natriuretic peptides, brain natriuretic factors, and renin-angiotensin system) may adversely interfere with the autonomic control [2].

Two emerging factors that need to be mentioned for the relation with and the influence on the adrenergic tone are represented by "old" classic cardiovascular risk factors with renewed interest. The first one is the asymmetric dimethylarginine, a marker of vascular dysfunction which in patients with chronic kidney disease has been shown to be a strong predictor of fatal and nonfatal cardiovascular events and cardiac organ damage [46, 47]. In these patients, dimethylarginine values showed an increase that was paralleled to the degree of the sympathetic activation (Fig. 6.2). The second "classic" risk marker which gained new interest in cardiovascular prognosis is uric acid, whose increased blood circulating levels have been associated with a greater incidence of hypertension, kidney disease, as well as vascular and cardiac events [48]. This marker has shown a link with adrenergic neural drive. In this case, however, the relationship appears to be significant only in patients with chronic kidney disease and not in healthy subjects or in hypertensive patients due to the close dependence of uric acid on the deranged renal function which "per se" is associated with an augmented sympathetic drive [45].

Future researches will be focalized on mechanisms of sympathetic function and in particular on the influence of genetic-neurobiology pathway of essential hypertension on the sympathetic neural drive. In selected populations, for example, an

overexpression of adrenergic alpha-1A-receptor gene [49] or $\beta_2$-adrenoreceptor polymorphism [50] has been shown to be related with adrenergic overactivity, and this is also the case for genetic hemochromatosis indicating the role of iron overload in sustaining the adrenergic overdrive of this condition [51]. The second area that will need to be developed concerns the relation between the sympathetic nervous system and the autoimmune and inflammatory systems [52].

## References


1. Esler MD (2011) The sympathetic nervous system through the ages: from Thomas Willis to resistant hypertension. Exp Physiol 96:611–622
2. Grassi G, Mark A, Esler M (2015) The sympathetic nervous system alterations in human hypertension. Circ Res 116:976–990
3. Hjemdahl P (1993) Plasma catecholamines: analytical challenges and physiological limitations. Clin Endocrinol Metab 7:307–353
4. Esler M, Jennings G, Korner P et al (1988) The assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. Hypertension 11:3–20
5. Schlaich MP, Lambert E, Kaye DM et al (2004) Sympathetic augmentation in hypertension: role of nerve firing, norepinephrine reuptake, and angiotensin neuromodulation. Hypertension 43:169–175
6. Bertinieri G, di Rienzo M, Cavallazzi A et al (1985) A new approach to analysis of the arterial baroreflex. J Hypertens 3:S79–S81
7. Mancia G, Grassi G (1995) Baroreceptor control of the circulation in man. An update. Clin Exp Hypertens 17:387–397
8. Halliwill JR (2000) Segregated signal averaging of sympathetic baroreflex responses in humans. J Appl Physiol 88:767–773
9. Charkoudian N, Martin EA, Dinenno FA et al (2004) Influence of increased central venous pressure on baroreflex control of sympathetic activity in humans. Am J Physiol Heart Circ Physiol 287:H1658–H166210
10. Pagani M, Lombardi F, Guzzetti S et al (1986) Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 59:178–193
11. Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology (1996) Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Eur Heart J 17:354–381
12. Grassi G, Esler MD (1999) How to assess sympathetic activity in humans. J Hypertens 17:719–734
13. Delius W, Hagbarth KE, Hogell A, Wallin BG (1972) General characteristics of sympathetic activity in human muscle nerves. Acta Physiol Scand 84:65–81
14. Grassi G, Bolla G, Seravalle G et al (1997) Comparison between reproducibility and sensitivity of muscle sympathetic nerve traffic and plasma noradrenaline in man. Clin Sci 92:285–289
15. Eckberg DL, Wallin BG, Fagius J et al (1989) Prospective study of symptoms after human microneurography. Acta Physiol Scand 137:567–569
16. Grassi G, Seravalle G, Dell'Oro R et al (2001) Participation of the hypothalamus-hypophysis axis in the sympathetic activation of human obesity. Hypertension 38:1316–1320
17. Guyenet PG (2006) The sympathetic control of blood pressure. Nat Rev Neurosci 7:335–346
18. Lohmeier TE, Dwyer TM, Irwin ED et al (2007) Prolonged activation of baroreflex abolishes obesity-induced hypertension. Hypertension 49:1307–1314
19. Jose PA, Eisner GM, Felder RA (2002) Role of dopamine receptors in the kidney in the regulation of blood pressure. Curr Opin Nephrol Hypertens 11:87–92
20. Kopp UC, DiBona GF (1993) Neural regulation of renin secretion. Semin Nephrol 13:543–551

21. Johns EJ, Kopp UC, DiBona GF (2011) Neural control of renal function. Compr Physiol 1:731–767
22. Iliescu R, Irwin ED, Georgakopoulos D, Lohmeier TE (2012) Renal responses to chronic suppression of central sympathetic outflow. Hypertension 60:749–756
23. Dampney RA, Coleman MJ, Fontes MA et al (2002) Central mechanisms underlying short- and long-term regulation of the cardiovascular system. Clin Exp Pharmacol Physiol 29:261–268
24. Lohmeier TE, Iliescu R (2015) The baroreflex as a long-term controller of arterial pressure. Physiology 30:148–158
25. Palatini P, Julius S (1997) Heart rate and cardiovascular risk. J Hypertens 15:3–17
26. Guzzetti S, Cogliati C, Turiel M et al (1988) Sympathetic predominance in essential hypertension: a study employing spectral analysis of heart rate variability. J Hypertens 6:711–717
27. Esler M, Lambert G, Jennings G (1989) Regional norepinephrine turnover in human hypertension. Clin Exp Hypertens 11:75–89
28. Anderson EA, Sinkey CA, Lawton WJ, Mark AL (1989) Elevated sympathetic nerve activity in borderline hypertensive humans. Evidence from direct intraneural recordings. Hypertension 14:177–183
29. Huggett RJ, Burns J, Mackintosh AF, Mary D (2004) Sympathetic neural activation in non diabetic metabolic syndrome and its further augmentation by hypertension. Hypertension 44:847–852
30. Grassi G, Dell'Oro R, Quarti-Trevano F et al (2005) Neuroadrenergic and reflex abnormalities in patients with metabolic syndrome. Diabetologia 48:1359–1365
31. Grassi G, Cattaneo BM, Seravalle G et al (1998) Baroreflex control of sympathetic nerve activity in essential and secondary hypertension. Hypertension 31:68–72
32. Egan BM, Stevens-Fabry S (2015) Prehypertension-prevalence, health risks and management strategies. Nat Rev Cardiol 12:289–300
33. Hering D, Kara T, Kucharska W et al (2013) High-normal blood pressure is associated with increased resting sympathetic activity but normal responses to stress tests. Blood Press 22:183–187
34. Seravalle G, Lonati L, Buzzi S et al (2015) Sympathetic nerve traffic and baroreflex function in optimal, normal and high-normal blood pressure states. J Hypertens 33:1411–1417
35. Pal GK, Adithan C, Dutta TK et al (2011) Assessment of sympathovagal imbalance by spectral analysis of heart rate variability in prehypertensive and hypertensive patients in Indian population. Clin Exp Hypertens 33:478–483
36. Grassi G, Seravalle G, Bertinieri G et al (2000) Sympathetic and reflex alterations in systodiastolic and systolic hypertension of the elderly. J Hypertens 18:587–593
37. DiBona GF (2013) Sympathetic nervous system and hypertension. Hypertension 61:556–560
38. Smith PA, Graham LN, Mackintosh AF et al (2002) Sympathetic neural mechanisms in white-coat hypertension. J Am Coll Cardiol 40:126–132
39. Grassi G, Seravalle G, Trevano FQ et al (2007) Neurogenic abnormalities in masked hypertension. Hypertension 50:537–542
40. Grassi G, Seravalle G, Quarti-Trevano F et al (2008) Adrenergic metabolic and reflex abnormalities in reverse and extreme dipper hypertensives. Hypertension 52:925–931
41. Greenwood JP, Scott EM, Stoker JB, Mary DA (2001) Hypertensive left ventricular hypertrophy: relation to peripheral sympathetic drive. J Am Coll Cardiol 38:1711–1717
42. Schlaich MP, Kaye DM, Lambert E et al (2003) Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. Circulation 108:560–565
43. Grassi G, Seravalle G, Quarti-Trevano F et al (2009) Sympathetic and baroreflex cardiovascular control in hypertension-related left ventricular dysfunction. Hypertension 53:205–209
44. Converse RL, Jacobsen TN, Toto RD et al (1992) Sympathetic overactivity in patients with chronic renal failure. N Engl J Med 327:1912–1918
45. Grassi G, Quarti-Trevano F, Seravalle G et al (2011) Early sympathetic activation in the initial clinical stages of chronic renal failure. Hypertension 57:846–851
46. Kielstein JT, Fliser D (2007) The past, present and future of ADMA in nephrology. Nephrol Ther 3:47–54

47. Grassi G, Seravalle G, Ghiadoni L et al (2011) Sympathetic nerve traffic and asymmetric dimethylarginine in chronic kidney disease. Clin J Am Soc Nephrol 6:2620–2627
48. Mancia G, Grassi G, Borghi C (2015) Hyperuricemia, urate deposition and the association with hypertension. Curr Med Res Opin 31(suppl 2):15–19
49. Grassi G, Padmanabhan S, Menni C et al (2011) Association between ADRA1A gene and the metabolic syndrome: candidate genes and functional counterpart in the PAMELA population. J Hypertens 29:1121–1127
50. Masuo K, Katsuya T, Fu Y et al (2005) Beta-2-adreneoreceptor polymorphisms relate to insulin resistance and sympathetic overactivity as early markers of metabolic disease in non-obese normotensive individuals. Am J Hypertens 18:1009–1014
51. Seravalle G, Piperno A, Mariani R et al (2016) Alterations in sympathetic nerve traffic in genetic hemochromatosis before and after iron depletion therapy: a microneurographic study. Eur Heart J 37:988–995
52. Pongratz G, Straub RH (2014) The sympathetic nervous response in inflammation. Arthritis Res Ther 16:504–526

# Hormonal Systems

# 7

Sébastien Foulquier, Ludovit Paulis, Elena Kaschina, Pawel Namsolleck, and Thomas Unger

## 7.1 Introduction

Hormonal systems are largely involved in blood pressure regulation and water and salt homeostasis. Importantly, they are also involved in development and progression of cardiovascular and renal diseases. Here, we discuss recent findings about the impact of renin-angiotensin, aldosterone, vasopressin, and natriuretic peptide systems on blood pressure regulation and development of hypertension.

## 7.2 The Renin-Angiotensin System

The renin-angiotensin system (RAS) is not only an important regulator of blood pressure and body fluid in short term but is also involved in the pathology of hypertension and high blood pressure-associated organ alterations. For this reason, it is one of the therapeutically most exploited neurohumoral systems [1]. Recently, novel RAS peptides and receptors were identified that extend our view of the RAS, provide a rationale for some previously unanswered questions, and suggest exciting putative therapeutic implications for the future.

S. Foulquier • P. Namsolleck • T. Unger (✉)
CARIM, Maastricht University, Maastricht, The Netherlands
e-mail: t.unger@maastrichtuniversity.nl

L. Paulis • E. Kaschina
Center for Cardiovascular Research (CCR), Charité - Universitätsmedizin Berlin, Berlin, Germany



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_7

### 7.2.1 From Renin to Angiotensin II

RAS activation starts with the release of renin from renal juxtaglomerular cells. These are innervated by sympathetic nerve fibers, localized closely to the afferent arteriole as well as to the cells of *macula densa* in the distal convoluted tubule. The release of renin is stimulated by several factors including β-sympathetic stimulation, reduced $Na^+$ load in the distal tubule, or reduced renal perfusion [2]. Renin is a glycoprotein that is synthetized in the form of prorenin and converted to its active form by the renal neuroendocrine convertase 1 or cathepsin B. However, prorenin is also constitutively being released from the kidneys at high concentration and might bind to the (pro)renin receptor (P)RR in the tissues [3]. The (P)RR enhances the activity of renin and unmasks the activity of prorenin. Independently on renin enzymatic activity, the (P)RR activates promyelocytic zinc finger (PLZF) [4], protein-phosphatidylinositol 3-kinase (PI3-K), and eventually mitogen-activated protein kinases (MAPKs) followed by anti-apoptosis, proliferation, and enhanced protein synthesis [5, 6]. However, the role of the (P)RR in the pathophysiology of cardiovascular diseases is still controversial [5, 7] as is the role of the renin-angiotensin systems described in a variety of tissues.

The enzymatic activity of renin converts the protein angiotensinogen [8] to the decapeptide angiotensin I (Ang I). This conversion represents the rate-limiting step in RAS activation. The substrate for the reaction, angiotensinogen, is expressed in abundance mainly by the liver and provides the source for most of the plasmatic Ang I. The rate of Ang I generation in the plasma is denominated plasma renin activity (PRA) and serves as an important diagnostic indicator. Some angiotensinogen is expressed also in tissues (including the kidneys) locally and serves as a substrate for the local paracrine Ang I formation.

The circulating and locally expressed carboxypeptidase angiotensin-converting enzyme (ACE) then converts Ang I to angiotensin II (Ang II) by cleaving the two C-terminal amino acids from Ang I [9]. ACE is a hydrolytic enzymatic glycoprotein with two active zinc-binding domains. Most of the ACE is membrane bound to endothelial cells (in particular in the lungs), but there is a soluble circulating ACE form as well. ACE also partly inactivates the NO-dependent vasodilator bradykinin [10]. Besides ACE, Ang I may also be converted to Ang II (in particular in conditions of inhibited ACE) by chymase, carboxypeptidase, cathepsin G, or tonin.

### 7.2.2 Classical Renin-Angiotensin System

In the initial classical RAS concept [11], Ang II was responsible for most of the RAS effects via its angiotensin AT1 receptor ($AT_1R$). The $AT_1R$ is abundantly expressed including vascular smooth muscle cells, renal tubular cells, mesangial cells, juxtaglomerular cells, cardiomyocytes, fibroblasts, suprarenal cortex, or central nervous system. The $AT_1R$ action is modulated by adaptors such as AT1 receptor-associated protein (ATRAP), $AT_1$ receptor-associated protein 1 (ARAP1), or the AT1R- and AT2R-interacting protein (ATIP) [12]. The $AT_1R$ is a seven-transmembrane domain $G_{q/i}$-coupled receptor. Its stimulation results in phospholipase C activation and adenylyl cyclase inhibition (see review for detailed signal transduction [13]). This translates

to the physiologic action of Ang II, of which arterial vasoconstriction was the first described [14]. Via renal vasoconstriction, $AT_1R$ stimulation leads to reduced renal blood flow and medullary blood flow with subsequent efferent arteriole constriction resulting in increased filtration pressure. On the other hand, $AT_1R$ activation on mesangial cells leads to their constriction and reduction of glomerular filtration area. In addition, the $AT_1R$ directly activates sodium reabsorption transporters in the proximal tubule [15–17]. As a result, the short-term effect of $AT_1R$ stimulation is blood pressure increase due to vasoconstriction, which is stabilized in midterm due to sodium retention and a shift of the diuresis-blood pressure curve to higher blood pressure values. In the central nervous system, the $AT_1R$ activates the hypothalamic thirst center and vasopressin release leading to further volume expansion and blood pressure rise. At the same time, however, the $AT_1R$ mediates a direct negative short feedback loop by inhibiting renin release from the juxtaglomerular cells [18], while the blood pressure-driven diuresis and sodium excretion generate a further long feedback loop on renin release.

In addition to the acute effects of $AT_1R$ activation, the stimulation of this receptor in long term produces further effects with important physiological implications. $AT_1R$ promotes inflammation, cardiomyocyte hypertrophy, proliferation of fibroblasts, and the synthesis of extracellular matrix [19]. While at first, these effects provide a mean to adapt to the increased hemodynamic load, they ultimately result in left ventricular hypertrophy and fibrosis, arteriosclerosis, atherosclerosis, and renal glomerulosclerosis [19]. The direct $AT_1R$-mediated effects are complemented by those of aldosterone (see "Aldosterone" paragraph).

### 7.2.3 Clinical Implications

Several clinical situations feature an increased RAS activity, most notably renovascular hypertension. Unilateral renal artery stenosis (due to atherosclerosis, fibromuscular dysplasia, or a congenital defect) leads to renin release and Ang II-dependent hypertension. Experimentally, such situation is mimicked by the two-kidney-one-clip (2K1C) hypertension model [20]. While the clipped kidney produces excessive amounts of renin, the other kidney allows for volume normalization. Clinically, renovascular hypertension can be diagnosed by the use of the ACE inhibitory test displaying a plasma renin activity increase after ACEI administration.

The therapeutic importance of the classical RAS concept is documented by the established use of RAS-blocking therapies such as ACE inhibitors (ACEIs), $AT_1R$ blockers (ARBs), and direct renin inhibitors (DRIs) but also mineralocorticoid receptor antagonists (MRAs) and β-blockers (BBs). First, large clinical trials in hypertension (CAPP, STOP-2) or high-risk patients (HOPE) have demonstrated that ACEIs were at least non-inferior or even superior compared to conventional standard therapy [21–23]. Then, the ARBs were shown to be non-inferior or superior to β-blockers [24], calcium antagonists [25], or ACE inhibitors [26] with regard to cardiovascular morbidity and mortality reduction in hypertension or high-risk patients. While both ACEIs and ARBs reduced the onset of new diabetes mellitus [27], the ARBs are better tolerated than ACEIs in terms of dry cough [26]. Finally, in 2007 the first-in-class DRI, aliskiren, was introduced. In head-to-head

comparison aliskiren was non-inferior in blood pressure reduction when compared to ARBs [28], ACEIs [29], hydrochlorothiazide [30], and atenolol [31]. However, clinical trials have also shown that a simultaneous dual RAS blockade should be avoided. In the ALTITUDE trial in patients with type 2 diabetes and renal impairment, aliskiren added on top of conventional antihypertensive treatment (including ACEI or ARB) increased the incidence of almost all primary end point components (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, resuscitated sudden death, doubling of serum creatinine, end-stage renal disease/renal death) [32]. In the ONTARGET trial, the ACEI + ARB combination did not provide any benefit compared to either monotherapy [26]. In the recent decade, our extended view of the RAS improved our understanding of a (dual) RAS modulation and suggested new possible therapeutic targets as well.

### 7.2.4 The Recent Fingerprint of RAS Peptides

The RAS should be viewed more as a complex net of peptides rather than a simple cascade [33]. The spectrum of angiotensin peptides is much broader than just Ang I and Ang II. The angiotensins are denominated according to their amino acid composition expressed as the ordinal number of the first and last amino acid with reference to its position in the decapeptide Ang I (i.e., 1–10) numbered from the amino-terminus to the carboxy-terminus. The concentrations of the angiotensin peptides are determined by the activity of the interlinking proteases and form a complex net in a dynamic equilibrium (Fig. 7.1). The angiotensin peptides exercise their physiological activity not only via the $AT_1R$ but also via $AT_2R$, $AT_3R$, $AT_4R$, or Mas receptor (Table 7.1) and at both systemic and tissular levels [34].

### 7.2.5 The Novel "Protective" Arm of RAS

The action of several of the angiotensin peptides and receptors included in the extended view of the RAS demonstrates properties and actions at least partly opposing the classical RAS concept. Thus, they are considered to be the "protective" arm of RAS [35]. It was hypothesized that the protective/deleterious RAS affects the physiological outcome in addition to the concentration of the Ang II alone [36]. Some of these angiotensin peptides and related enzymes are of particular interest.

Under basal conditions, the $AT_2R$ is much less expressed compared to the $AT_1R$. However, in several cardiovascular pathologies, such as hypertension or left ventricular hypertrophy, the $AT_2R$ expression is increased [19]. Similar to the $AT_1R$, the $AT_2R$ is a seven-transmembrane domain G-coupled receptor, but its intracellular signaling pathways appear uncanonical. The $AT_2$-associated pathways include NO/cGMP activation [37], inhibition of mitogen-activated protein kinases (MAPKs) by protein phosphatases [38], phospholipase A2 stimulation [39], or disruption of $AT_1R$ signaling by $AT_1R$-$AT_2R$ heterodimerization [40]. Similar to the $AT_1R$, the effects of $AT_2R$ stimulation are modulated by adaptor proteins such as the

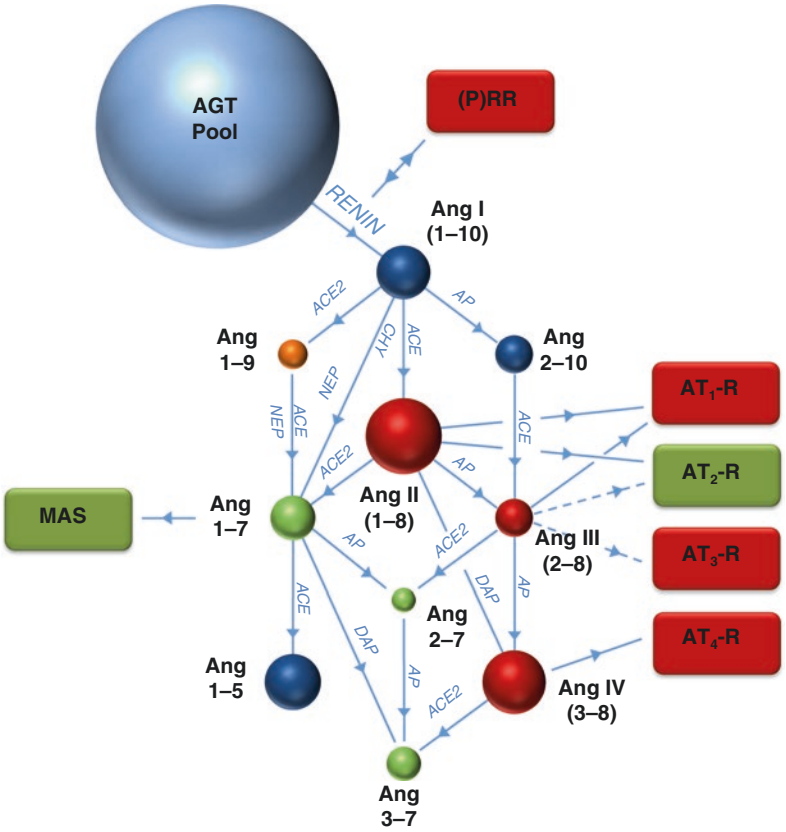



**Fig. 7.1** The RAS-Fingerprint. Angiotensinogen (AGT) and angiotensin peptides (identified by first-last amino acid in brackets) interlinked by the respective peptidases: *ACE* angiotensin-converting enzyme, *ACE2* angiotensin-converting enzyme 2, *NEP* neprilysin (neutral endopeptidase), *AP* aminopeptidases, *DAP* dipeptidyl aminopeptidase. The peptides are linked to several receptors, such as the angiotensin AT1 receptor ($AT_1R$), AT2 receptor ($AT_2R$), AT3 receptor ($AT_3R$), and AT4 receptor ($AT_4R$, equivalent to IRAP, insulin-regulated aminopeptidase), the Mas receptor, and the (pro)renin receptor ((P)RR). The RAS is distinctly modulated by different established therapies (*RI* renin inhibitor, *ACEI* ACE inhibitor, *ARB* angiotensin receptor blocker) (modified with permission from Attaquant Ltd.)

$AT_1R$- and $AT_2R$-interacting protein (ATIP = ATBP) or $AT_2R$-binding protein of 50 kDa [12, 41]. The functional effects associated with $AT_2R$ stimulation include antiproliferation, anti-inflammation, vasodilation, and axonal regeneration [42–46]. Using the selective $AT_2R$ agonist, compound 21 [47], it was demonstrated that the $AT_2R$ stimulation improved systolic and diastolic function in rats after myocardial infarction [48, 49], reduced vascular fibrosis in two models of experimental hypertension [50, 51], protected against nephropathy in doxorubicin-treated rats [52] and in 2K1C hypertension [53], and improved cognitive/neurological outcome in diabetic mice [54], spinal cord injury [55], or autoimmune encephalitis [56].

**Table 7.1** Effects of RAS receptor modulation

| | |
|---|---|
| AT1R activation | Vasoconstriction<br>Sodium reabsorption, sodium and water retention<br>Thirst triggering and oxytocin release<br>Adrenocorticotropin, prolactin, oxytocin release<br>Increased sympathetic nerve activity<br>Blood pressure increase<br>Fibrosis, Apoptosis<br>Inflammation<br>Proliferation (e.g., vascular smooth muscle cells, fibroblasts)<br>Extracellular matrix synthesis and fibrosis<br>Cardiomyocyte hypertrophy<br>Aldosterone secretion |
| AT2R activation | Anti-inflammatory effects<br>Antifibrotic effects<br>Antiproliferative effects<br>Apoptosis<br>Neuroprotection and neuroregeneration<br>NO release<br>Vasodilation, Nephroprotection |
| AT4R (IRAP) inhibition | Anti-inflammatory effects<br>Antifibrotic effects<br>NO release<br>Memory and learning improvements |
| Mas activation | Anti-inflammatory effects<br>Antifibrotic effects<br>Antiproliferative effect on vascular smooth muscle cells<br>Increased baroreflex sensitivity<br>NO release |

Modified from Romero et al. [113]

In contrast to the $AT_1R$ and $AT_2R$, much less is known about the $AT_3R$ and $AT_4R$ [57]. $AT_4R$ (also the insulin-regulated aminopeptidase, IRAP) is widely expressed in several tissues including the myocardium, and its expression is upregulated in pathological situations [58]. The major natural ligand for this receptor is the Ang IV (3–8) which has some low affinity for the $AT_1R$ and $AT_2R$ as well [59]. By binding to the $AT_4R$, Ang IV (3–8) inhibits its aminopeptidase activity with putative anti-inflammatory and antiproliferative activity. Up to date, it was shown that Ang IV (3–8) via the $AT_4R$ enhances atrial natriuretic peptide A levels [60] and protects against myocardial ischemia-reperfusion injury by activating PI3K-Akt-mTOR pathway and inhibiting apoptosis [61].

For the Mas receptor, the natural ligand is the Ang (1–7). The mas receptor is a seven-transmembrane domain unconventional G-protein-coupled receptor sharing a 31% sequence identity with the $AT_2R$ [62]. The intracellular pathways and functional effects triggered by Mas- and $AT_2R$ stimulation are strikingly similar. They include phosphatase stimulation and antiproliferative and anti-inflammatory effects [63]. The blockade of either $AT_2R$ or Mas receptor seems to block the effects of the other receptor, probably due to their heterodimerization [63]. The non-peptide Mas agonist, AVE-0991, decreased mean arterial pressure in

DOCA-salt-induced hypertension in rats and protected against renal injury [64–66]. With regard to the effects of the Mas receptor, the pathways responsible for Ang (1–7) formation gain interest. Ang (1–7) might be formed from Ang II (1–8) via the activity of angiotensin-converting enzyme 2 (ACE2). ACE2 is a carboxypeptidase cleaving the last C-terminal amino acid. Alternatively, Ang (1–7) may be produced from Ang I (1–10) by the sequential activity of ACE2 and ACE with the Ang (1–9) as an intermediate or directly by the activity of the neutral endopeptidase (NEP, neprilysin). Indeed, the ACE2 levels in stroke prone spontaneously hypertensive are reduced [67], and recombinant human ACE2 prevented cardiac remodeling in Ang II-treated ACE2 knockout mice [68]. On the other hand, in healthy volunteers, recombinant ACE2 did not produce a significant effect in blood pressure despite reducing Ang II (1–8) and increasing Ang (1–7) and Ang (1–5) levels [69]. NEP inhibition was investigated as a possible antihypertensive therapeutic target because it cleaves some vasoactive factors such as endothelin, natriuretic peptides, and kinins [70]. Due to its effect on Ang I (1–10) cleavage and Ang (1–7) production, NEP inhibition needs to be combined with RAS blockade. The trials OCTAVE and OVERTURE showed that combined ACE/NEP inhibition was effective in hypertension and heart failure, but was also associated with more frequent angioedema [71, 72]. When NEP inhibition was combined with an ARB in the LCZ696 molecule, it reduced sitting systolic and diastolic blood pressure more than the corresponding ARB doses without any angioedema in this study [73]. In patients with heart failure and preserved ejection fraction, LCZ696 effectively reduced N-terminal pro b-type natriuretic peptide levels and preserved glomerular filtration rate [74, 75]. In heart failure with reduced ejection fraction, LCZ696 reduced the primary end point by 20%, all-cause mortality by 16%, and cardiovascular mortality by 20% compared to ACEI causing the premature halt of the PARADIGM-HF trial [76].

## 7.3 Aldosterone

In 1952 *Sylvia and James Tait* isolated a steroid hormone from adrenal cortex and named it electrocortin.[1] Two years later, in collaboration with *Tadeusz Reichstein*, they elucidated the entire chemical structure as 11β-21-dihydroxy-18-oxo-pregn-4-ene-3,20-dione and renamed it aldosterone.[1] This most potent sodium-retaining factor in mammals was termed a mineralocorticoid and has become a focus of hypertension research.

In 1958, *Franz Gross* suggested that the kidney releases an aldosterone-stimulating factor responsible for aldosterone secretion [77]. By that, he was the first to discover the cross talk between kidney and adrenal gland. Based on the finding that the inverse relationship between sodium balance and the secretion of aldosterone is reflected in the content of renin in the kidney, Franz Gross proposed that the renin-angiotensin system might play a part in the regulation of the adrenal function [77]. Later on, several groups of investigators could confirm that Ang II stimulates aldosterone secretion.[1] The other major stimulus for aldosterone

secretion, potassium, was described by *Giroud* and colleagues in 1956 [78]. Since then, aldosterone has been established as the primary mineralocorticoid that plays a central role in the regulation of blood pressure, blood volume, and salt household.

### 7.3.1 Aldosterone Synthesis

Aldosterone binds to mineralocorticoid receptors (MR) in the kidney, colon, and sweat glands and induces sodium (and water) reabsorption and potassium excretion [79]. Aldosterone is synthesized from cholesterol in the *zona glomerulosa* of the adrenal cortex by a series of enzymatic reactions. Its production is regulated by the *CYP11B2* gene which encodes aldosterone synthase (*ALDOS*, cytochrome *P450 11B2*) (Fig. 7.2). This enzyme, located in the mitochondria, catalyzes the final three rate-limiting steps of aldosterone synthesis from deoxycorticosterone. The glucocorticoid, cortisol, has a higher affinity to MR than aldosterone, but in kidneys and other target tissues for aldosterone, the enzyme 11-beta-hydroxysteroid dehydrogenase (11-beta-HSD2) metabolizes cortisol to cortisone which does not bind to the MR. In the case of deficiency of this enzyme, cortisol acts as a mineralocorticoid.

The main regulators of aldosterone synthesis and secretion are Ang II [80], the concentration of extracellular potassium, and adrenocorticotropic hormone (ACTH) [81] (Fig. 7.2). Aldosterone release is controlled by the juxtaglomerular apparatus, which is sensitive to the composition of the fluid in the distal tube. A decrease in sodium chloride concentration of the filtrate is sensed by *macula densa* cells which stimulate the release of renin. This leads to the formation of Ang II and stimulation of the aldosterone synthesis via the activation of the AT1R which, in turn, upregulates the *CYP11 B2* gene encoding *ALDOS* in the *zona glomerulosa* of the adrenal cortex. The stimulant effect of Ang II on aldosterone synthesis and release is enhanced under conditions of hyponatremia or hyperkaliemia. In part of hypertensive individuals, the sensitivity of the adrenal gland to Ang II and, subsequently, aldosterone production is modulated by dietary salt intake and sympathetic activation [82]. Moreover, chronic stimulation by Ang II induces *zona glomerulosa* hypertrophy and hyperplasia, increased *CYP11B2* expression, and, hence, aldosterone secretion [83].

Low plasma sodium or high plasma potassium concentrations affect the *zona glomerulosa* cells of the adrenal directly, stimulating aldosterone release. Increased extracellular potassium causes *zona glomerulosa* cell membrane depolarization, leading to the opening of voltage-dependent L- and T-type calcium channels, rise in calcium, and activation of calmodulin and CaM kinases which phosphorylate transcription factors to stimulate *CYP11B2* gene transcription [84]. Secretory products from adipocytes have also been suggested to upregulate *ALDOS* expression and stimulate the synthesis of aldosterone [85].

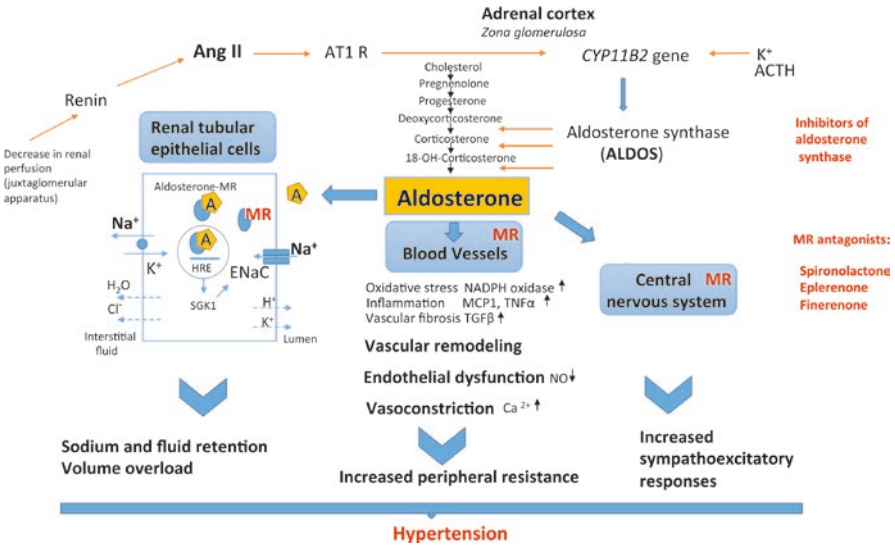



**Fig. 7.2** Mechanisms of aldosterone-mediated arterial hypertension. Renal sodium and water retention, increased peripheral resistance, and stimulation of the sympathetic nervous system are the major pathogenetic pathways of aldosterone-induced hypertension. Renin is synthesized by the juxtaglomerular cells of the kidney. Renin catalyzes the conversion of angiotensinogen to angiotensin I, which is converted by angiotensin-converting enzyme (ACE) to angiotensin II (Ang II). Ang II, via the AT1 receptor (AT1R), increases the synthesis of aldosterone by upregulating the *CYP11B2* gene, which encodes the enzyme aldosterone synthase (ALDOS) in the *zona glomerulosa* of the adrenal cortex. ALDOS catalyzes the synthesis of aldosterone in the adrenal cortex. In the kidney, aldosterone binds to the cytoplasmic mineralocorticoid receptor (MR); the aldosterone-MR complex migrates to the nucleus and leads to a gene-specific transcription of genes crucial for transepithelial sodium transport such as the epithelial sodium channel (ENaC) and the $Na^+/K^+$ adenosine triphosphatase. Sodium and fluid retention cause volume overload. Aldosterone excess in the vessels promotes vascular remodeling and induces inflammation, oxidative stress, endothelial dysfunction, and vasoconstriction. Brain MRI plays a role in increased sympathoexcitatory responses. Excess aldosterone secretion can be counteracted by aldosterone antagonists or by selective inhibitors of aldosterone synthase. Abbreviations: *ACTH* adrenocorticotropic hormone, *Ang II* angiotensin II, *AT1* angiotensin AT1 receptor, *A* aldosterone, *ALDOS* aldosterone synthase, *MR* mineralocorticoid receptor, *ENaC* epithelial $Na^+$ channel, *NADPH* nicotinamid-denin-dinucleotid-phosphate, *MCP1* macrophage chemoattractant protein-1, *TNF-α* tumor necrosis factor alpha, *TGF-s* transforming growth factor beta, *NO* nitric oxide

### 7.3.2 Primary Aldosteronism

The role of aldosterone in hypertension has been first suggested by *Michał Lityński* in 1953 [86]. *Conn and Louis* (1954) provided the causal evidence when they treated a case of hypertension by surgical removal of large adrenal adenoma [87].

Primary aldosteronism or hyperaldosteronism, also known as Conn's syndrome, is characterized by hypertension and an inappropriately high aldosterone levels that

cannot be suppressed by sodium loading. Moreover, patients may have hypokalemia and low plasma renin activity. It is assumed that volume expansion associated with increased aldosterone levels inhibits renin secretion. Therefore, the aldosterone-to-renin ratio is recommended as screening tool for primary aldosteronism [88]. Underlying causes of primary aldosteronism include idiopathic hyperaldosteronism, primary adrenal (glomerulosa) hyperplasia, familial hyperaldosteronism, and aldosterone-producing adenoma or carcinoma. Primary aldosteronism may account for more than 10% of patients with hypertension [89].

### 7.3.3 Aldosterone and Hypertension

Secondary hyperaldosteronism occurs by a perceived drop in intravascular volume due to reduced cardiac output. In patients with cardiac failure, for instance, aldosterone may reach plasma levels up to 60-fold higher in comparison with healthy subjects [90].

Clinical evidence shows that aldosterone contributes to the pathogenesis of hypertension beyond primary aldosteronism [91]. *Jaques Genest* et al. also suggested that human arterial hypertension is a state of mild chronic hyperaldosteronism [92]. Later, results from the Framingham Heart Disease Epidemiology Study demonstrated that aldosterone levels within the upper part of the physiological range predispose normotensive subjects to the development of hypertension [93]. Moreover, up to 15% of hypertensive patients have increased aldosterone-to-renin ratios, and in patients with drug-resistant hypertension, this parameter was reported to rise up to 25% [94]. Remarkably, genetic risk factor such as polymorphisms of the *CYP11B2* gene, which encodes ALDOS, may contribute to hypertension in subjects with a raised aldosterone-to-renin ratio [95].

### 7.3.4 Mechanisms of Aldosterone Action in Hypertension

The major pathogenetic pathways of aldosterone-induced hypertension include renal sodium and water retention, increased peripheral resistance, and stimulation of the sympathetic nervous system [91] (Fig. 7.2).

In the kidney, aldosterone induces genomic and non-genomic effects. In the epithelial cells of the late distal tubule and collecting duct, aldosterone binds to cytoplasmic MR, which is a member of the nuclear receptor family of ligand-dependent transcription factors [96]. The aldosterone-MR complex migrates to the nucleus and binds on the DNA to a specific hormone response element which leads to a gene-specific transcription. The transcribed genes are crucial for transepithelial sodium transport, including the epithelial sodium channel (ENaC), the Na+/K+ adenosine triphosphatase, and their regulatory proteins. Serum- and glucocorticoid-induced kinase 1 (SGK1), an aldosterone-induced regulatory protein, leads to retrieve of ENaC at the apical surface by phosphorylating an ubiquitin ligase Nedd4-2. As a result, sodium reabsorption is sustained. The reabsorbed

sodium is transported to the extracellular compartment via the action of the $Na^+$/$K^+$ adenosine triphosphatase at the basolateral surface. Thus, the reabsorption of $Na^+$ (and subsequent reabsorption of $Cl^-$ and $H_2O$) and secretion of $K^+$ and $H^+$ are increased [83].

In addition to genomic effects described above, aldosterone induces rapid effects predominantly in non-epithelial cells such as vascular smooth cells, endothelial cells, cardiac myocytes, and kidney cells [97]. These non-genomic actions are mediated through second messenger systems IP3, DAG, cyclic AMP, and subsequent $Ca^{2+}$ regulation [97] and may be important for vascular regulation.

The effects of aldosterone on blood pressure regulation extend beyond increased intravascular fluid retention and volume overload. Aldosterone modulates vascular tone by increasing pressor responses to catecholamines and impairing the vasodilatory response to acetylcholine as well as by upregulation of the $AT_1$ receptor [83]. Hyperaldosteronism also causes vasoconstriction by limiting bioavailability of endothelial nitric oxide and by increasing intracellular calcium in the vascular smooth cells [98]. In addition, aldosterone excess promotes vascular hypertrophy and fibrosis followed by vascular remodeling and increased arterial stiffness [99]. Hyperaldosteronism also activates inflammation and oxidative stress, alters fibrinolysis by increasing plasminogen activator inhibitor-1 expression, and promotes tissue apoptosis and fibrosis [100]. Importantly, the cellular pathways regulated by aldosterone via the MR and Ang II via its $AT_1R$ type seem to reinforce each other [101].

Experimental studies demonstrated that aldosterone agonists and antagonists influence blood pressure when they are infused directly into the brain [102]. Brain MR may play a role in increased salt appetite and increased sympathoexcitatory responses [91], although the central sites and mechanisms of mineralocorticoid-mediated pressor responses remain controversial [103].

### 7.3.5 Aldosterone Antagonists

Excess aldosterone secretion can be counteracted by aldosterone antagonists (Fig. 7.2). This class of drugs offers therapeutic benefits for both lowering blood pressure and preventing end-organ damage. Spironolactone, the first MR antagonist, was developed more than 50 years ago [104]. It attenuates the effects of aldosterone and is used for the treatment of hypertension, primary aldosteronism, and peripheral edema associated with heart failure. Monotherapy with spironolactone was shown to be effective in patients with low-renin essential hypertension [105]. In patients with low renin levels and high aldosterone-to-renin ratio, spironolactone decreased blood pressure as effectively as thiazide diuretics [106]. Low-dose spironolactone is also beneficial by patients with resistant hypertension even irrespective of renin and aldosterone concentrations [107, 108]. Moreover, a recent randomized, double-blind, crossover trial PATHWAY-2 demonstrated that spironolactone was the most effective add-on drug for the treatment of resistant hypertension [109]. However, spironolactone lacks specificity for the MR. It activates also

steroid progesterone and androgen receptors leading to progestational and antiandrogenic side effects such as menstrual irregularities in women and sexual dysfunction with gynecomastia in men. This led to the development of a more selective, "second-generation" aldosterone receptor antagonist eplerenone which is less prone to cause steroid-like side effects.

Eplerenone provides well-tolerated blood pressure reduction in patients with low-renin essential hypertension and mild-to-moderate hypertension or in hypertensive patients when administered as add-on therapy [91]. Unfortunately, eplerenone features a reduced potency [110]. Therefore, despite of its better tolerability over spironolactone [111], the indication for hypertension is not recognized except in the presence of intolerance to spironolactone [112].

Hyperkaliemia is a serious dose-related adverse effect of both spironolactone and eplerenone. The risk of hyperkalemia is minimized by serum $K^+$ and renal function monitoring and avoidance of concurrent therapies associated with hyperkalemia.

Other nonsteroidal aldosterone antagonists are being developed [113]. Finerenone, previously called BAY94-8662, for instance, has greater affinity to the MR than eplerenone [114]. In patients with chronic heart failure and renal disease, finerenone may achieve equivalent organ-protective effects with reduced levels of electrolyte disturbance compared with steroid-based MR antagonists [115]. However, finerenone does not significantly influence systolic blood pressure [114].

An alternative approach is to inhibit aldosterone synthesis by selective inhibitors of aldosterone synthase [110, 116] (Fig. 7.2). The first orally active aldosterone synthase inhibitor, LC1699, has been tested in patients with resistant hypertension and primary hyperaldosteronism [110]. Unfortunately, due to lack of selectivity, LC 1699 at higher doses also inhibits 11-beta-hydroxylase which regulates cortisol synthesis. Thus, more selective substances will have to be developed. FAD 286, an aromatase inhibitor, decreased plasma aldosterone concentrations and thereby decreased blood pressure and improved cardiac and renal target organ damage in several animal models [113].

Altogether, recent scientific advances highlight the role of aldosterone as a key cardiovascular hormone. Inhibition of aldosterone action can be beneficial in the treatment of hypertension and end-organ damage.

## 7.4 Vasopressin

Vasopressin (or arginine vasopressin, AVP) is a nonapeptide produced by the neurons of the hypothalamus [117]. Initially identified in 1895 as a pressor hormone [118], it has been recognized two decades later as a potent antidiuretic peptide and is therefore also known as "antidiuretic hormone" (ADH) [119]. The differential pressor and diuretic actions are mediated by different G-protein-coupled vasopressin receptors. These encompass three main subtypes: the vasopressin V1a, V1b, and V2 receptors (V1aR, V1bR, V2R). The V1aR are expressed abundantly in vascular smooth muscle cells, and their stimulation is responsible for the vasopressor effect, while the V1bR are pituitary receptors stimulating the release of ACTH. Both V1aR and V1bR

mediate their main actions via the Gq-phosphatidylinositol and 1,2-diacylglycerol signaling pathway [120]. The V2R, mainly localized in the renal collecting duct, are involved in the antidiuretic action of vasopressin [121]. Its intracellular signaling involves the Gs-adenylate cyclase/cAMP/PKA pathway that results in an increased expression and insertion of aquaporin-2 channels with a subsequent increased water reabsorption across the cells from the collecting duct [122].

Since vasopressin levels have been found elevated in animal models of hypertension [123, 124] and in some forms of human hypertension [121, 125], the potential contribution of vasopressin to the development of hypertension will be addressed.

### 7.4.1 Vasopressor Contribution

Blockade of the V1aR for 4 weeks in prehypertensive SHR could attenuate the development of hypertension in adult SHR [126]. This was further supported by an increase of plasma vasopressin and of renal V1aR gene and protein expressions parallel to hypertension development [127]. However, once hypertension was fully established, plasma vasopressin decreased and V1aR gene and protein expressions were downregulated [127]. This was observed together with an undisturbed V2R expression over the studied period in SHR, and it was not present in the normotensive strain. The authors suggested that the administration of V1aR antagonists in the prehypertensive state could thus allow the prevention of hypertension in patients at risk.

However, in another hypertensive model (L-NAME), V1aR antagonism could not attenuate hypertension and renal dysfunction [128]. A further blood pressure increase was even observed at the end of treatment although renal and mesenteric vasoconstriction to vasopressin was attenuated [128]. This suggested that V1aR activation does not contribute to hypertension induced by inhibition of NO synthesis.

Moreover, the vasoconstrictor nature of vasopressin has been questioned by the observation of vasopressin-induced vasodilation in some studies [129–132]. The differential vasoreactive response to vasopressin may reflect different experimental environments [133, 134] but may also be linked to the binding of vasopressin to endothelial oxytocin- and P2 purinergic receptors (OTR and P2R, respectively) [135, 136]. Binding of vasopressin to P2R stimulates phospholipase A2 and nitric oxide synthase, resulting in increased production of prostacyclin and nitric oxide, respectively, both leading to vasodilatation [137]. Binding to the endothelial OTR also results in a release of nitric oxide and vasodilation. Therefore, further knowledge of the function and distribution of vasopressin receptors in the course of hypertension development seems essential to understand the apparent contradictory effects of vasopressin on vascular function. In addition, while it is known that vasopressin can potentiate the vasoconstriction induced by norepinephrine [138] and Ang II [139–141], the underlying mechanisms remain to be discovered in order to unveil a potential contribution of vasopressin-mediated increased vascular resistance to the development of hypertension.

Finally, clinical studies are also not conclusive. In well-hydrated volunteers and in patients with a mild form of essential hypertension, V1bR blockade did not alter blood pressure [142, 143]. However in patients with more severe forms of hypertension, in which plasma vasopressin was found to be elevated, V1R blockade induced a modest but consistent blood pressure decrease [144]. More recently, in hypertensive patients, blockade of the V1aR with a synthetic antagonist during osmotic stimulation resulted in a transient vasodilation without blood pressure reduction [145].

### 7.4.2 Antinatriuretic Contribution

An increased plasma osmolality triggers the secretion of vasopressin from vasopressinergic neurons in the neurohypophysis. It has been suggested that increased vasopressin levels could participate in the blood pressure elevation, not via its V1aR-mediated effects (which actually facilitate sodium excretion) but via actions mediated by V2R [121]. The acute administration of a selective V2R agonist was able to increase urine osmolarity, to reduce urine flow rate, and to reduce sodium excretion in rats as well as in humans [121]. Following a prolonged V2R stimulation, blood pressure was even raised by ~10 mmHg in normotensive rats. In addition, treatment with a selective nonpeptide V2R antagonist in DOCA-salt hypertensive mice or SHR could limit or even prevent the rise in blood pressure [146, 147].

### 7.4.3 Central Contribution

Vasopressin is synthesized by neurons located in the paraventricular nucleus and median preoptic and supraoptic nuclei. Those neurons can be depolarized by hypertonic conditions promoting thus the release of a vasopressin precursor or hyperpolarized by hypotonic conditions to limit its release. Finally, the vasopressin precursor migrates to the posterior pituitary, from which it is released into the circulation [133].

First evidences for a central contribution were obtained in studies involving spontaneously hypertensive rats (SHR-SP) in which vasopressin concentrations in plasma and brain stem were reduced compared to normotensive Wistar Kyoto (WKY) rats [148, 149]. Recent investigations have been performed to assess whether vasopressin neurons are excited in hypertensive states [150]. This was studied in an inducible angiotensin-dependent hypertensive model, the Cyp1a1-Ren2 rat. The basal firing rate of vasopressin neurons was higher in hypertensive rats. In addition, the baroreflex-induced inhibition of vasopressin neurons was lost in hypertensive rats [150]. This demonstrates that the activity of vasopressin neurons is increased at the onset of hypertension, potentially due to a reduced baroreflex inhibition of those neurons.

The excitatory state of vasopressin neurons has also been studied recently in the context of salt-dependent hypertension [151]. It is known that the plasmatic

concentration of vasopressin is elevated in salt-dependent hypertensive models, such as the deoxycorticosterone acetate-salt model [152–155]. In this model, the authors could demonstrate that vasopressin neurons of the hypertensive animals exhibited a depolarizing excitatory response via the γ-aminobutyric acid (GABA), whereas GABA functions as an inhibitory transmitter for vasopressin neurons in control animals. This GABAergic excitation of vasopressin neurons was associated with an increased vasopressin release and a blood pressure increase [151].

Taken together, the exact contribution of vasopressin to the development of hypertension remains unclear and seems to depend on the type and stage of hypertension. Further work with vasopressin analogues is thus required to decipher its role in the development and maintenance of hypertension.

## 7.5 Natriuretic Peptides

The presence of natriuretic peptides (NP) has been postulated over 50 years ago; however only in 1981, *Bold et al*. demonstrated their endocrine function in regulating fluid homeostasis [156]. In the following years, three distinct natriuretic peptides have been isolated and described: ANP atrial natriuretic factor (ANF), isolated from rat atrium [157], as well as BNP and CNP, both purified from porcine brain extracts [158, 159]. In 1995 *Lang et al*. described for the first time a sensitive and specific radioimmunoassay for ANF [160]. Primarily NPs have been linked to natriuresis and diuresis. Recently, other physiological functions of NPs have been described, including vasodilation, anti-inflammation, and anti-fibrosis [161]. In the following, structure and synthesis, biological functions in health and disease, as well as novel pharmacological strategies targeting NPs will be discussed.

### 7.5.1 Expression, Structure, and Synthesis of NP and Its Receptors

All NPs are synthesized as precursors, i.e., prepro-NPs, and processed to pro-NPs by peptidases [162]. The 126 amino acid (AA) pro-ANP is primarily expressed and stored in granules in atria and upon stimulation released and converted to the mature 28 AA ANP by corin, a transmembrane serine protease [163]. The 108 AA pro-BNP is mainly expressed in cardiac ventricles and cleaved by corin or furin to its 32 AA biologically active form BNP [164]. The human 103 AA pro-CNP is widely expressed in the brain tissue; however it is also synthesized in the kidney, bone, blood vessels, and heart [165]. Furin mediates conversion of pro-CNP to its active form CNP-53 [166] which may further be processed to CNP-22 by an unknown extracellular enzyme [167].

There are three distinct natriuretic peptide receptors, NPR-A, NPR-B, and NPR-C, but only the first two mediate the well-known physiological actions of NPs [161]. Binding of NPs to NPR-A and NPR-B activates guanylyl cyclase resulting in the synthesis of cGMP (Fig. 7.3), an intracellular second messenger. GMP, in turn,

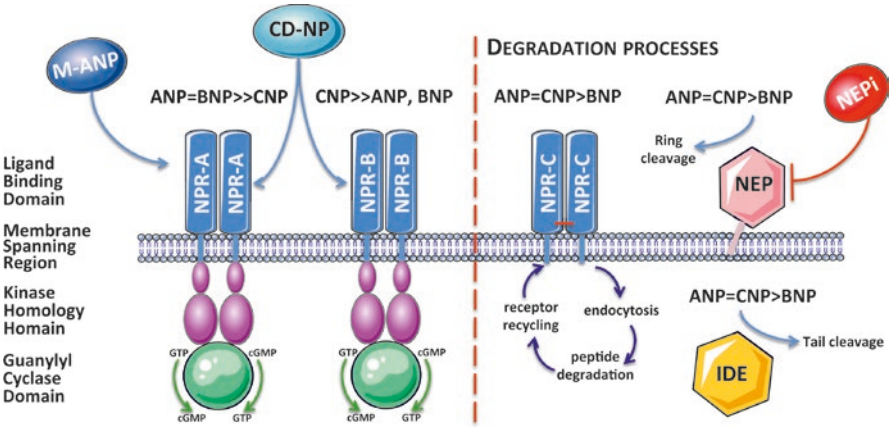



**Fig. 7.3** Natriuretic peptide system. Natriuretic peptide-binding receptors (blue), intracellular signaling (generation of cGMP), and degradation processes (NPR-C receptor, NEP, and IDE). Abbreviations: *NPR* natriuretic peptide receptor, *ANP* A-type (atrial) natriuretic peptide, *BNP* B-type (brain) natriuretic peptide, *CNP* C-type natriuretic peptide, *M-ANP* pharmacological agonist of NPR-A receptor, *CD-NP* pharmacological agonist of NPR-A and NPR-B receptors, *NEP* neutral endopeptidase (neprilysin), *NEPi* pharmacological inhibitor of NEP, *IDE* insulin-degrading enzyme, *GTP* guanosine triphosphate, *cGMP* cyclic guanosine monophosphate

mediates the physiological effects of NP by binding to the three major effectors: cGMP-gated ion channels, phosphodiesterases (PDEs), and cGMP-dependent protein kinases (PKGs) [167]. The third NP receptor, NPR-C, has no guanylyl cyclase domain, and it is primarily viewed as a clearance receptor that removes NPs from the circulation through receptor-mediated internalization and degradation (Fig. 7.3) [161]. In addition to the NPR-C-mediated clearance, NPs can be enzymatically degraded by neutral endopeptidase (NEP) [167] and insulin-degrading enzyme (IDE) [168] (Fig. 7.3).

### 7.5.2 Biological Function in Health and Disease

Classically, NPs have been linked to natriuresis and diuresis due to renal hemodynamic and direct tubular actions. ANP increases glomerular filtration rate [169] and inhibits sodium reabsorption in the proximal and distal nephrons [170] and tubular water transport in cortical collecting ducts [169]. Finally, the inhibitory effect of systemically or centrally applied ANP on Ang II-mediated sodium and water transport has been demonstrated [171, 172]. *Unger et al*. showed that ANP, in contrast to its peripheral natriuretic actions, is antinatriuretic when centrally applied [172, 173].

Infusion of either ANP or BNP lowers blood pressure in animals, whereas CNP has no significant impact on hemodynamics [174]. In contrast, in hypertensive human subjects, only ANP showed a blood pressure-lowering effect [175] whereas BNP did not [176]. Furthermore, in human healthy volunteers, infusion of either ANP or BNP concomitantly with Ang II lowered blood pressure to a similar extent,

indicating that both NPs have an impact on pressor responses to angiotensin [177]. The mechanisms involved in the BP-lowering effects of NPs are complex and include not only the abovementioned increased natriuresis and diuresis but also arterial vasodilation, vascular permeability, and direct suppression of the renin-angiotensin-aldosterone system and sympathetic nervous system [178].

Preclinical studies have demonstrated that NPs can protect against pathological cardiac remodeling, including hypertrophy, inflammation, and fibrosis [161, 162, 170]. Knocking out of ANP or NPR-A in mice led to cardiac hypertrophy in a blood pressure-independent manner [179, 180], whereas ANP overexpression resulted in smaller hearts as compared to wild-type animals [181]. Anti-inflammatory actions of ANP [182], BNP [183], and CNP [184] in cardiac tissue have been demonstrated in animal models of cardiac hypertrophy, myocardial infarction, and myocarditis. In addition, all three NPs promote antifibrosis in cardiac tissue [182, 185, 186].

### 7.5.3 Pharmacological Strategies Targeting NPs

Intravenous administration of NPs had beneficial effects in animal models of cardiovascular and renal diseases. However, due to the short half-life, native or recombinant NPs cannot be applied in routine clinical use. Therefore, recombinant forms of NPs that are resistant to enzymatic degradation have been developed.

M-ANP (Fig. 7.3) possesses a greater resistance to enzymatic degradation than native ANP [187]. In preclinical studies, it has BP-lowering effects, promotes natriuresis and diuresis, increases renal blood flow and GFR, and suppresses the RAAS [187, 188]. Currently, M-ANP undergoes clinical trials in patients with hypertension [189].

A novel class of natriuretic peptides, represented by CD-NP (cenderitide), with greater resistance to enzymatic degradation has been developed [190]. In contrast to CNP, CD-NP activates both NPR-A and NPR-B receptors (Fig. 7.3), promotes subsequent natriuresis and diuresis, inhibits cardiac fibrosis, and reduces systolic blood pressure [162, 191].

Another strategy to target NPs is NEP inhibition (Fig. 7.3), which also inhibits the degradation of NPs and activates NP receptors by raising the concentrations of endogenous NPs. However, clinical trials with pure NEP inhibitors showed no effects but several side effects related to the rising concentration of other vasoactive peptides (including Ang I, Ang II, substance P, and endothelin) [161]. Therefore, NEP inhibition with concomitant RAS inhibition was considered to be a better choice.

The most extensively studied dual NEP/ACE inhibitor was omapatrilat [192]. Although this compound showed a significant reduction in composite end points compared to lisinopril in heart failure patients in the IMPRESS trial [193], larger trials like OVERTURE failed to show any advantage over enalapril in combined risk of death or hospitalization for heart failure [71]. An increased incidence of angioedema, most likely due to the bradykinin-potentiating effects of ACE inhibition, in subsequent studies led to the interruption of the clinical development of omapatrilat [192].

In view of the abovementioned side effects of NEP inhibition (alone or in combination with ACE inhibition), a combination of NEP inhibition with AT1R

blockade instead of ACE inhibition was thought to be of advantage. The first class angiotensin receptor neprilysin inhibitor (ARNI) is LCZ696, which comprises molecular moieties of the AT1 receptor antagonist, valsartan, and of the NEP inhibitor prodrug, sacubitril, at a 1:1 molar ratio in a single molecule [194]. In preclinical studies, LCZ696 engendered pronounced vasodilatation, natriuresis, diuresis, and inhibition of fibrosis and hypertrophy [191]. In clinical studies, LCZ696 lowers BP and reduces NT-pro-BNP, a marker of LV wall stress, left atrial dimension, and volume and volume index in hypertensive and heart failure patients [76, 195, 196].

Natriuretic peptides play an important role not only in water and salt homeostasis but also provide tissue protection in cardiovascular and renal diseases. The complexity of the natriuretic peptide system including the ligand-specific effects of NPs, signaling pathways mediated by the NP receptors, and the cross talk between NP system and RAAS and the sympathetic nervous system requires further investigation. This may lead to a development of novel pharmacological strategies, targeting the NP system more selectively and with higher efficacy than currently available drugs.

## References

1. Weir MR, Dzau VJ (1999) The renin-angiotensin-aldosterone system: a specific target for hypertension management. Am J Hypertens 12(12 Pt 3):205S–213S
2. Danser AH, Derkx FH, Schalekamp MA et al (1998) Determinants of interindividual variation of renin and prorenin concentrations: evidence for a sexual dimorphism of (pro)renin levels in humans. J Hypertens 16(6):853–862
3. Nguyen G, Delarue F, Burcklé C et al (2002) Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. J Clin Invest 109(11):1417–1427
4. Schefe JH, Menk M, Reinemund J et al (2006) A novel signal transduction cascade involving direct physical interaction of the renin/prorenin receptor with the transcription factor promyelocytic zinc finger protein. Circ Res 99(12):1355–1366
5. Funke-Kaiser H, Zollmann FS, Schefe JH, Unger T (2010) Signal transduction of the (pro) renin receptor as a novel therapeutic target for preventing end-organ damage. Hypertens Res 33(2):98–104
6. Schefe JH, Unger T, Funke-Kaiser H (2008) PLZF and the (pro)renin receptor. J Mol Med 86(6):623–627
7. Krop M, Lu X, Danser AHJ, Meima ME (2013) The (pro)renin receptor. A decade of research: what have we learned? Pflugers Arch 465(1):87–97
8. Nasjletti A, Masson GM (1972) Studies on angiotensinogen formation in a liver perfusion system. Circ Res 31(9 Suppl 2):187–120
9. Skeggs LT, Marsh WH, Kahn JR, Shumway NP (1954) The existence of two forms of hypertension. J Exp Med 99(3):275–282
10. Unger T (2002) The role of the renin-angiotensin system in the development of cardiovascular disease. Am J Cardiol 89(2A):3A–9A; discussion 10A
11. Oparil S, Tregear GW, Koerner T et al (1971) Mechanism of pulmonary conversion of angiotensin I to angiotensin II in the dog. Circ Res 29(6):682–690
12. Mogi M, Iwai M, Horiuchi M (2009) New insights into the regulation of angiotensin receptors. Curr Opin Nephrol Hypertens 18(2):138–143
13. Touyz RM, Schiffrin EL (2000) Signal transduction mechanisms mediating the physiological and pathophysiological actions of angiotensin II in vascular smooth muscle cells. Pharmacol Rev 52(4):639–672
14. Braun-Menendez E, Fasciolo JC, Leloir LF, Muñoz JM (1940) The substance causing renal hypertension. J Physiol Lond 98(3):283–298

15. Burns KD, Li N (2003) The role of angiotensin II-stimulated renal tubular transport in hypertension. Curr Hypertens Rep 5(2):165–171
16. Li H, Weatherford ET, Davis DR et al (2011) Renal proximal tubule angiotensin AT1A receptors regulate blood pressure. Am J Physiol Regul Integr Comp Physiol 301(4):R1067–R1077
17. Mamenko M, Zaika O, Prieto MC et al (2013) Chronic angiotensin II infusion drives extensive aldosterone-independent epithelial Na+ channel activation. Hypertension 62(6):1111–1122
18. Shricker K, Holmer S, Krämer BK et al (1997) The role of angiotensin II in the feedback control of renin gene expression. Pflugers Arch 434(2):166–172
19. De Gasparo M, Catt KJ, Inagami T et al (2000) International union of pharmacology XXIII. The angiotensin II receptors. Pharmacol Rev 52(3):415–472
20. Goldblatt H, Lynch J, Hanzal RF, Summerville WW (1934) Studies on experimental hypertension: I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. J Exp Med 59(3):347–379
21. Hansson L, Lindholm LH, Niskanen L et al (1999) Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 353(9153):611–616
22. Hansson L, Lindholm LH, Ekbom T et al (1999) Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 354(9192):1751–1756
23. Yusuf S, Sleight P, Pogue J et al (2000) Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 342(3):145–153
24. Dahlöf B, Devereux RB, Kjeldsen SE et al (2002) Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 359(9311):995–1003
25. Julius S, Kjeldsen SE, Weber M et al (2004) Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 363(9426):2022–2031
26. Investigators ONTARGET, Yusuf S, Teo KK, Pogue J et al (2008) Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 358(15):1547–1559
27. Elliott WJ, Meyer PM (2007) Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet 369(9557):201–207
28. Stanton A, Jensen C, Nussberger J, O'Brien E (2003) Blood pressure lowering in essential hypertension with an oral renin inhibitor, aliskiren. Hypertension 42(6):1137–1143
29. Andersen K, Weinberger MH, Egan B et al (2008) Comparative efficacy and safety of aliskiren, an oral direct renin inhibitor, and ramipril in hypertension: a 6-month, randomized, double-blind trial. J Hypertens 26(3):589–599
30. Schmieder RE, Philipp T, Gueredíaga J et al (2009) Long-term antihypertensive efficacy and safety of the oral direct renin inhibitor aliskiren: a 12-month randomized, double-blind comparator trial with hydrochlorothiazide. Circulation 119(3):417–425
31. Dietz R, Dechend R, Yu C-M et al (2008) Effects of the direct renin inhibitor aliskiren and atenolol alone or in combination in patients with hypertension. J Renin-Angiotensin-Aldosterone Syst 9(3):163–175
32. Parving H-H, Brenner BM, McMurray JJV et al (2009) Aliskiren trial in type 2 diabetes using cardio-renal endpoints (ALTITUDE): rationale and study design. Nephrol Dial Transplant 24(5):1663–1671
33. Dzau VJ, Sasamura H, Hein L (1993) Heterogeneity of angiotensin synthetic pathways and receptor subtypes: physiological and pharmacological implications. J Hypertens Suppl 11(3):S13–S18
34. Paul M, Poyan Mehr A, Kreutz R (2006) Physiology of local renin-angiotensin systems. Physiol Rev 86(3):747–803

35. Unger T, Steckelings UM, dos Santos R (eds) (2015) The protective arm of the renin angiotensin system—functional aspects and therapeutic implications, 1st edn. Academic Press, Elsevier
36. Paulis L, Rajkovicova R, Simko F (2015) New developments in the pharmacological treatment of hypertension: dead-end or a glimmer at the horizon? Curr Hypertens Rep 17(6):557
37. Gohlke P, Pees C, Unger T (1998) AT2 receptor stimulation increases aortic cyclic GMP in SHRSP by a kinin-dependent mechanism. Hypertension 31(1 Pt 2):349–355
38. Fischer TA, Singh K, O'Hara DS et al (1998) Role of AT1 and AT2 receptors in regulation of MAPKs and MKP-1 by ANG II in adult cardiac myocytes. Am J Phys 275(3 Pt 2):H906–H916
39. Nouet S, Nahmias C (2000) Signal transduction from the angiotensin II AT2 receptor. Trends Endocrinol Metab;11(1):1–6
40. AbdAlla S, Lother H, Abdel-tawab AM, Quitterer U (2001) The angiotensin II AT2 receptor is an AT1 receptor antagonist. J Biol Chem 276(43):39721–39726
41. Wruck CJ, Funke-Kaiser H, Pufe T et al (2005) Regulation of transport of the angiotensin AT2 receptor by a novel membrane-associated Golgi protein. Arterioscler Thromb Vasc Biol 25(1):57–64
42. Batenburg WW, Garrelds IM, Bernasconi CC et al (2004) Angiotensin II type 2 receptor-mediated vasodilation in human coronary microarteries. Circulation 109(19):2296–2301
43. Lucius R, Gallinat S, Rosenstiel P et al (1998) The angiotensin II type 2 (AT2) receptor promotes axonal regeneration in the optic nerve of adult rats. J Exp Med 188(4):661–670
44. Rompe F, Artuc M, Hallberg A et al (2010) Direct angiotensin II type 2 receptor stimulation acts anti-inflammatory through epoxyeicosatrienoic acid and inhibition of nuclear factor kappaB. Hypertension 55(4):924–931
45. Stoll M, Steckelings UM, Paul M et al (1995) The angiotensin AT2-receptor mediates inhibition of cell proliferation in coronary endothelial cells. J Clin Invest 95(2):651–657
46. Vincent J-M, Kwan YW, Chan SL et al (2005) Constrictor and dilator effects of angiotensin II on cerebral arterioles. Stroke 36(12):2691–2695
47. Wan Y, Wallinder C, Plouffe B et al (2004) Design, synthesis, and biological evaluation of the first selective nonpeptide AT2 receptor agonist. J Med Chem 47(24):5995–6008
48. Kaschina E, Grzesiak A, Li J et al (2008) Angiotensin II type 2 receptor stimulation: a novel option of therapeutic interference with the renin-angiotensin system in myocardial infarction? Circulation 118(24):2523–2532
49. Lauer D, Slavic S, Sommerfeld M et al (2014) Angiotensin type 2 receptor stimulation ameliorates left ventricular fibrosis and dysfunction via regulation of tissue inhibitor of matrix metalloproteinase 1/matrix metalloproteinase 9 axis and transforming growth factor β1 in the rat heart. Hypertension 63(3):e60–e67
50. Paulis L, Becker STR, Lucht K et al (2012) Direct angiotensin II type 2 receptor stimulation in Nω-nitro-L-arginine-methyl ester-induced hypertension: the effect on pulse wave velocity and aortic remodeling. Hypertension 59(2):485–492
51. Rehman A, Leibowitz A, Yamamoto N et al (2012) Angiotensin type 2 receptor agonist compound 21 reduces vascular injury and myocardial fibrosis in stroke-prone spontaneously hypertensive rats. Hypertension 59(2):291–299
52. Hrenák J, Arendášová K, Rajkovičová R et al (2013) Protective effect of captopril, olmesartan, melatonin and compound 21 on doxorubicin-induced nephrotoxicity in rats. Physiol Res 62(Suppl 1):S181–S189
53. Matavelli LC, Huang J, Siragy HM (2011) Angiotensin $AT_2$ receptor stimulation inhibits early renal inflammation in renovascular hypertension. Hypertension 57(2):308–313
54. Iwanami J, Mogi M, Tsukuda K et al (2014) Possible synergistic effect of direct angiotensin II type 2 receptor stimulation by compound 21 with memantine on prevention of cognitive decline in type 2 diabetic mice. Eur J Pharmacol 724:9–15
55. Namsolleck P, Boato F, Schwengel K et al (2013) AT2-receptor stimulation enhances axonal plasticity after spinal cord injury by upregulating BDNF expression. Neurobiol Dis 51:177–191

56. Valero-Esquitino V, Lucht K, Namsolleck P et al (2015) Direct angiotensin AT2-receptor stimulation attenuates T-cell and microglia activation and prevents demyelination in experimental autoimmune encephalomyelitis in mice. Clin Sci (Lond) 128:95–109
57. Zaman MA, Oparil S, Calhoun DA (2002) Drugs targeting the renin-angiotensin-aldosterone system. Nat Rev Drug Discov 1(8):621–636
58. Chai SY, Fernando R, Peck G, Ye S-Y, Mendelsohn FA, Jenkins TA et al (2004) The angiotensin IV/AT4 receptor. Cell Mol Life Sci 61(21):2728–2737
59. Yang R, Smolders I, Dupont AG (2011) Blood pressure and renal hemodynamic effects of angiotensin fragments. Hypertens Res 34(6):674–683
60. Park YA, Choi CH, Do IG et al (2014) Dual targeting of angiotensin receptors (AGTR1 and AGTR2) in epithelial ovarian carcinoma. Gynecol Oncol 135(1):108–117
61. Park BM, Cha SA, Lee SH, Kim SH (2016) Angiotensin IV protects cardiac reperfusion injury by inhibiting apoptosis and inflammation via AT4R in rats. Peptides 79:66–74
62. Iwai M, Horiuchi M (2009) Devil and angel in the renin-angiotensin system: ACE-angiotensin II-AT1 receptor axis vs. ACE2-angiotensin-(1-7)-Mas receptor axis. Hypertens Res 32(7):533–536
63. Villela D, Leonhardt J, Patel N et al (2015) Angiotensin type 2 receptor (AT2R) and receptor Mas: a complex liaison. Clin Sci 128(4):227–234
64. Barroso LC, Silveira KD, Lima CX et al (2012) Renoprotective effects of AVE0991, a non-peptide Mas receptor agonist, in experimental acute renal injury. Int J Hypertens 2012:808726
65. Silveira KD, Barroso LC, Vieira AT et al (2013) Beneficial effects of the activation of the angiotensin-(1-7) MAS receptor in a murine model of adriamycin-induced nephropathy. PLoS One 8(6):e66082
66. Singh Y, Singh K, Sharma PL (2013) Effect of combination of renin inhibitor and Mas-receptor agonist in DOCA-salt-induced hypertension in rats. Mol Cell Biochem 373(1–2):189–194
67. Rentzsch B, Todiras M, Iliescu R et al (2008) Transgenic angiotensin-converting enzyme 2 overexpression in vessels of SHRSP rats reduces blood pressure and improves endothelial function. Hypertension 52(5):967–973
68. Zhong J, Basu R, Guo D et al (2010) Angiotensin-converting enzyme 2 suppresses pathological hypertrophy, myocardial fibrosis, and cardiac dysfunction. Circulation 122(7):717–728, 18 p following 728
69. Haschke M, Schuster M, Poglitsch M, Loibner H, Salzberg M, Bruggisser M et al (2013) Pharmacokinetics and pharmacodynamics of recombinant human angiotensin-converting enzyme 2 in healthy human subjects. Clin Pharmacokinet 52(9):783–792
70. Corti R, Burnett JC, Rouleau JL et al (2001) Vasopeptidase inhibitors: a new therapeutic concept in cardiovascular disease? Circulation 104(15):1856–1862
71. Packer M, Califf RM, Konstam MA et al (2002) Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation 106(8):920–926
72. Tabrizchi R (2001) Omapatrilat. Bristol-Myers Squibb. Curr Opin Investig Drugs 2(10):1414–1422
73. Ruilope LM, Dukat A, Böhm M et al (2010) Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. Lancet 375(9722):1255–1266
74. Solomon SD, Zile M, Pieske B et al (2012) The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet 380(9851):1387–1395
75. Voors AA, Gori M, Liu LCY et al (2015) Renal effects of the angiotensin receptor neprilysin inhibitor LCZ696 in patients with heart failure and preserved ejection fraction. Eur J Heart Fail 17(5):510–517
76. McMurray JJV, Packer M, Desai AS et al (2014) Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 371(11):993–1004
77. Gross F (1958) Renin and hypertension, physiological or pathological agents? Klin Wochenschr 36(15):693–706

78. Tait SAS, Tait JF, Coghlan JP (2004) The discovery, isolation and identification of aldosterone: reflections on emerging regulation and function. Mol Cell Endocrinol 217(1–2):1–21
79. Fuller PJ (2015) Novel interactions of the mineralocorticoid receptor. Mol Cell Endocrinol 408:33–37
80. Mulrow PJ, Ganong WF (1961) Stimulation of aldosterone secretion by angiotensin. II. A preliminary report. Yale J Biol Med 33:386–395
81. Quinn SJ, Williams GH (1988) Regulation of aldosterone secretion. Annu Rev Physiol 50:409–426
82. Oelkers W, Brown JJ, Fraser R et al (1974) Sensitization of the adrenal cortex to angiotensin II in sodium-deplete man. Circ Res 34(1):69–77
83. Connell JMC, Davies E (2005) The new biology of aldosterone. J Endocrinol 186(1):1–20
84. Spät A, Hunyady L (2004) Control of aldosterone secretion: a model for convergence in cellular signaling pathways. Physiol Rev 84(2):489–539
85. Ehrhart-Bornstein M, Lamounier-Zepter V, Schraven A et al (2003) Human adipocytes secrete mineralocorticoid-releasing factors. Proc Natl Acad Sci U S A 100(24):14211–14216
86. Kucharz EJ (2007) Michał Lityński--a forgotten author of the first description on primary hyperaldosteronism. Pol Arch Med Wewn 117(1–2):57–58
87. Conn JW, Louis LH (1956) Primary aldosteronism, a new clinical entity. Ann Intern Med 44(1):1–15
88. Rossi GP, Bisogni V, European Society of Hypertension Working Group on Endocrine Hypertension (2016) A useful tool to improve the case detection rate of primary aldosteronism: the aldosterone-renin ratio (ARR)-App. J Hypertens 34(5):1019–1021
89. Rossi GP, Bernini G, Caliumi C et al (2006) A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. J Am Coll Cardiol 48(11):2293–2300
90. Weber KT (2001) Aldosterone in congestive heart failure. N Engl J Med 345(23):1689–1697
91. Tomaschitz A, Pilz S, Ritz E et al (2010) Aldosterone and arterial hypertension. Nat Rev Endocrinol 6(2):83–93
92. Genest J, Lemieux G, Davignon A et al (1956) Human arterial hypertension: a state of mild chronic hyperaldosteronism? Science 123(3195):503–505
93. Vasan RS, Evans JC, Larson MG et al (2004) Serum aldosterone and the incidence of hypertension in nonhypertensive persons. N Engl J Med 351(1):33–41
94. Calhoun DA, Nishizaka MK, Zaman MA et al (2002) Hyperaldosteronism among black and white subjects with resistant hypertension. Hypertension 40(6):892–896
95. Lim PO, Macdonald TM, Holloway C et al (2002) Variation at the aldosterone synthase (CYP11B2) locus contributes to hypertension in subjects with a raised aldosterone-to-renin ratio. J Clin Endocrinol Metab 87(9):4398–4402
96. Arriza JL, Weinberger C, Cerelli G et al (1987) Cloning of human mineralocorticoid receptor complementary DNA: structural and functional kinship with the glucocorticoid receptor. Science 237(4812):268–275
97. Grossmann C, Gekle M (2009) New aspects of rapid aldosterone signaling. Mol Cell Endocrinol 308(1–2):53–62
98. Arima S, Kohagura K, Xu H-L et al (2003) Nongenomic vascular action of aldosterone in the glomerular microcirculation. J Am Soc Nephrol 14(9):2255–2263
99. Briet M, Schiffrin EL (2013) Treatment of arterial remodeling in essential hypertension. Curr Hypertens Rep 15(1):3–9
100. Schrier RW, Masoumi A, Elhassan E (2010) Aldosterone: role in edematous disorders, hypertension, chronic renal failure, and metabolic syndrome. Clin J Am Soc Nephrol 5(6):1132–1140
101. Lemarié CA, Paradis P, Schiffrin EL (2008) New insights on signaling cascades induced by cross-talk between angiotensin II and aldosterone. J Mol Med 86(6):673–678
102. Gomez-Sanchez EP (1986) Intracerebroventricular infusion of aldosterone induces hypertension in rats. Endocrinology 118(2):819–823
103. Geerling JC, Loewy AD (2009) Aldosterone in the brain. Am J Physiol Renal Physiol 297(3):F559–F576

104. Wolf RL, Mendlowitz M, Roboz J et al (1966) Treatment of hypertension with spironolactone. Double-blind study. JAMA 198(11):1143–1149
105. Douglas JG, Hollifield JW, Liddle GW (1974) Treatment of low-renin essential hypertension. Comparison of spironolactone and a hydrochlorothiazide-triamterene combination. JAMA 227(5):518–521
106. Hood SJ, Taylor KP, Ashby MJ, Brown MJ (2007) The spironolactone, amiloride, losartan, and thiazide (SALT) double-blind crossover trial in patients with low-renin hypertension and elevated aldosterone-renin ratio. Circulation 116(3):268–275
107. Nishizaka MK, Zaman MA, Calhoun DA (2003) Efficacy of low-dose spironolactone in subjects with resistant hypertension. Am J Hypertens 16(11 Pt 1):925–930
108. Chapman N, Dobson J, Wilson S et al (2007) Effect of spironolactone on blood pressure in subjects with resistant hypertension. Hypertension 49(4):839–845
109. Williams B, MacDonald TM, Morant S et al (2015) Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 386(10008):2059–2068
110. Namsolleck P, Unger T (2014) Aldosterone synthase inhibitors in cardiovascular and renal diseases. Nephrol Dial Transplant 29(Suppl 1):i62–i68
111. Tamargo J, Solini A, Ruilope LM (2014) Comparison of agents that affect aldosterone action. Semin Nephrol 34(3):285–306
112. Mancia G, Fagard R, Narkiewicz K et al (2013) 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 34(28):2159–2219
113. Romero CA, Orias M, Weir MR (2015) Novel RAAS agonists and antagonists: clinical applications and controversies. Nat Rev Endocrinol 11(4):242–252
114. Bramlage P, Swift SL, Thoenes M et al (2016) Non-steroidal mineralocorticoid receptor antagonism for the treatment of cardiovascular and renal disease. Eur J Heart Fail 18(1):28–37
115. Pitt B, Kober L, Ponikowski P et al (2013) Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. Eur Heart J 34(31):2453–2463
116. Azizi M, Amar L, Menard J (2013) Aldosterone synthase inhibition in humans. Nephrol Dial Transplant 28(1):36–43
117. Swaab DF, Nijveldt F, Pool CW (1975) Distribution of oxytocin and vasopressin in the rat supraoptic and paraventricular nucleus. J Endocrinol 67(3):461–462
118. Oliver G, Schäfer EA (1895) On the physiological action of extracts of pituitary body and certain other glandular organs: preliminary communication. J Physiol Lond 18(3):277–279
119. Verney EB (1947) The antidiuretic hormone and the factors which determine its release. Proc R Soc Lond B Biol Sci 135(878):25–106
120. Finley JJ, Konstam MA, Udelson JE (2008) Arginine vasopressin antagonists for the treatment of heart failure and hyponatremia. Circulation 118(4):410–421
121. Bankir L, Bichet DG, Bouby N (2010) Vasopressin V2 receptors, ENaC, and sodium reabsorption: a risk factor for hypertension? Am J Physiol Renal Physiol 299(5):F917–F928
122. Nielsen S, Chou CL, Marples D et al (1995) Vasopressin increases water permeability of kidney collecting duct by inducing translocation of aquaporin-CD water channels to plasma membrane. Proc Natl Acad Sci U S A 92(4):1013–1017
123. Yagil C, Ben-Ishay D, Yagil Y (1996) Disparate expression of the AVP gene in Sabra hypertension-prone and hypertension-resistant rats. Am J Phys 271(4 Pt 2):F806–F813
124. Share L, Crofton JT (1982) Contribution of vasopressin to hypertension. Hypertension 4(5 Pt 2):III85–III92
125. Zhang X, Hense HW, Riegger GA, Schunkert H (1999) Association of arginine vasopressin and arterial blood pressure in a population-based sample. J Hypertens 17(3):319–324
126. Burrell LM, Phillips PA, Risvanis J et al (1995) Attenuation of genetic hypertension after short-term vasopressin V1A receptor antagonism. Hypertension 26(5):828–834

127. Burrell LM, Risvanis J, Dean RG et al (2013) Age-dependent regulation of renal vasopressin V(1A) and V2 receptors in rats with genetic hypertension: implications for the treatment of hypertension. J Am Soc Hypertens 7(1):3–13
128. Loichot C, Cazaubon C, Grima M et al (2000) Vasopressin does not effect hypertension caused by long-term nitric oxide inhibition. Hypertension 35(2):602–608
129. Walker BR, Haynes J, Wang HL, Voelkel NF (1989) Vasopressin-induced pulmonary vasodilation in rats. Am J Phys 257(2 Pt 2):H415–H422
130. Evora PR, Pearson PJ, Schaff HV (1993) Arginine vasopressin induces endothelium-dependent vasodilatation of the pulmonary artery. V1-receptor-mediated production of nitric oxide. Chest 103(4):1241–1245
131. Suzuki Y, Satoh S, Oyama H et al (1993) Regional differences in the vasodilator response to vasopressin in canine cerebral arteries in vivo. Stroke 24(7):1049–1053. discussion 1053–4
132. Rudichenko VM, Beierwaltes WH (1995) Arginine vasopressin-induced renal vasodilation mediated by nitric oxide. J Vasc Res 32(2):100–105
133. Holmes CL, Landry DW, Granton JT (2003) Science review: vasopressin and the cardiovascular system part 1—receptor physiology. Crit Care 7(6):427–434
134. García-Villalón AL, Garcia JL, Fernández N et al (1996) Regional differences in the arterial response to vasopressin: role of endothelial nitric oxide. Br J Pharmacol 118(7):1848–1854
135. Thibonnier M, Conarty DM, Preston JA et al (1998) Molecular pharmacology of human vasopressin receptors. Adv Exp Med Biol 449:251–276
136. Zenteno-Savin T, Sada-Ovalle I, Ceballos G, Rubio R (2000) Effects of arginine vasopressin in the heart are mediated by specific intravascular endothelial receptors. Eur J Pharmacol 410(1):15–23
137. Boarder MR, Weisman GA, Turner JT, Wilkinson GF (1995) G protein-coupled P2 purinoceptors: from molecular biology to functional responses. Trends Pharmacol Sci 16(4):133–139
138. Noguera I, Medina P, Segarra G et al (1997) Potentiation by vasopressin of adrenergic vasoconstriction in the rat isolated mesenteric artery. Br J Pharmacol 122(3):431–438
139. Emori T, Hirata Y, Ohta K et al (1991) Cellular mechanism of endothelin-1 release by angiotensin and vasopressin. Hypertension 18(2):165–170
140. Caramelo C, Okada K, Tsai P et al (1990) Interaction of arginine vasopressin and angiotensin II on Ca2+ in vascular smooth muscle cells. Kidney Int 38(1):47–54
141. Iversen BM, Arendshorst WJ (1998) ANG II and vasopressin stimulate calcium entry in dispersed smooth muscle cells of preglomerular arterioles. Am J Phys 274(3 Pt 2):F498–F508
142. Bussien JP, Waeber B, Nussberger J et al (1984) Does vasopressin sustain blood pressure of normally hydrated healthy volunteers? Am J Phys 246(1 Pt 2):H143–H147
143. Waeber B, Nussberger J, Hofbauer KG et al (1986) Clinical studies with a vascular vasopressin antagonist. J Cardiovasc Pharmacol 8(Suppl 7):S111–S116
144. Papadoliopoulou-Diamandopoulou N, Papagalanis N, Gavras I, Gavras H (1987) Vasopressin in end-stage renal disease: relationship to salt, catecholamines and renin activity. Clin Exp Hypertens A 9(7):1197–1208
145. Thibonnier M, Kilani A, Rahman M et al (1999) Effects of the nonpeptide V(1) vasopressin receptor antagonist SR49059 in hypertensive patients. Hypertension 34(6):1293–1300
146. Okada H, Suzuki H, Kanno Y, Saruta T (1995) Effect of nonpeptide vasopressin receptor antagonists on developing, and established DOCA-salt hypertension in rats. Clin Exp Hypertens 17(3):469–483
147. Okada H, Suzuki H, Kanno Y et al (1994) Chronic and selective vasopressin blockade in spontaneously hypertensive rats. Am J Phys 267(6 Pt 2):R1467–R1471
148. Lang RE, Rascher W, Unger T, Ganten D (1981) Reduced content of vasopressin in the brain of spontaneously hypertensive as compared to normotensive rats. Neurosci Lett 23(2):199–202
149. Rascher W, Lang RE, Unger T et al (1982) Vasopressin in brain of spontaneously hypertensive rats. Am J Phys 242(4):H496–H499
150. Han SY, Bouwer GT, Seymour AJ et al (2015) Induction of hypertension blunts baroreflex inhibition of vasopressin neurons in the rat. Eur J Neurosci 42(9):2690–2698

151. Kim Y-B, Kim YS, Kim WB et al (2013) GABAergic excitation of vasopressin neurons: possible mechanism underlying sodium-dependent hypertension. Circ Res 113(12):1296–1307
152. Crofton JT, Share L, Shade RE et al (1979) The importance of vasopressin in the development and maintenance of DOC-salt hypertension in the rat. Hypertension 1(1):31–38
153. DiPette DJ, Gavras I, North WG et al (1982) Vasopressin in salt-induced hypertension of experimental renal insufficiency. Hypertension 4(3 Pt 2):125–130
154. Hinojosa C, Shade RE, Haywood JR (1986) Plasma vasopressin concentration in high sodium renal hypertension. J Hypertens 4(5):529–534
155. Rascher W, Lang RE, Taubitz M et al (1981) Vasopressin-induced increase in total peripheral resistance in deoxycorticosterone acetate hypertensive rats is buffered by the baroreceptor reflex. Clin Sci 61(Suppl 7):153s–156s
156. De Bold AJ, Borenstein HB, Veress AT, Sonnenberg H (1981) A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci 28(1):89–94
157. Flynn TG, de Bold ML, de Bold AJ (1983) The amino acid sequence of an atrial peptide with potent diuretic and natriuretic properties. Biochem Biophys Res Commun 117(3):859–865
158. Sudoh T, Kangawa K, Minamino N, Matsuo H (1988) A new natriuretic peptide in porcine brain. Nature 332(6159):78–81
159. Sudoh T, Minamino N, Kangawa K, Matsuo H (1990) C-type natriuretic peptide (CNP): a new member of natriuretic peptide family identified in porcine brain. Biochem Biophys Res Commun 168(2):863–870
160. Lang RE, Thölken H, Ganten D et al (1985) Atrial natriuretic factor—a circulating hormone stimulated by volume loading. Nature 314(6008):264–266
161. Volpe M (2014) Natriuretic peptides and cardio-renal disease. Int J Cardiol 176(3):630–639
162. Volpe M, Carnovali M, Mastromarino V (2016) The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment. Clin Sci 130(2):57–77
163. Wu F, Yan W, Pan J et al (2002) Processing of pro-atrial natriuretic peptide by corin in cardiac myocytes. J Biol Chem 277(19):16900–16905
164. Semenov AG, Tamm NN, Seferian KR et al (2010) Processing of pro-B-type natriuretic peptide: furin and corin as candidate convertases. Clin Chem 56(7):1166–1176
165. Komatsu Y, Nakao K, Suga S et al (1991) C-type natriuretic peptide (CNP) in rats and humans. Endocrinology 129(2):1104–1106
166. Wu C, Wu F, Pan J et al (2003) Furin-mediated processing of Pro-C-type natriuretic peptide. J Biol Chem 278(28):25847–25852
167. Potter LR, Abbey-Hosch S, Dickey DM (2006) Natriuretic peptides, their receptors, and cyclic guanosine monophosphate-dependent signaling functions. Endocr Rev 27(1):47–72
168. Müller D, Schulze C, Baumeister H, Buck F, Richter D (1992) Rat insulin-degrading enzyme: cleavage pattern of the natriuretic peptide hormones ANP, BNP, and CNP revealed by HPLC and mass spectrometry. Biochemistry 31(45):11138–11143
169. Levin ER, Gardner DG, Samson WK (1998) Natriuretic peptides. N Engl J Med 339(5):321–328
170. Saito Y (2010) Roles of atrial natriuretic peptide and its therapeutic use. J Cardiol 56(3):262–270
171. Harris PJ, Thomas D, Morgan TO (1987) Atrial natriuretic peptide inhibits angiotensin-stimulated proximal tubular sodium and water reabsorption. Nature 326(6114):697–698
172. Rohmeiss P, Demmert G, Rettig R, Unger T (1989) Centrally administered atrial natriuretic factor inhibits central angiotensin-induced natriuresis. Brain Res 502(1):198–203
173. Unger T, Badoer E, Gareis C et al (1990) Atrial natriuretic peptide (ANP) as a neuropeptide: interaction with angiotensin II on volume control and renal sodium handling. Br J Clin Pharmacol 30(Suppl 1):83S–88S
174. Charles CJ, Espiner EA, Richards AM et al (1996) Comparative bioactivity of atrial, brain, and C-type natriuretic peptides in conscious sheep. Am J Phys 270(6 Pt 2):R1324–R1331
175. Franco-Saenz R, Somani P, Mulrow PJ (1992) Effect of atrial natriuretic peptide (8-33-Met ANP) in patients with hypertension. Am J Hypertens 5(5 Pt 1):266–275

176. Lazzeri C, Franchi F, Porciani C et al (1995) Systemic hemodynamics and renal function during brain natriuretic peptide infusion in patients with essential hypertension. Am J Hypertens 8(8):799–807
177. Cargill RI, Struthers AD, Lipworth BJ (1995) Comparative effects of atrial natriuretic peptide and brain natriuretic peptide on the aldosterone and pressor responses to angiotensin II in man. Clin Sci 88(1):81–86
178. Gupta DK, Wang TJ (2015) Natriuretic peptides and cardiometabolic health. Circ J 79(8):1647–1655
179. Feng JA, Perry G, Mori T et al (2003) Pressure-independent enhancement of cardiac hypertrophy in atrial natriuretic peptide-deficient mice. Clin Exp Pharmacol Physiol 30(5–6):343–349
180. Knowles JW, Esposito G, Mao L et al (2001) Pressure-independent enhancement of cardiac hypertrophy in natriuretic peptide receptor A-deficient mice. J Clin Invest 107(8):975–984
181. Barbee RW, Perry BD, Ré RN et al (1994) Hemodynamics in transgenic mice with overexpression of atrial natriuretic factor. Circ Res 74(4):747–751
182. Fujita S, Shimojo N, Terasaki F et al (2013) Atrial natriuretic peptide exerts protective action against angiotensin II-induced cardiac remodeling by attenuating inflammation via endothelin-1/endothelin receptor A cascade. Heart Vessel 28(5):646–657
183. Pan Y, Zhu W, Ma J et al (2011) Therapeutic effects of continuous infusion of brain natriuretic peptides on postmyocardial infarction ventricular remodelling in rats. Arch Cardiovasc Dis 104(1):17–28
184. Obata H, Yanagawa B, Tanaka K et al (2007) CNP infusion attenuates cardiac dysfunction and inflammation in myocarditis. Biochem Biophys Res Commun 356(1):60–66
185. Kapoun AM, Liang F, O'Young G et al (2004) B-type natriuretic peptide exerts broad functional opposition to transforming growth factor-beta in primary human cardiac fibroblasts: fibrosis, myofibroblast conversion, proliferation, and inflammation. Circ Res 94(4):453–461
186. Soeki T, Kishimoto I, Okumura H et al (2005) C-type natriuretic peptide, a novel antifibrotic and antihypertrophic agent, prevents cardiac remodeling after myocardial infarction. J Am Coll Cardiol 45(4):608–616
187. McKie PM, Ichiki T, Burnett JC (2012) M-atrial natriuretic peptide: a novel antihypertensive protein therapy. Curr Hypertens Rep 14(1):62–69
188. McKie PM, Cataliotti A, Ichiki T et al (2014) M-atrial natriuretic peptide and nitroglycerin in a canine model of experimental acute hypertensive heart failure: differential actions of 2 cGMP activating therapeutics. J Am Heart Assoc 3(1):e000206
189. Burnett JC, McKie P, Heublein D et al (2015) MANP: a novel particulate guanylyl cyclase A receptor/cGMP activator for resistant hypertension: preliminary first in human clinical trial results. BMC Pharmacol Toxicol 16(Suppl 1):A3
190. Schweitz H, Vigne P, Moinier D et al (1992) A new member of the natriuretic peptide family is present in the venom of the green mamba (Dendroaspis angusticeps). J Biol Chem 267(20):13928–13932
191. Von Lueder TG, Krum H (2015) New medical therapies for heart failure. Nat Rev Cardiol 12(12):730–740
192. Tummala R, Bhadra R, Gupta A, Ghosh RK (2016) Combined neprilysin and RAS inhibition in cardiovascular diseases: a review of clinical studies. J Cardiovasc Pharmacol. doi:10.197/FJC.0000000000000402
193. Rouleau JL, Pfeffer MA, Stewart DJ et al (2000) Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. Lancet 356(9230):615–620
194. Gu J, Noe A, Chandra P et al (2010) Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). J Clin Pharmacol 50(4):401–414
195. Kario K, Sun N, Chiang F-T et al (2014) Efficacy and safety of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, in Asian patients with hypertension: a randomized, double-blind, placebo-controlled study. Hypertension 63(4):698–705
196. Jhund PS, Claggett B, Packer M et al (2014) Independence of the blood pressure lowering effect and efficacy of the angiotensin receptor neprilysin inhibitor, LCZ696, in patients with heart failure with preserved ejection fraction: an analysis of the PARAMOUNT trial. Eur J Heart Fail 16(6):671–677

# Vasoactive Peptides

# 8

Juan Carlos Yugar-Toledo, Ana Paula C. Faria, and Heitor Moreno

## Abbreviations

| | |
|---|---|
| ACE | Angiotensin-converting enzyme |
| Ang I | Angiotensin I |
| Ang II | Angiotensin II |
| Ang III | Angiotensin III |
| Ang IV | Angiotensin IV |
| ANP | Atrial natriuretic peptide |
| $AT_1R$ | Angiotensin II type 1 receptor |
| $AT_2R$ | Angiotensin II type 2 receptor |
| AVP | Vasopressin |
| B1 | Bradykinin type 1 receptor |
| B2 | Bradykinin type 2 receptor |
| BNP | Brain natriuretic peptide |
| CD8 | Cluster of differentiation 8 |
| CD-80 | Cluster of differentiation 80 |
| CD-86 | Cluster of differentiation 86 |
| DNA | Deoxyribonucleic acid |
| ERK-1 | Extracellular signal-regulated kinases types 1 |
| ERK-2 | Extracellular signal-regulated kinases types 2 |
| Hsp27 | Heat shock protein 27 |
| IFN-γ | Interferon gamma |

J.C. Yugar-Toledo
São José do Rio Preto Medicine Faculty—FAMERP, São José do Rio Preto, Sao Paulo, Brazil

A.P.C. Faria • H. Moreno (✉)
Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas, Brazil
e-mail: hmoreno@uol.com.br



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_8

| | |
|---|---|
| IL-1β | Interleukin-1β |
| IL-23 | Interleukin-23 |
| IL-6 | Interleukin-6 |
| LVH | Left ventricular hypertrophy |
| MAPK | Mitogen-activated protein kinase |
| MMP | Metalloproteinase |
| MMP-2 | Metalloproteinase-2 |
| MMP-9 | Metalloproteinase-9 |
| MMPs | Metalloproteinases |
| NO | Nitric oxide |
| NPY | Neuropeptide Y |
| NTS | Nucleus of the tractus solitarius |
| $PGI_2$ | Prostacyclin |
| RAAS | Renin-angiotensin-aldosterone system |
| ROS | Reactive oxygen species |
| TGF β-1 | Transforming growth factor β-1 |
| TIMPs | Tissue inhibitor of metalloproteinases |

## 8.1 Introduction

Vasoactive peptides have an important role in vascular tone regulation, and their imbalance determines high blood pressure levels and cardiovascular remodeling in arterial hypertension: lack of balance in the renin-angiotensin-aldosterone system (RAAS) as well as in its receptors ($AT_1R$ and $AT_2R$), deactivation of the kallikrein-kinin vasodilator products, decreases of cardiac natriuretic peptides (ANP and BNP) and vasopressin (AVP), and vasoconstriction induced by neuropeptide Y (NPY) are the most significant disorders related to the pathophysiology of vessel inflammation, increased activity of vascular growth factors, and myocardial damage in this complex disease. This chapter will approach the structure, biosynthesis, and pathophysiological mechanisms involved in both human hypertension and cardiovascular impairment in the presence of these peptide system alterations. Also, in spite of not being peptide systems, but correlated to those described here, metalloproteinases, adipocytokines, and immune activation deserve some general considerations because of their interactions with the pathophysiology of hypertensive heart disease.

## 8.2 Classical Renin-Angiotensin-Aldosterone System

Activation of the renin-angiotensin-aldosterone system (RAAS) results in the release of several vasoactive peptides. The classical cascade of this system begins with the synthesis of angiotensinogen, a globulin of 14 amino acids produced by the liver and distributed in the bloodstream. Angiotensinogen undergoes proteolytic conversion to angiotensin I (Ang I) by the action of renin, a proteolytic enzyme synthesized in the

juxtaglomerular apparatus of the kidneys. Renin is considered a key enzyme in RAAS activation as it acts on prorenin/renin receptors, which are transmembrane receptors highly expressed in mesangial cells, adipocytes, heart cells, brain cells, and the vascular smooth muscle [1, 2]. Prorenin accounts for 70–90% of the circulating renin in normal subjects, and its binding to prorenin/renin receptors promotes an increase in the catalytic conversion of angiotensinogen to Ang I [3, 4]. Also, the binding of prorenin to its receptor activates an intracellular signaling cascade with the activation of mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinases types 1 and 2 (ERK-1 and ERK-2) and the phosphorylation of heat shock protein 27 (Hsp27), which promotes an increase in the synthesis of DNA, collagen type 1, fibronectin, and transforming growth factor β-1 (TGF β-1). All of these are important mediators of tissue remodeling and the fibrotic process [4].

The inactive decapeptide Ang I, formed by the cleavage of angiotensinogen, is converted into an octapeptide vasoconstrictor, angiotensin II (Ang II), by the action of the angiotensin-converting enzyme (ACE). ACE is a dipeptidyl carboxypeptidase found mainly in the endothelium of the pulmonary capillaries (40%) and other vascular beds (60%) such as the heart and coronary arteries [5, 6]. This enzyme also takes part in the kallikrein-kinin system promoting the inactivation of bradykinin, a potent vasodilator [7–9]. The reduction of bradykinin stimulation on its type 1 (B1) and type 2 (B2) receptors decreases the release of NO from endothelial cells and the production of arachidonic acid from phospholipase $A_2$, the latter leading to less formation of other vasodilators including prostacyclin ($PGI_2$) [10–13]. Even though the RAAS cascade is widely distributed throughout the body, the main source of renin is the juxtaglomerular apparatus while ACE is present on the cell surface of endothelial cells, especially in the lungs. The current view is that >90% of tissue Ang II is synthesized locally and not taken up from plasma but depends on renin and largely, if not completely, on hepatic angiotensinogen [14, 15].

## 8.3 Angiotensin II and AT Receptors ($AT_1R$ and $AT_2R$)

Ang II acts on Ang II type 1 ($AT_1R$) and Ang II type 2 ($AT_2R$) receptors, two receptors with opposite actions. The binding of Ang II to the $AT_1R$ receptor causes contraction of vascular smooth muscle cells (vasoconstriction), interstitial fibrosis, cell growth, cell migration, and release of aldosterone from the adrenal gland [16]. Aldosterone apart from raising the blood pressure is implicated in the pathogenesis of cardiac hypertrophy, fibrosis, cardiac and vascular remodeling, ventricular arrhythmias, and atrial fibrillation [17–20]. Recent studies show that Ang II seems to form oxygen free radicals besides being present in inflammation processes, atherosclerotic disease, and vascular aging [21]. $AT_1R$ is found in large numbers in the kidneys, heart, liver, vessels, and brain. Ang II via $AT_2R$ promotes protective actions by inducing vasodilation and the release of NO and inhibiting cell growth (Fig. 8.1).

It is well known that hyperactivity of the sympathetic nervous system, another pivotal mechanism present in hypertension, leads to increased activity of renal beta-receptors resulting in the conversion of prorenin to the active form of renin, thus triggering activation of the RAAS cascade.

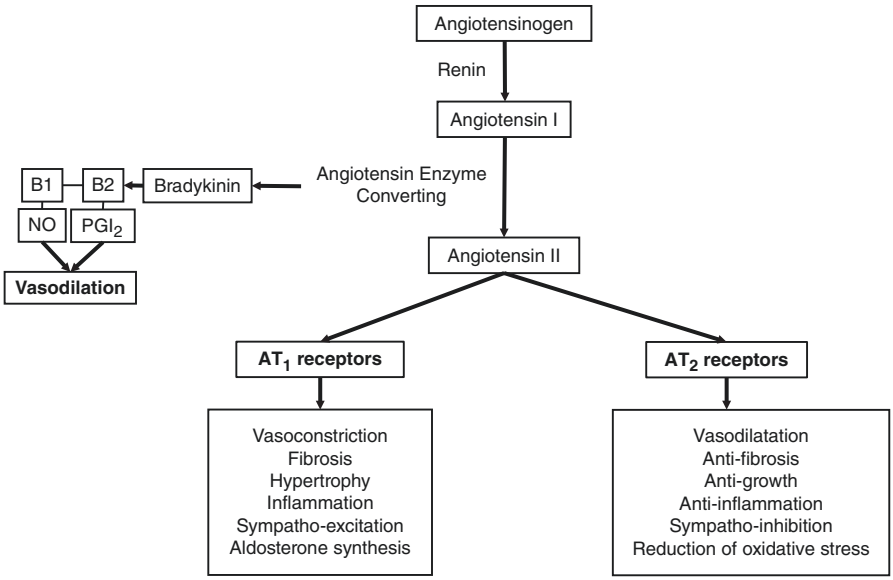



**Fig. 8.1** Activation of classical renin-angiotensin-aldosterone system (RAAS) cascade results in vasoconstriction, fibrosis, hypertrophy, inflammation, and sympathoexcitation and increases blood pressure and target organ damage. Angiotensin I (Ang I), formed by the cleavage of angiotensinogen under the action of renin, is converted into angiotensin II (Ang II) by the action of the ACE. Furthermore, activation of ACE promotes the inactivation of bradykinin. Bradykinin acts on type 1 (B1) and type 2 (B2) receptors, both of which stimulate the release of NO from endothelial cells. B2 receptors activate phospholipase $A_2$ that releases arachidonic acid leading to the formation of other vasodilators including prostacyclin. Ang II acts on Ang II type 1 ($AT_1R$) and Ang II type 2 ($AT_2R$) receptors, two receptors with opposite actions

Finally, the effects of angiotensin II (Ang II), via $AT_1R/AT_2R$, on vascular remodeling and constriction/vasodilation involve transforming growth factor-β (TGF-β) signaling by the TGF-β receptor and mitogen-activated protein kinase (MAPK) activation after $AT_1R$ stimulation. These mechanisms regulate the transcription of target genes such as those in matrix metalloproteinases (MMPs), plasminogen activator inhibitor-1 (PAI-1), and connective tissue growth factor (CTGF) resulting in cardiac and vascular proliferation, increased extracellular matrix production and fibrosis, differentiation, and inflammation. In summary, through these complex and imbricated intracellular systems, cardiovascular remodeling and target organ damage are due to the activation of pathways that promote proliferation, migration, apoptosis, and balance between the synthesis/degradation of the extracellular matrix of cardiac and vascular proteins [22].

## 8.4 Nonclassical Renin-Angiotensin-Aldosterone Pathways

Some recent RAAS pathways are composed by angiotensin 1-7 (Ang 1-7), angiotensin 1-9 (Ang 1-9), angiotensin 1-12 (Ang 1-12), angiotensin III (Ang III), angiotensin IV (Ang IV), and other new components of this system. The actions of these

pathways are opposite to those of the classical RAAS pathway promoting vasodilation by the release of vasodilator substances such as NO and prostaglandins and causing natriuresis and reducing oxidative stress [23].

Ang II, when cleaved by angiotensin-converting enzyme 2 (ACE-2) and other endopeptidases, produces Ang 1-7. This heptapeptide (Ang 1-7) when bound to its MAS receptor, a G protein (GPCR), has a vasodilating effect potentiating bradykinin-induced vasodilation, and thus it plays an important counter-regulation role to the vasoconstrictor effect of Ang II. Other beneficial effects of Ang 1-7 have also been described, such as protection against heart failure, reduction of thrombosis, interstitial fibrosis, cell proliferation and myocardial hypertrophy, and modulation of the production of arginine-vasopressin peptide AVP (antidiuretic hormone—ADH) [24].

Ang 1-9 is found in the plasma of healthy individuals and in patients taking ACE inhibitors or $AT_1R$ blockers. Experimentally, increased plasma concentrations of Ang 1-9 were demonstrated in the cardiac tissue of rats after heart attacks. The main product of the degradation of Ang II in human hearts is Ang 1-9. It is probably formed by the action of chymases, ACE, or carboxypeptidase A. Furthermore, the main cleavage product of Ang I in human platelets is Ang 1-9 and not Ang II as was thought [25]. Recently, protective effects of Ang 1-9 against cardiac and vascular remodeling have been described [26].

Ang 1-12 is described as a pro-peptide resulting from the breakdown of angiotensinogen; now it is considered a precursor to the formation of tissue angiotensin. Some studies have shown that this angiotensin may be a functional precursor in the formation of Ang I in the absence of circulating renin [27]. Ang 1-12 has been detected in the intestine, liver, lung, adrenal glands, heart, brain, and pancreas at higher levels than the levels of Ang I [28]. One of the observations that supports the hypothesis that Ang 1-12 can act as an endogenous substrate for the production of Ang II came from the fact that its vasoconstrictor effect is prevented by blocking the RAAS with ACE inhibitors or Ang II receptor blockers (ARBs) in experimental models [29].

Studies show that the conversion of Ang1-12 into Ang II is mediated by ACE in the systemic circulation and by chymase in the heart [30, 31]. Divergence from Ang1-12 metabolic pathways may be highly tissue specific, as one report suggested that neprilysin could also act as Ang 1-12 convertase in the kidney. Neprilysin is a metalloproteinase member of the M13 family of proteases which also includes endothelin-converting enzyme (ECE). Neprilysin activity in the kidney is much higher than the activity of renal ACE, suggesting that neprilysin converts Ang 1-12 into Ang I in the kidney.

New findings demonstrate the existence of additional alternate mechanisms for the generation of angiotensin peptide upstream from Ang I. Chymase is the critical Ang II-forming enzyme in humans, and so renin is not the only enzyme that generates Ang II; this increases the complexity of the RAAS [27].

Ang A is a peptide of the RAAS synthesized by enzymatic decarboxylation of Ang II. It has an $AT_1R$-dependent vasoconstrictor effect similar to Ang II, increasing the blood pressure, promoting coronary vasoconstriction, and reducing the myocardial contractility force and heart rate. The importance of the participation of Ang A in the RAAS highlights the significance of the observation of the limited effects of $AT_1R$ blockers [32].

Almandine is a recently identified peptide of the RAAS, with biological activity similar to Ang 1-7; it has a vasodilating effect and an action on Mas-related gene D (MrgD) receptors of the central nervous system. Almandine is formed by the action of ACE-2 on Ang A, thus reinforcing the important role of ACE-2 in the RAAS. Experimentally, almandine has antihypertensive and cardioprotective effects (Fig. 8.2) [33].

## 8.5 Physiological Role of Angiotensin III and IV

In physiological conditions, Ang II under the action of aminopeptidase A is converted into Ang III. Circulating Ang III is found at low concentrations; however, it exists in various organs, especially in the brain, kidneys, and heart [34].

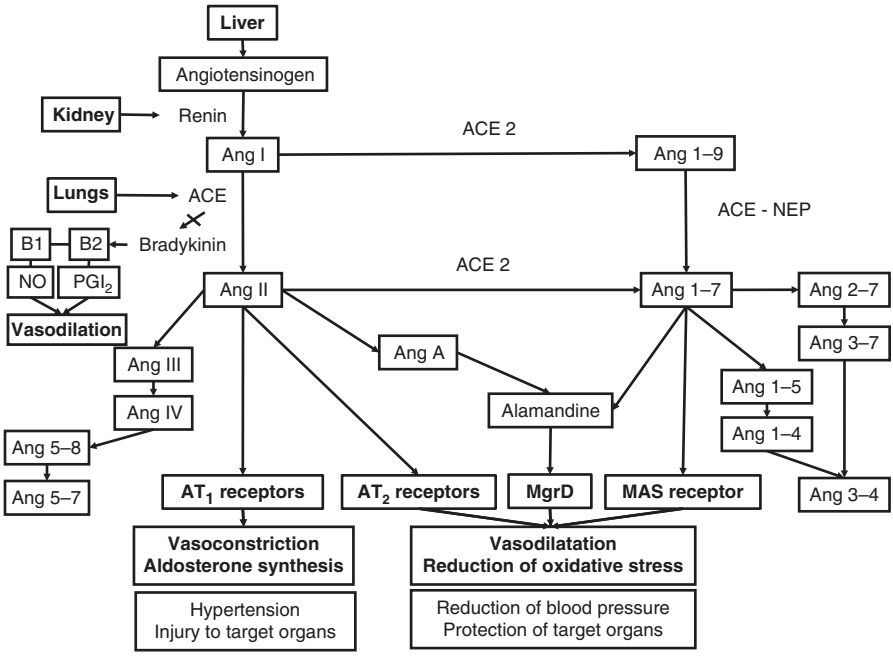



**Fig. 8.2** Nonclassical renin-angiotensin-aldosterone system (RAAS) pathways—composed by angiotensin 1-7 (Ang 1-7), angiotensin 1-9 (Ang 1-9), angiotensin 1-12 (Ang 1-12), angiotensin III (Ang III), angiotensin IV (Ang IV), and other new components of this system. The actions of these pathways are opposite to those of the classical RAAS pathway promoting vasodilation by the release of vasodilator substances such as NO and prostaglandins and causing natriuresis and reducing oxidative stress. Ang II, when cleaved by angiotensin-converting enzyme 2 (ACE-2) and other endopeptidases (neutral endopeptidases—NEP), produces Ang 1-7, which, when bound to its MAS receptor, a G protein (GPCR), has a vasodilating effect potentiating bradykinin-induced vasodilation. Other beneficial effects of Ang 1-7 include protection against heart failure, the reduction of thrombosis, interstitial fibrosis, cell proliferation and myocardial hypertrophy, and modulation of the production of arginine-vasopressin peptide AVP. Alamandine is a recently identified peptide with biological activity similar to Ang 1-7; it acts on Mas-related gene D (MrgD) receptors of the central nervous system. Alamandine is formed by the action of ACE-2 from angiotensin A

Ang III is a potent inducer of AVP production, increasing central sympathetic activity and promoting the release of aldosterone and causing vasoconstriction in a manner similar to Ang II. It is also known that it acts on the solitary tract/vagal complex causing changes in baroreflex sensitivity in a similar way to Ang II. One of the peculiarities of Ang III is that its production is not completely blocked by ACE inhibitors as Ang III is produced by other pathways. To date, there is no evidence for a specific Ang III receptor. In the kidney, Ang III normally binds to the $AT_1R$ and $AT_2R$ receptors, and the reported natriuretic and anti-natriuretic effects of Ang III may be dose dependent on whether the $AT_1R$ or $AT_2R$ receptor is activated [35, 36] (Fig. 8.3).

The major endogenous receptor ligand for $AT_2R$-mediated natriuretic responses appears to be Ang III and not Ang II [37]. Recent studies have demonstrated that Ang II must be metabolized to Ang III by aminopeptidase A in order to induce natriuresis and that inhibition of aminopeptidase N increases intrarenal Ang III and Ang III-induced natriuresis [38].

Ang IV is formed from Ang III by the action of aminopeptidase N. Ang IV is a biologically active peptide that became of great interest after insulin-regulated

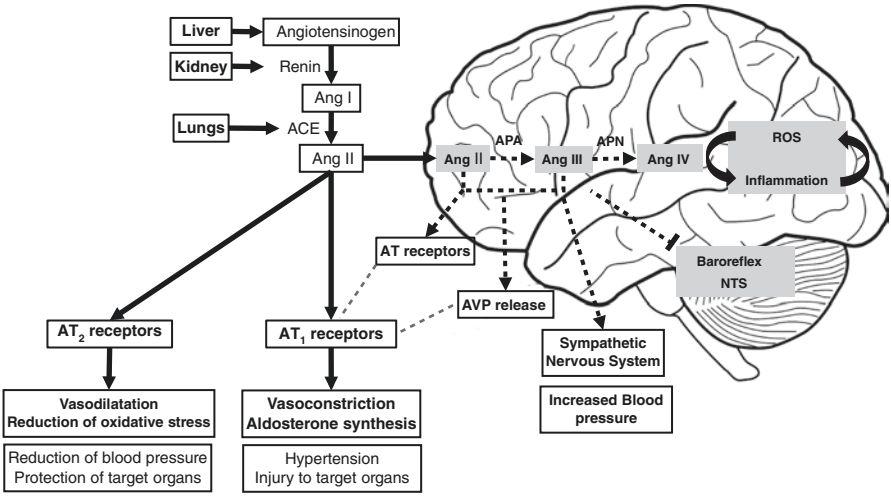



**Fig. 8.3** The brain renin-angiotensin-aldosterone system (RAAS) pathway. In physiological conditions, Ang II under the action of aminopeptidase A (APA) is converted into Ang III especially in the brain, kidneys, and heart. Ang III is a potent inducer of arginine-vasopressin peptide (AVP) production, increases central sympathetic activity, and releases and inhibits baroreflex, thereby increasing blood pressure, releasing aldosterone, and causing vasoconstriction in a manner similar to Ang II. One of the peculiarities of Ang III is that its production is not completely blocked by ACE inhibitors as Ang III is produced by other pathways. Ang IV is formed from Ang III by the action of aminopeptidase N. Ang IV is a biologically active peptide that became of great interest after insulin-regulated aminopeptidase (IRAP) was described. Ang IV has a binding site probably for an AT4 receptor. The solid bold arrows indicate RAAS classical pathways, the dotted arrows indicate brain RAAS pathways, the dotted gray lines indicate cross talk between the systems, and the solid bold line indicates inhibition of baroreflex. *ROS* reactive oxygen species, *NTS* nucleus of the tractus solitarius

aminopeptidase (IRAP) was described. Ang IV has a binding site probably for an AT4 receptor [39]. With an important role in cognitive function, renal function, and growth of cardiac fibroblasts and vascular smooth muscle cells, Ang IV, when bound to its receptor, causes renal vasodilation and increased expressions of plasminogen activator inhibitor-1 (PAI-1), interleukin-6, intercellular adhesion molecules (ICAM-1), and tumor necrosis factor [40].

## 8.6 Cardiac Natriuretic Peptides (ANP and BNP)

After the initial description of the existence of natriuretic peptides with vasodilatory activity by De Bold et al. [41], atrial natriuretic (ANP) and brain natriuretic peptides (BNP) produced in atrial and ventricular cardiomyocytes were identified and considered cardiac natriuretic hormones (CHN) with endocrine, autocrine, and paracrine activity. Moreover, a natriuretic peptide, called C-type natriuretic peptide (CNP), is produced by endothelial cells, and a peptide named urodilatin, encoded by the same gene as ANP and with similar characteristics, is produced in kidney tubular cells and secreted in the urine.

The activity of the cardiac natriuretic hormone system depends on both the production/release of these peptides and the activation of inactive precursors (proANP and proBNP) in peripheral tissues and signal transduction by specific receptors.

Prohormones (proANP and proBNP), synthesized by cardiomyocytes, are cleaved into two fragments, a long inactive fragment which includes the NT peptide (NT-proANP and NT-proBNP) and a short active fragment (ANP and BNP). The proANP and proBNP are stored by atrial cardiomyocytes in secretory granules.

The main stimulus for the secretion/release of ANP and BNP is distension of the atrial and ventricular cardiomyocytes [42, 43]. However, endothelin-1, alpha-adrenergic agonists, and Ang II also stimulate the production/release of cardiac natriuretic peptides [44]. Furthermore, other mediators, such as vasopressin, glucocorticoids, thyroid hormones, steroids, and cytokines such as TNF-alpha and interleukin-1 and interleukin-6, can also stimulate the production and secretion of cardiac natriuretic peptides [45, 46]. NO has a regulatory role as it inhibits the production/release of these peptides. The involvement of glucagon-like peptide-1 (GLP-1) was recently implicated in the regulation of the production/release of ANP. This incretin secreted by endocrine cells in the small intestine stimulates insulin secretion in the pancreas. Consequently, GLP-1 analogs or dipeptidyl peptidase-4 inhibitors can help to control the blood pressure in diabetic patients [47]. The observation of the expression of GLP-1 receptor genes in the atria with subsequent activation promoted by the production/release of ANP suggests that the antihypertensive effect of GLP-1 receptor agonists is mediated by this pathway.

Cardiac natriuretic peptides (ANP and BNP) and CNP have similar biological effects including direct diuresis, natriuresis, vasodilation, and anti-inflammatory action on smooth muscle cells and cardiomyocytes [48] as well as a protective effect against vascular dysfunction and vascular remodeling [49]. These effects are mediated

by adenylate cyclase-coupled receptors (NPR-A) and guanylate cyclase-coupled receptors (NPR-B) which are widely distributed throughout the body, including in the kidneys, vascular smooth muscle, adrenal glands, brain, and heart. The biological effects of ANP and BNP are mediated by the NPR-A receptor, while the NPR-B receptor is linked to CNP signaling. A third specific receptor, the natriuretic peptide receptor C (NPR-C), which is not bound to guanylate cyclase, has the essential function of removing all natriuretic peptides (Fig. 8.4) [50].

Natriuretic peptides play an important role in maintaining blood pressure and blood volume [51]. These peptides regulate blood pressure by the direct relaxation of vascular smooth muscles, suppression of RAAS activity, reduced aldosterone secretion, reduced activation of the sympathetic system, and inhibition of endothelin-1 secretion. Intravascular volume control is obtained by directly influencing electrolyte balance via changes in endothelial permeability and the inhibition of

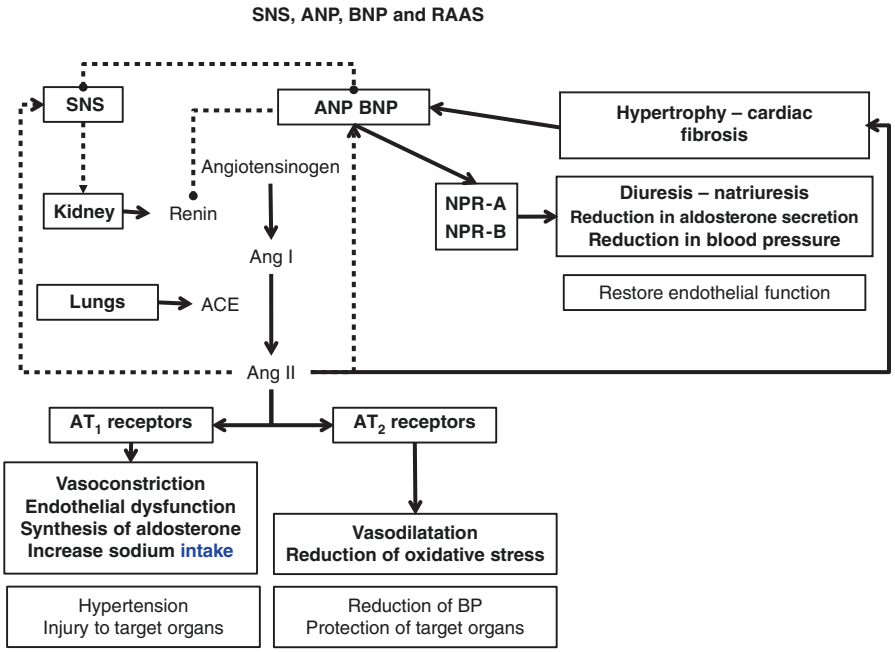



**Fig. 8.4** Schematic representation of the relationships in the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), atrial natriuretic peptide (ANP), and brain natriuretic peptide (BNP). *ACE* angiotensin-converting enzyme, *Ang* angiotensin, *ANP* atrial natriuretic peptide, *BNP* B-type natriuretic peptide, *BP* blood pressure, *NP* natriuretic peptide, *RAAS* renin-angiotensin-aldosterone system, *SNS* sympathetic nervous system. These peptides regulate blood pressure by the direct relaxation of vascular smooth muscles, suppression of RAAS activity, reduced aldosterone secretion, reduced activation of the sympathetic system, and inhibition of endothelin-1 secretion. Intravascular volume control is obtained by directly influencing electrolyte balance via changes in endothelial permeability and the inhibition of sodium reabsorption in the proximal and distal nephrons, resulting in natriuresis, diuresis, and reduction of intravascular volume and blood pressure. The solid lines indicate principal pathways, whereas the dotted lines indicate negative feedback

sodium reabsorption in the proximal and distal nephrons, resulting in natriuresis, diuresis, and reduction of intravascular volume and blood pressure. These changes in electrolyte balance are mediated by ANP and BNP. Moreover, ANP increases renal plasma flow and the glomerular filtration rate, thereby optimizing renal function. However, ANP changes the endothelial capillary permeability promoting redistribution of plasma proteins and fluid between the interstitial and intravascular spaces [52, 53]. These classical endocrine functions are important mechanisms of cardiac natriuretic peptides. Meanwhile, autocrine and paracrine activities involve the inhibition or reduction of cardiovascular remodeling, hypertrophy, fibrosis, and inflammation [54]. Both ANP and BNP participate in this protective mechanism against the actions of Ang II, endothelin-1, sympathetic activity, and inflammatory mediators that participate in cardiovascular remodeling and inflammation, playing an important role by neutralizing the effects of the activation of the RAAS and sympathetic nervous system.

Cardiac natriuretic peptides are cleared from circulation by endocytosis via NPR-C and by degradation by neprilysin (NEP), an endopeptidase expressed primarily in the kidneys, which is dependent on zinc bound to the membrane that hydrolyzes peptides on the amino side of hydrophobic residues. Neprilysin has a short NT domain, a cytoplasmic transmembrane helix, and a C-terminal extracellular domain with a zinc atom as the active site [55].

NEP has a high affinity for ANP and CNP and less affinity for BNP. However, NEP also degrades other vasoactive peptides both vasodilating peptides (such as substance P and bradykinin) and vasoconstrictors (such as Ang II and endothelin-1); therefore, it has an important role in maintaining the balance between vasodilator and vasoconstrictor peptides.

Knowledge of cardiovascular and renal effects of ANPs is an important therapeutic tool for hypertension and conditions associated with volume overload [55, 56]. Accordingly, improvements in the endogenous activity of these peptides and the inactivation of the degradation pathway by inhibiting NEP and blocking other components of the RAAS are alternatives to increase the activity of cardiac natriuretic peptides (Fig. 8.5).

## 8.7 Vasopressin (AVP)

AVP is synthesized and released by the neurohypophysis (posterior lobe of the pituitary gland) in response to reduced blood volume, a drop in blood pressure, or hypernatremia. AVP participates in the maintenance of body water, regulating the osmotic balance and blood pressure by influencing water excretion by the kidneys. Baroreceptors, located in the carotid sinus, aortic arch, and left atrium, detect blood pressure reductions and directly stimulate neurons located in the supraoptic and hypothalamic paraventricular nuclei promoting the release of AVP. Furthermore, hypothalamic osmoreceptors detect variations <1% in plasma osmolality and trigger the release of AVP with a consequent reduction of renal medullary flow that exerts a powerful antidiuretic effect and increases permeability to water in

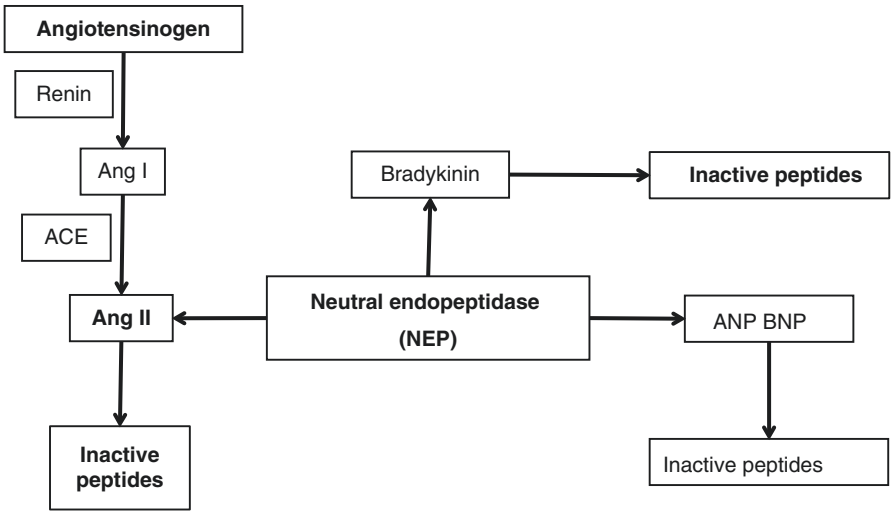



**Fig. 8.5** Schematic representation to show the central role of vasopeptidase inhibition for the metabolism of angiotensin II, bradykinin, and natriuretic peptides

collecting tubules [57]. Extrapituitary AVP production occurs in the sympathetic ganglia, kidney, and testis. The synthesis of AVP involves pre-pro-AVP and pro-AVP precursors that are cleaved by a cascade of enzymes including copeptin (CTproAVP) and neurophysin II [58].

AVP is also an important mediator of adaptive response to acute and chronic stress with the activation of the hypothalamic-pituitary-adrenal axis and sympathetic catecholaminergic system in response to stimuli such as physical stress and acute events involving reductions in blood pressure or blood volume. In these circumstances, the release of AVP exceeds its normal concentration by 100 to 1000 times [59].

The plasma half-life of AVP is 5–20 min, and clearance of AVP occurs through the kidney (50–70%) and to a lesser extent through the liver. Inactivation by circulating and endothelial endopeptidases and aminopeptidase also occurs. AVP acts on three types of receptors, V1a, V2, and V3 (V1b receptors) [60]. Acting on V1a receptors located in vascular smooth muscle cells, platelets, and smooth muscle of the uterus, AVP causes arteriolar vasoconstriction, while on V1a receptors, located in hepatocytes, it promotes glycogenolysis.

Activation of the V2 receptor is associated with an increase in the intracellular cyclic AMP concentration which increases the expression of aquaporin-2 channels in the apical membrane of the tubular cell of the distal nephron and subsequent reabsorption of water into the interstitium [61]. V3 receptors (also called V1b receptors) distributed in the anterior pituitary gland, brain, pancreas, and heart are involved in the secretion of the adrenocorticotropic hormone (ACTH), synthesis and release of insulin and glucagon, body temperature control, and neuromodulation of memory (Fig. 8.6).

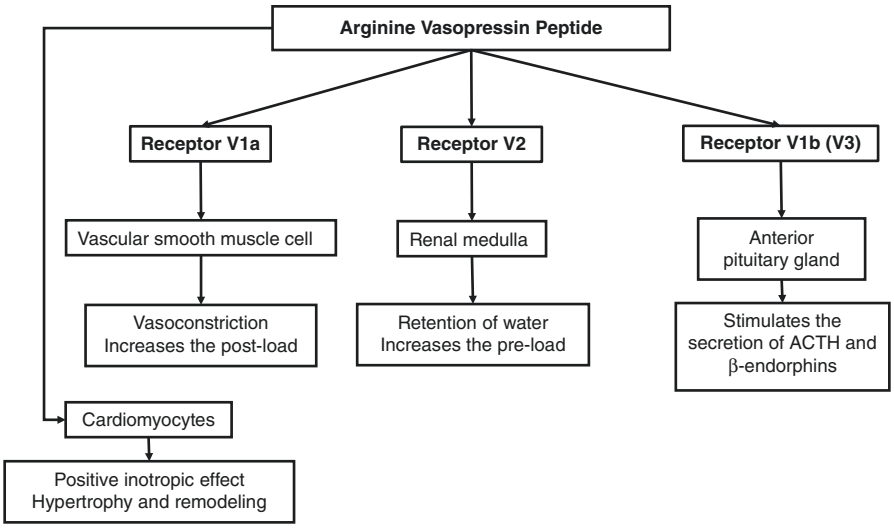



**Fig. 8.6** Arginine-vasopressin peptide (AVP): the role of each AVP subtype receptor on blood pressure and the kidney

AVP plasma concentrations are low (1–3 pg/mL) under physiological conditions; however, their concentration can reach 10–20 pg/mL promoting intense renal vasoconstriction with significant changes in the pressure/diuresis/natriuresis. However, AVP also promotes cutaneous, splanchnic, and coronary vasoconstriction and vasodilatation in the muscular territory, which together results in variable effects on the blood pressure. Important inhibitory effects of baroreflex and the sympathetic nervous system are observed with AVP resulting in attenuation of the potent vasoconstrictor effect of this peptide. Consequently, modest blood pressure elevations are seen with physiological elevations of AVP, and thus the antidiuretic effect of AVP occurs without modification of the induced diuresis pressure. It is noteworthy that in the absence of autonomic reflex mechanisms, the vasopressor effect of AVP is exacerbated. This situation is common in patients with diabetes and autonomic dysfunction, a condition in which a V1 receptor blocker causes significant reductions in blood pressure. Also interesting is the observation of the effect of blockade of AVP V1 receptors in individuals of African descent who respond better to this therapy than non-African descendants. The true role of AVP in hypertension is not fully understood as differences in AVP plasma levels are observed between men (30%) and women (7%). However, high AVP concentrations are found in patients with malignant hypertension, heart failure, and preeclampsia; in these water retention conditions, the redistribution of volume and regional flow can cause greater elevations in blood pressure [57, 62].

## 8.8 Neuropeptide Y

NPY is widely distributed in the central nervous system, including in the hypothalamus, ventrolateral region of the medulla oblongata (bulb), nucleus of the tractus solitarius, locus coeruleus, and preganglionic neurons of the spinal cord. It has an important inhibitory effect of sympathetic neurotransmission, and it is a mediator of the central leptin signaling pathway and potentiates the release of vasopressin in the neurohypophysis. By these mechanisms, NYP participates in the control of thirst, appetite, blood pressure, and the energy metabolism [63].

NPY, expressed in the sympathetic ganglia and the fibers that innervate blood vessels and the heart and kidneys, also has actions in the peripheral nervous system; it coexists with norepinephrine in peripheral neurons to promote a potent vasoconstrictor effect. The effects of NPY are mediated by the Y1, Y2, and Y5 receptors. NPY bound to Y1 receptors inhibits adenylate cyclase and increases in intracellular calcium. In the central nervous system, Y1 receptors are associated with hypotension, while peripheral stimulation via Y1 receptors causes vasoconstriction and potentiation of the vasoconstriction effects of norepinephrine, Ang II, and serotonin, particularly in small vessels of the coronary, cerebral, and splanchnic beds [64].

NPY generally acts on postsynaptic Y2 receptors reducing the concentration of intracellular calcium by the inhibition of N-type calcium channels in nerve endings. In the central nervous system, vascular bed, heart, and kidneys, NPY inhibits the release of neurotransmitters including norepinephrine and glutamate [65].

The stimulation of Y5 receptors by NPY promotes natriuresis and is involved in cardiovascular remodeling [66].

Increased plasma levels of NPY can be found in situations of exacerbated sympathetic activity such as stress, exercise, hemorrhage, and myocardial infarction. However, NPY, unlike other vasoactive peptides that cause vasoconstriction and an antidiuretic effect, promotes increased urine output, reducing the release of renin, increasing the release of ANP, and changing the function of the $Na^+/K^+$-ATPase pump in the proximal tubule of the nephron with marked diuretic and antihypertensive effects [67].

## 8.9 Non-Peptide Systems Related to Hypertensive Disease

### 8.9.1 Metalloproteinases

Matrix MMPs are a family of zinc-dependent proteases that are widely known to degrade the components of the extracellular matrix. Interestingly, many other roles of these enzymes, especially in the cardiovascular system, are now being extensively studied [68, 69]. However, whereas abnormal MMP levels have been

described in many conditions associated with increased cardiovascular risk [70–72], it is perplexing that there are inconsistent findings with regard to MMP levels in hypertensive patients. While some studies showed increased MMP levels/activity in hypertensive patients compared with normotensive controls [73–76], other studies showed similar levels or decreased levels. It is possible that the significant differences between studies may reflect a lack of the control of relevant factors that may modify MMP levels in patients including drug treatment and accompanying diseases, as well as pre-analytical issues, such as the use of inappropriate samples to assess circulating MMP levels.

The balance between MMPs and tissue inhibitor of metalloproteinases (TIMPs) is essential for cardiovascular remodeling [77, 78]. For example, MMP-2 and MMP-9 have also been associated with arterial hypertension by degradation of the extracellular matrix, elastin, and collagen type IV and are also involved in the breakdown of interstitial collagen types I, II, and III. Thus, elevated levels of MMPs can result in a change in the elastin/collagen ratio and a reduction in the elasticity of the vascular wall. On the other hand, increased activity of TIMPs is associated with reduced degradation of collagen type I, which plays an important role in the pathophysiology of hypertension as well as in resistance to antihypertensive medication [79–81].

### 8.9.2 Adipocytokines

Adipocytokines, such as adiponectin, resistin, and leptin, are hormones produced by the fatty tissue and may be involved in multiple pathologic conditions, including inflammation and arterial stiffness in hypertension. Interestingly, the RAAS components have been associated with adiponectin and resistin plasma concentrations, and one study demonstrated that aldosterone inhibits adiponectin expression and protein production in 3T3-L1 adipocytes, suggesting that adiponectin may mediate the action of aldosterone in insulin resistance and cardiovascular events [82]. Also noteworthy, patients with primary hyperaldosteronism demonstrated higher resistin levels and cardiac morphological changes, independently of the presence of metabolic syndrome, suggesting a possible aldosterone-mediated resistin role in patients with cardiovascular risk [83].

Besides its renal effects on decreasing natriuresis, leptin has additional detrimental effects in the cardiovascular system such as promoting atherosclerosis by stimulating monocyte migration inflammation and thrombosis processes, hypertrophy of cardiomyocytes, and myocardial extracellular matrix remodeling [84, 85]. Clinical trials have demonstrated that the majority of obese patients have increased levels of leptin accompanied by selective leptin resistance status that explains, at least partially, obesity-associated hypertension.

Resistin is a protein predominantly synthesized by macrophages, but it is also in the adipose tissue and is increased under inflammatory conditions [86]. Some studies demonstrated that levels of this adipokine are increased in obesity, insulin resistance, and hypertension [87]. However, these findings are conflicting and the lack of studies

has provided some challenges to achieve clear conclusions. Moreover, resistin showed proinflammatory properties by increasing secretion of cell adhesion molecules and other cytokines such as tumor necrosis factor-α and interleukin-6 [88].

Adiponectin is the most abundant adipokine produced by adipocytes. Low plasma levels of adiponectin are considered a predictor of cardiovascular outcomes in the general population and among patients with diabetes [89]. Moreover, it is associated with endothelial dysfunction, progression of left ventricular hypertrophy (LVH), and arterial stiffness [90]. Previous studies have shown that hypoadiponectinemia is an independent risk factor for hypertension and resistant hypertension and also predicts the development of hypertension in normotensive patients after adjustment for confounding factors [91]. Interestingly, the RAAS components have been associated with adiponectin regulation, and the direct effect of aldosterone on adipose tissue has been investigated. Patients with hyperaldosteronism have lower levels of adiponectin compared with hypertensive patients. Thus, pharmacologic strategies to increase adiponectin levels may be beneficial to prevent cardiovascular damage and metabolic disorders in hypertension.

### 8.9.3 Immune Activation

Vascular oxidative injury accompanies many common conditions associated with hypertension. Very recent experiments have defined a link between oxidative stress and immune activation in hypertension. These have shown that hypertension is associated with the formation of reactive oxygen species in dendritic cells that leads to the formation of gamma ketoaldehydes or isoketals. These rapidly adduct to protein lysines and are presented by dendritic cells as neoantigens that activate T cells and promote hypertension. Thus, cells of both the innate and adaptive immune systems contribute to dysfunction and end-organ damage in hypertension. Therapeutic interventions to reduce activation of these cells may prove beneficial in reducing end-organ damage and prevent the consequences of hypertension including myocardial infarction, heart failure, renal failure, and stroke [92].

In experimental models of hypertension, dendritic cells with highly oxidative proteins (isoketals) accumulated IL-6, IL-1β, and IL-23 and CD80 and CD86 costimulatory molecules. These "activated" dendritic cells promoted T cell, particularly $CD8^+$, proliferation, the production of IFN-γ and IL-17A, and hypertension. Reactive oxygen species scavengers such as tempol normalized blood pressure and prevented vascular inflammation, aortic stiffening, and hypertension, events associated with T-cell activation. Together, these results define a pathway linking vascular oxidant stress to immune activation and aortic stiffening and provide an insight into the systemic inflammation encountered in common vascular diseases such as hypertension [93].

Interestingly, plasma F2-isoprostanes, which are produced in concert with these oxidatively modified proteins, were found elevated in humans with treated hypertension and were markedly elevated in patients with resistant hypertension. These oxidative-modified proteins were also markedly elevated in circulating monocytes

from humans with hypertension. These data reveal that hypertension activates dendritic cells, in large part by promoting the formation of isoketals, and suggest that reducing isoketals has potential as a treatment strategy for this disease [94].

These translational findings correlating the immune system and hypertension may have clinical application in further clinical studies.

## 8.10 Final Considerations

Because of the diversity of local and systemic actions, interactions with other new and important blood pressure regulation systems as well as cardiovascular remodeling pathophysiology, further research, and better biological understanding of the vasoactive peptides constitute a cornerstone for future steps in hypertension therapy.

## References

1. Nguyen G, Delarue F, Burckle C, Bouzhir L, Giller T, Sraer JD (2002) Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. J Clin Invest 109(11):1417–1427
2. Atlas SA (2007) The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. J Manag Care Pharm 13(8 Suppl B):9–20
3. Nguyen G (2006) Renin/prorenin receptors. Kidney Int 69(9):1503–1506
4. Campbell DJ (2008) Critical review of prorenin and (pro)renin receptor research. Hypertension 51(5):1259–1264
5. Giestas A, Palma I, Ramos MH (2010) Renin-angiotensin-aldosterone system (RAAS) and its pharmacologic modulation. Acta Medica Port 23(4):677–688
6. Bernstein KE, Ong FS, Blackwell WL et al (2013) A modern understanding of the traditional and nontraditional biological functions of angiotensin-converting enzyme. Pharmacol Rev 65(1):1–46
7. Pellacani A, Brunner HR, Nussberger J (1994) Plasma kinins increase after angiotensin-converting enzyme inhibition in human subjects. Clin Sci (Lond) 87(5):567–574
8. Campbell DJ (1995) Angiotensin converting enzyme (ACE) inhibitors and kinin metabolism: evidence that ACE inhibitors may inhibit a kininase other than ACE. Clin Exp Pharmacol Physiol 22(12):903–911
9. Tom B, Dendorfer A, Danser AH (2003) Bradykinin, angiotensin-(1-7), and ACE inhibitors: how do they interact? Int J Biochem Cell Biol 35(6):792–801
10. Erdos EG, Marcic BM (2001) Kinins, receptors, kininases and inhibitors—where did they lead us? Biol Chem 382(1):43–47
11. Schmaier AH (2003) The kallikrein-kinin and the renin-angiotensin systems have a multilayered interaction. Am J Physiol Regul Integr Comp Physiol 285(1):R1–R13
12. Erdos EG, Tan F, Skidgel RA (2010) Angiotensin I-converting enzyme inhibitors are allosteric enhancers of kinin B1 and B2 receptor function. Hypertension 55(2):214–220
13. Sharma JN (2013) The kinin system in hypertensive pathophysiology. Inflammopharmacology 21(1):1–9
14. van Kats JP, Schalekamp MA, Verdouw PD et al (2001) Intrarenal angiotensin II: interstitial and cellular levels and site of production. Kidney Int 60(6):2311–2317
15. Matsusaka T, Niimura F, Shimizu A et al (2012) Liver angiotensinogen is the primary source of renal angiotensin II. J Am Soc Nephrol 23(7):1181–1189

16. Karnik SS, Unal H, Kemp JR et al (2015) International Union of Basic and Clinical Pharmacology. XCIX. Angiotensin receptors: interpreters of pathophysiological Angiotensinergic stimuli [corrected]. Pharmacol Rev 67(4):754–819
17. Rossi G, Boscaro M, Ronconi V, Funder JW (2005) Aldosterone as a cardiovascular risk factor. Trends Endocrinol Metab 16(3):104–107
18. Funder JW (2007) The role of aldosterone and mineralocorticoid receptors in cardiovascular disease. Am J Cardiovasc Drugs 7(3):151–157
19. Gaddam KK, Pimenta E, Husain S, Calhoun DA (2009) Aldosterone and cardiovascular disease. Curr Probl Cardiol 34(2):51–84
20. Nagata K (2008) Mineralocorticoid antagonism and cardiac hypertrophy. Curr Hypertens Rep 10(3):216–221
21. Chappell MC (2016) Biochemical evaluation of the renin-angiotensin system: the good, bad, and absolute? Am J Physiol Heart Circ Physiol 310(2):H137–H152
22. Hunyady L, Catt KJ (2006) Pleiotropic AT1 receptor signaling pathways mediating physiological and pathogenic actions of angiotensin II. Mol Endocrinol 20(5):953–970
23. Chappell MC (2012) Nonclassical renin-angiotensin system and renal function. Compr Physiol 2(4):2733–2752
24. Bader M (2013) ACE2, angiotensin-(1-7), and mas: the other side of the coin. Pflugers Arch 465(1):79–85
25. Kramkowski K, Mogielnicki A, Leszczynska A, Buczko W (2010) Angiotensin-(1-9), the product of angiotensin I conversion in platelets, enhances arterial thrombosis in rats. J Physiol Pharmacol 61(3):317–324
26. McKinney CA, Fattah C, Loughrey CM et al (2014) Angiotensin-(1-7) and angiotensin-(1-9): function in cardiac and vascular remodelling. Clin Sci (Lond) 126(12):815–827
27. Ferrario CM, Varagic J, Habibi J et al (2009) Differential regulation of angiotensin-(1-12) in plasma and cardiac tissue in response to bilateral nephrectomy. Am J Physiol Heart Circ Physiol 296(4):H1184–H1192
28. Jessup JA, Trask AJ, Chappell MC et al (2008) Localization of the novel angiotensin peptide, angiotensin-(1-12), in heart and kidney of hypertensive and normotensive rats. Am J Physiol Heart Circ Physiol 294(6):H2614–H2618
29. Ahmad S, Varagic J, Groban L et al (2014) Angiotensin-(1-12): a chymase-mediated cellular angiotensin II substrate. Curr Hypertens Rep 16(5):429
30. Ahmad S, Simmons T, Varagic J et al (2011) Chymase-dependent generation of angiotensin II from angiotensin-(1-12) in human atrial tissue. PLoS One 6(12):e28501
31. Ahmad S, Wei CC, Tallaj J et al (2013) Chymase mediates angiotensin-(1-12) metabolism in normal human hearts. J Am Soc Hypertens 7(2):128–136
32. Coutinho DC, Foureaux G, Rodrigues KD et al (2014) Cardiovascular effects of angiotensin a: a novel peptide of the renin-angiotensin system. J Renin-Angiotensin-Aldosterone Syst 15(4):480–486
33. Lautner RQ, Villela DC, Fraga-Silva RA et al (2013) Discovery and characterization of alamandine: a novel component of the renin-angiotensin system. Circ Res 112(8):1104–1111
34. Reaux-Le Goazigo A, Iturrioz X, Fassot C et al (2005) Role of angiotensin III in hypertension. Curr Hypertens Rep 7(2):128–134
35. Fournie-Zaluski MC, Fassot C, Valentin B et al (2004) Brain renin-angiotensin system blockade by systemically active aminopeptidase a inhibitors: a potential treatment of salt-dependent hypertension. Proc Natl Acad Sci U S A 101(20):7775–7780
36. Gao J, Marc Y, Iturrioz X et al (2014) A new strategy for treating hypertension by blocking the activity of the brain renin-angiotensin system with aminopeptidase A inhibitors. Clin Sci (Lond) 127(3):135–148
37. Padia SH, Kemp BA, Howell NL et al (2008) Conversion of renal angiotensin II to angiotensin III is critical for AT2 receptor-mediated natriuresis in rats. Hypertension 51(2):460–465
38. Carey RM, Padia SH (2013) Role of angiotensin AT(2) receptors in natriuresis: intrarenal mechanisms and therapeutic potential. Clin Exp Pharmacol Physiol 40(8):527–534

39. Vanderheyden PM (2009) From angiotensin IV binding site to AT4 receptor. Mol Cell Endocrinol 302(2):159–166
40. Demaegdt H, De Backer JP, Lukaszuk A et al (2012) Angiotensin IV displays only low affinity for native insulin-regulated aminopeptidase (IRAP). Fundam Clin Pharmacol 26(2):194–197
41. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H (1981) A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci 28(1):89–94
42. Liang F, Gardner DG (1999) Mechanical strain activates BNP gene transcription through a p38/NF-kappaB-dependent mechanism. J Clin Invest 104(11):1603–1612
43. Kuwahara K, Kinoshita H, Kuwabara Y et al (2010) Myocardin-related transcription factor a is a common mediator of mechanical stress- and neurohumoral stimulation-induced cardiac hypertrophic signaling leading to activation of brain natriuretic peptide gene expression. Mol Cell Biol 30(17):4134–4148
44. McGrath MF, de Bold AJ (2005) Determinants of natriuretic peptide gene expression. Peptides 26(6):933–943
45. Matsubara H, Hirata Y, Yoshimi H et al (1987) Effects of steroid and thyroid hormones on synthesis of atrial natriuretic peptide by cultured atrial myocytes of rat. Biochem Biophys Res Commun 145(1):336–343
46. Kawano H, Nagayoshi Y, Soejima H et al (2008) B-type natriuretic peptide after hormone therapy in postmenopausal women with chest pain and normal coronary angiogram. Menopause 15(2):352–356
47. Russell-Jones D, Gough S (2012) Recent advances in incretin-based therapies. Clin Endocrinol (Oxf) 77(4):489–499
48. Qian JY, Haruno A, Asada Y et al (2002) Local expression of C-type natriuretic peptide suppresses inflammation, eliminates shear stress-induced thrombosis, and prevents neointima formation through enhanced nitric oxide production in rabbit injured carotid arteries. Circ Res 91(11):1063–1069
49. Villar IC, Panayiotou CM, Sheraz A et al (2007) Definitive role for natriuretic peptide receptor-C in mediating the vasorelaxant activity of C-type natriuretic peptide and endothelium-derived hyperpolarising factor. Cardiovasc Res 74(3):515–525
50. Clerico A, Recchia FA, Passino C, Emdin M (2006) Cardiac endocrine function is an essential component of the homeostatic regulation network: physiological and clinical implications. Am J Physiol Heart Circ Physiol 290(1):H17–H29
51. Rubattu S, Sciarretta S, Valenti V et al (2008) Natriuretic peptides: an update on bioactivity, potential therapeutic use, and implication in cardiovascular diseases. Am J Hypertens 21(7):733–741
52. Woodard GE, Rosado JA (2008) Natriuretic peptides in vascular physiology and pathology. Int Rev Cell Mol Biol 268:59–93
53. Potter LR, Yoder AR, Flora DR et al (2009) Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. Handb Exp Pharmacol 191:341–366
54. Calvieri C, Rubattu S, Volpe M (2012) Molecular mechanisms underlying cardiac antihypertrophic and antifibrotic effects of natriuretic peptides. J Mol Med (Berl) 90(1):5–13
55. Mangiafico S, Costello-Boerrigter LC, Andersen IA et al (2013) Neutral endopeptidase inhibition and the natriuretic peptide system: an evolving strategy in cardiovascular therapeutics. Eur Heart J 34(12):886–893c
56. Volpe M (2014) Natriuretic peptides and cardio-renal disease. Int J Cardiol 176(3):630–639
57. Bakris G, Bursztyn M, Gavras I et al (1997) Role of vasopressin in essential hypertension: racial differences. J Hypertens 15(5):545–550
58. Bolignano D, Cabassi A, Fiaccadori E et al (2014) Copeptin (CTproAVP), a new tool for understanding the role of vasopressin in pathophysiology. Clin Chem Lab Med 52(10):1447–1456
59. Goncharova ND (2013) Stress responsiveness of the hypothalamic-pituitary-adrenal axis: age-related features of the vasopressinergic regulation. Front Endocrinol (Lausanne) 4:26
60. Mavani GP, DeVita MV, Michelis MF (2015) A review of the nonpressor and nonantidiuretic actions of the hormone vasopressin. Front Med (Lausanne) 2:19

61. Kwon TH, Frokiaer J, Nielsen S (2013) Regulation of aquaporin-2 in the kidney: a molecular mechanism of body-water homeostasis. Kidney Res Clin Pract 32(3):96–102
62. Manning M, Misicka A, Olma A et al (2012) Oxytocin and vasopressin agonists and antagonists as research tools and potential therapeutics. J Neuroendocrinol 24(4):609–628
63. Lee EW, Michalkiewicz M, Kitlinska J et al (2003) Neuropeptide Y induces ischemic angiogenesis and restores function of ischemic skeletal muscles. J Clin Invest 111(12):1853–1862
64. Hodges GJ, Jackson DN, Mattar L, Johnson JM, Shoemaker JK (2009) Neuropeptide Y and neurovascular control in skeletal muscle and skin. Am J Physiol Regul Integr Comp Physiol 297(3):R546–R555
65. Reichmann F, Holzer P (2016) Neuropeptide Y: a stressful review. Neuropeptides 55:99–109
66. Shanks J, Herring N (2013) Peripheral cardiac sympathetic hyperactivity in cardiovascular disease: role of neuropeptides. Am J Physiol Regul Integr Comp Physiol 305(12):R1411–R1420
67. Herring N, Paterson DJ (2009) Neuromodulators of peripheral cardiac sympatho-vagal balance. Exp Physiol 94(1):46–53
68. Chow AK, Cena J, Schulz R (2007) Acute actions and novel targets of matrix metalloproteinases in the heart and vasculature. Br J Pharmacol 152(2):189–205
69. Schulz R (2007) Intracellular targets of matrix metalloproteinase-2 in cardiac disease: rationale and therapeutic approaches. Annu Rev Pharmacol Toxicol 47:211–242
70. Palei AC, Sandrim VC, Cavalli RC, Tanus-Santos JE (2008) Comparative assessment of matrix metalloproteinase (MMP)-2 and MMP-9, and their inhibitors, tissue inhibitors of metalloproteinase (TIMP)-1 and TIMP-2 in preeclampsia and gestational hypertension. Clin Biochem 41(10–11):875–880
71. Belo VA, Souza-Costa DC, Lana CM et al (2009) Assessment of matrix metalloproteinase (MMP)-2, MMP-8, MMP-9, and their inhibitors, the tissue inhibitors of metalloproteinase (TIMP)-1 and TIMP-2 in obese children and adolescents. Clin Biochem 42(10-11):984–990
72. Goncalves FM, Jacob-Ferreira AL, Gomes VA et al (2009) Increased circulating levels of matrix metalloproteinase (MMP)-8, MMP-9, and pro-inflammatory markers in patients with metabolic syndrome. Clin Chim Acta 403(1-2):173–177
73. Yasmin MECM, Wallace S et al (2005) Matrix metalloproteinase-9 (MMP-9), MMP-2, and serum elastase activity are associated with systolic hypertension and arterial stiffness. Arterioscler Thromb Vasc Biol 25(2):372
74. Derosa G, D'Angelo A, Ciccarelli L et al (2006) Matrix metalloproteinase-2, -9, and tissue inhibitor of metalloproteinase-1 in patients with hypertension. Endothelium 13(3):227–231
75. Onal IK, Altun B, Onal ED et al (2009) Serum levels of MMP-9 and TIMP-1 in primary hypertension and effect of antihypertensive treatment. Eur J Intern Med 20(4):369–372
76. Friese RS, Rao F, Khandrika S et al (2009) Matrix metalloproteinases: discrete elevations in essential hypertension and hypertensive end-stage renal disease. Clin Exp Hypertens 31(7):521–533
77. Nagase H, Visse R, Murphy G (2006) Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc Res 69(3):562–573
78. Marchesi C, Dentali F, Nicolini E et al (2012) Plasma levels of matrix metalloproteinases and their inhibitors in hypertension: a systematic review and meta-analysis. J Hypertens 30(1):3–16
79. Benjamin MM, Khalil RA (2012) Matrix metalloproteinase inhibitors as investigative tools in the pathogenesis and management of vascular disease. EXS 103:209–279
80. Fontana V, Silva PS, Gerlach RF, Tanus-Santos JE (2012) Circulating matrix metalloproteinases and their inhibitors in hypertension. Clin Chim Acta 413(7-8):656–662
81. Sabbatini AR, Barbaro NR, de Faria AP et al (2016) Increased circulating tissue inhibitor of metalloproteinase-2 is associated with resistant hypertension. J Clin Hypertens (Greenwich) 18(10):969–975
82. Li P, Zhang XN, Pan CM et al (2011) Aldosterone perturbs adiponectin and PAI-1 expression and secretion in 3T3-L1 adipocytes. Horm Metab Res 43(7):464–469
83. Iacobellis G, Petramala L, Cotesta D et al (2010) Adipokines and cardiometabolic profile in primary hyperaldosteronism. J Clin Endocrinol Metab 95(5):2391–2398

84. Martin SS, Qasim A, Reilly MP (2008) Leptin resistance: a possible interface of inflammation and metabolism in obesity-related cardiovascular disease. J Am Coll Cardiol 52(15):1201–1210
85. Northcott JM, Yeganeh A, Taylor CG et al (2012) Adipokines and the cardiovascular system: mechanisms mediating health and disease. Can J Physiol Pharmacol 90(8):1029–1059
86. Patel L, Buckels AC, Kinghorn IJ et al (2003) Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. Biochem Biophys Res Commun 300(2):472–476
87. Yaturu S, Daberry RP, Rains J, Jain S (2006) Resistin and adiponectin levels in subjects with coronary artery disease and type 2 diabetes. Cytokine 34(3-4):219–223
88. Bokarewa M, Nagaev I, Dahlberg L et al (2005) Resistin, an adipokine with potent proinflammatory properties. J Immunol 174(9):5789–5795
89. Hong SJ, Park CG, Seo HS et al (2004) Associations among plasma adiponectin, hypertension, left ventricular diastolic function and left ventricular mass index. Blood Press 13(4):236–242
90. de Faria AP, Ritter AM, Sabbatini AR et al (2016) Deregulation of soluble adhesion molecules in resistant hypertension and its role in cardiovascular remodeling. Circ J 80(5):1196–1201
91. de Faria AP, Modolo R, Fontana V, Moreno H (2014) Adipokines: novel players in resistant hypertension. J Clin Hypertens (Greenwich) 16(10):754–759
92. McMaster WG, Kirabo A, Madhur MS, Harrison DG (2015) Inflammation, immunity, and hypertensive end-organ damage. Circ Res 116(6):1022–1033
93. Wu J, Saleh MA, Kirabo A et al (2016) Immune activation caused by vascular oxidation promotes fibrosis and hypertension. J Clin Invest 126(1):50–67
94. Kirabo A, Fontana V, de Faria AP et al (2014) DC isoketal-modified proteins activate T cells and promote hypertension. J Clin Invest 124(10):4642–4656

# Endothelial Function

# 9

Rosa Maria Bruno, Agostino Virdis, and Stefano Taddei

## 9.1 Endothelial Function: Basic Concepts

The endothelium consists in a cellular monolayer that covers the inner wall of all vessels in the cardiovascular system. While until the beginning of the 1980s the endothelium was considered a passive stratum with the main role of filter between the bloodstream and the vascular wall, now it is considered as the biggest autocrine-paracrine organ in humans, involved in the regulation of multiple biological processes in different settings, including cardiovascular system, immune system, central nervous system, and erectile function, producing a variety of different molecules, among which the most important is nitric oxide (NO). More than 30 years ago, Furchgott et al. demonstrated that in isolated rabbit aorta, acetylcholine-induced vasodilation occurred only in the presence of an intact endothelium, releasing an endothelium-derived relaxing factor [1], which was later identified as NO [2].

During the last three decades, a large body of evidence identified endothelial dysfunction consequent to a reduced NO availability as the early step of the atherosclerotic process and as a pivotal mechanism in the pathophysiology of cardiovascular disease. Standardized methodologies were set up for invasive and noninvasive techniques. Concomitantly, several pathways and mechanisms of endothelial dysfunction in different conditions and vascular districts have been demonstrated. Furthermore, endothelial function has been extensively utilized for cardiovascular risk stratification, to test new cardiovascular drugs, and to investigate the clinical impact of emerging cardiovascular risk factors, such as environmental factors and non-primarily cardiovascular diseases [3, 4].

NO is produced from the amino acid L-arginine, the enzyme NO synthase (NOS), whose isoform present in the endothelium is called endothelial NOS (eNOS). NO release from endothelium is determined by receptor-mediated mechanisms

R.M. Bruno • A. Virdis • S. Taddei (✉)
Department of Clinical and Experimental Medicine, University of Pisa,
Via Roma 67, 56126 Pisa, Italy
e-mail: stefano.taddei@med.unipi.it


A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_9

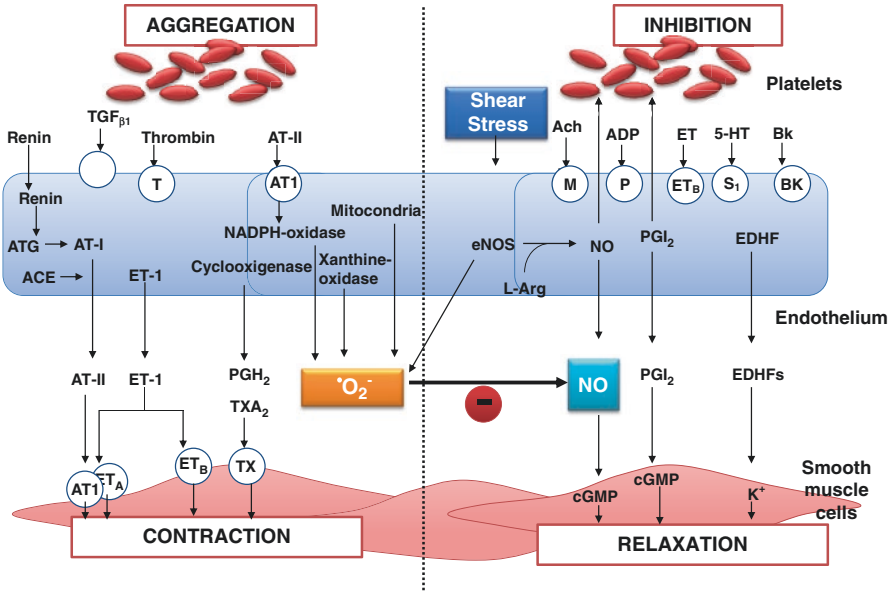



**Fig. 9.1** Nitric oxide (NO) and other endothelium-derived factors and their role on vascular homeostasis. *TGF* transforming growth factor, *AT* angiotensin, *ATG* angiotensinogen, *ET* endothelin, *ACE* angiotensin converting enzyme, *TX* thromboxane, *PG* prostaglandin, *NADPH* nicotinamide adenine dinucleotide phosphate, *eNOS* endothelial NO synthase, *L-Arg* L-Arginine, *ACh* acetylcholine, *ADP* adenosine diphosphate, *cGMP* cyclic guanosine monophosphate, *EDHF* endothelium-derived hyperpolarizing factors, *5-HT* serotonin, and *BK* bradykinin. Cited, with permission from [5]

(acetylcholine, bradykinin, serotonin, substance P, adenosine diphosphate), but also by mechanical stimuli (Fig. 9.1) [5]. In particular, shear stress, namely, tangential cyclic stress generated on vascular walls by blood flow, is probably the most powerful mechanism of stimulated NO release [2, 6].

Once NO is produced by endothelial cells, it diffuses through cell membranes reaching vascular smooth muscle cells; there, NO activates cytosolic guanylate cyclase and thus elevates intracellular levels of cyclic guanosine monophosphate (cGMP), which acts as a second messenger, inducing vasodilation by the reduction of cytosolic concentration of calcium ion. At this level, NO exerts its cardiovascular protective role by relaxing media smooth muscle cells, preventing leukocyte adhesion and migration into the arterial wall, muscle cell proliferation, platelet adhesion and aggregation, and adhesion molecule expression.

The half-life of NO and therefore its biological activity are critically influenced by the presence of reactive oxygen species (ROS) such as superoxide: this free radical rapidly reacts with NO to form the highly reactive intermediate peroxynitrite ($ONOO^-$). The formation of nitroso compounds has multiple negative effects: reducing NO availability, having direct vasoconstrictor and cytotoxic effects, and impairing the activity of the prostacyclin synthase and eNOS. Other ROS, such as

the dismutation product of superoxide, hydrogen peroxide, and hypochlorous acid, cannot be considered as free radicals, but have a powerful oxidizing capacity, which further contributes to oxidative stress within vascular tissues [7]. It is widely documented that in several disease conditions, including the presence of cardiovascular risk factors such as hypertension, ROS excess is predominant, and the endothelium undergoes functional and structural alterations, thus losing its protective role and becoming a proatherosclerotic structure. In the earliest stages, the principal endothelial alteration is merely functional and addressed as "endothelial dysfunction" [4]. The fundamental feature of this condition is the impaired NO bioavailability. This can be the consequence of either a reduced production by NO synthase (e.g., due to high levels of asymmetric dimethylarginine, ADMA, a competitive inhibitor of eNOS) or, more frequently, as above mentioned, of an increased breakdown by ROS. Finally, NO actions may be antagonized by endothelium-derived contracting factors [8].

As already mentioned, endothelial dysfunction in the peripheral and in the coronary arteries loses its vascular protective role, thus becoming not only a contributor to the progression of atherosclerosis but also a marker for cardiovascular risk and cardiovascular events.

Endothelial dysfunction, detected as the presence of reduced vasodilating response to endothelial stimuli, has been associated with major cardiovascular risk factors, such as aging, hyperhomocysteinemia, postmenopausal state, smoking, diabetes, hypercholesterolemia, and hypertension. The presence of multiple risk factors, each contributing to the development of impaired NO bioavailability by different mechanisms, may be able to determine a progressive worsening of endothelial function. Accordingly, some authors hypothesized that endothelial dysfunction may be not only a consequence or a collateral feature of risk factors but also a possible pathogenetic mechanism for their onset, though to date conflicting evidence exists [9].

## 9.2 Endothelial Dysfunction in Hypertension

Homogeneous literature convincingly demonstrates that endothelial dysfunction is a hallmark of the hypertensive patient [10, 11]. So far the main cause of hypertension-related endothelial dysfunction, in humans as well as in experimental animals, has been identified with an increased NO breakdown. In particular, hypertension-related endothelial dysfunction has been demonstrated to be the consequence of increased production of ROS [11], mainly superoxide anions, which are highly reactive and destroy NO, thus reducing its bioavailability [7]. Various enzymatic and nonenzymatic sources of ROS have been described to be activated in endothelial cells, smooth muscle cells, and inflammatory cells within the arterial wall of hypertensive patients, including nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, cyclooxygenase [12], xanthine oxidase, and uncoupled eNOS [13] (Fig. 9.1). In the attempt to compensate for NO deficiency, endothelium-dependent vasodilation is partially maintained by the production and release of endothelium-derived

vasodilators other than NO, such as prostanoids and other endothelium-derived hyperpolarizing factors [14].

Despite this large body of evidence coming from mechanistic studies, the exact relationship between endothelial dysfunction and hypertension is still a matter of debate, with some authors suggesting a "vicious circle" hypothesis, which is a bidirectional relationship [9]. However, several facts go against this hypothesis, as summarized below.

First, it is important to remember that endothelial dysfunction is not a specific feature of hypertension, but it is also a feature of other pathological conditions, i.e., diabetes mellitus, hypercholesterolemia, hyperhomocysteinemia, and obesity, not characterized by high blood pressure, in which reduced NO availability occurs [4]. Furthermore, in large cross-sectional population studies, an association between the degree of endothelial dysfunction and blood pressure values has been demonstrated, though not univocally [15, 16]. Indeed, the association of endothelial function with BP values depends also upon the technique used, with a direct correlation with flow-mediated dilation (FMD) and an inverse correlation with peripheral arterial tonometry [17, 18]. Thus, whether a cause-effect relationship exists, and which is its direction, is still a matter of debate. For example, the presence of elevated blood pressure in a cohort of Finnish teenagers was predictive of impaired FMD after 21 years of follow-up [19], while to our knowledge, no prospective study has tested yet the hypothesis that lower FMD predisposes to future development of hypertension.

One of the facts in favor of a role for endothelial dysfunction in the development of hypertension relates to genetic aspects. Taddei et al. found that normotensive offspring of hypertensive patients had significantly impaired response to ACh in comparison to normotensive offspring of normotensive patients, due to a defect in the L-arginine-NO pathway [20]. Conversely, other studies found only a modest heritability of FMD in the Framingham study participants [16], while the heritability of BP values is considerably higher [21].

Endothelial dysfunction has been associated with vascular target organ damage. The first observation of a relationship between increased carotid intima-media thickness (IMT) and endothelial dysfunction was shown in the forearm microcirculation of untreated hypertensive patients [22]. In a cross-sectional study in middle-aged healthy men, there was no evident correlation between brachial FMD and IMT [23], whereas FMD predicted IMT progression in hypertensive, postmenopausal women [24]. Similarly, endothelial function was not related with arterial stiffness, measured as pulse wave velocity, in healthy subjects [25] and in nondiabetic hypertensive patients, while a significant relationship in hypertensive patients with diabetes shows up [26]. In contrast, a weaker relationship has been found with cardiac and renal organ damage. For example, Treasure et al. found that left ventricular hypertrophy is associated with impaired endothelium-mediated relaxation in human coronary resistance vessels of hypertensive patients [27], while in other studies no significant difference in FMD was observed between patients with or without left ventricular hypertrophy or among patients with different geometric patterns [28]. Furthermore, despite that both microalbuminuria and endothelial dysfunction are considered as expressions of endothelial pathology, no correlation between urinary

**Table 9.1** Summary of the effect of antihypertensive drugs on endothelial function in the macro- and in the microcirculation

| Drug classes | Macrocirculation (coronary epicardial artery, brachial artery) | Microcirculation (coronary and forearm microcirculation) |
|---|---|---|
| Thiazide diuretics | = | = |
| Aldosterone antagonists | = ↑ | ↑ |
| Beta-blockers | = ↑ | = |
| Calcium channel blockers | = ↑ | ↑↑ |
| ACE inhibitors | ↑↑ | =↑ |
| AT1-receptor blockers | =↑ | =↑ |
| Renin inhibitors | = | ↑ |

Adapted, with permission, from [30]

albumin excretion and vasodilatation in response to acetylcholine or to sodium nitroprusside in the forearm microcirculation occurred in essential hypertensive patients [29].

Several nonpharmacological and pharmacological approaches have been demonstrated to improve or reverse endothelial dysfunction (Table 9.1), although their effect is never selective and usually also targets one or more traditional cardiovascular risk factors [9, 30]. Although in acute studies the use of high-dose antioxidant vitamins is extremely effective in restoring normal endothelial function, interventional studies using oral administration of these substances (i.e., vitamins C and E) failed to provide consistent data. However, recently, other antioxidant compounds, such as the flavonoids contained in red wine and chocolate, have been found to ameliorate endothelial function in peripheral large arteries. Among cardiovascular drugs, β-blockers and diuretics are invariably found to have little or no effect on endothelium-dependent vasodilation. On the other side, calcium channel blockers have been consistently shown to reverse impaired endothelium-dependent vasodilation, mainly in the microcirculation, with conflicting results in the brachial artery flow-mediated dilation. ACE inhibitors and angiotensin receptor blockers have been shown to ameliorate endothelium-dependent vasodilation in several experimental settings, exploring both coronary and peripheral large arteries, but conflicting results have been obtained in the microcirculation. Also lipid-lowering drugs such as statins and insulin-sensitizing agents such as glitazones are able to improve endothelial function. Given these data, it is conceivable that the therapeutic correction of endothelial dysfunction may lead to an improvement of prognosis in patients with cardiovascular risk factors or cardiovascular disease. However, scant data are available on this topic, and most of the conclusions that can be drawn are highly speculative. Antihypertensive drugs per se do not necessarily improve endothelial function [31], and compounds improving vascular function such as antioxidants [32] do not necessarily lower blood pressure or may do it through different mechanisms [33].

Taken together, these results do not support the hypothesis that endothelial dysfunction might induce hypertension. On the other hand, a possible exception may be represented by preeclampsia, a hypertensive condition complicating up to 15% of human pregnancies, whose incidence is on the rise due to increased maternal age and obesity: in this disease, endothelial dysfunction might play a pathogenetic role and represent a reasonable therapeutic target [34].

The most important open question is probably which is the prognostic role of endothelial dysfunction in hypertension. Other biomarkers of subclinical atherosclerosis have outperformed endothelial function testing in prediction of cardiovascular events in the general population, though to date a number of methodological issues avoid to draw firm conclusions [35, 36]; furthermore, few studies specifically addressed this question in the hypertensive population. Indeed, in 172 prospectively identified uncomplicated hypertensive patients, followed up for 95 months, a reduced FMD was associated with an increased risk of cardiovascular events after adjustment for traditional cardiovascular risk factors [37]. However, there is the intriguing possibility that serial assessments by noninvasive techniques might increase the predictive value and the clinical significance of endothelial dysfunction. Lack of restoration of endothelial function despite optimal treatment might identify a subset of "non-responders," who might be suitable for new therapeutic approaches, specifically targeting the endothelium. This hypothesis was tested in patients with systemic lupus erythematosus [38], in patients with coronary artery disease [39], but also in a sample of 400 postmenopausal hypertensive women without evidence of coronary artery disease at baseline and 6 months after effectively treating blood pressure. In those women whose FMD has not improved, there was a sevenfold increase in cardiovascular events during follow-up [40]. In this scenario, the possibility of improving endothelial function pharmacologically in hypertensive patients is appealing (Table 9.1). Furthermore, nutraceuticals as well as other cardiovascular drugs might have a beneficial effect on vascular function and might help reduce the residual cardiovascular risk in hypertensive patients [41].

## References

1. Furchgott RF, Zawadzki JV (1980) The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 288(5789):373–376
2. Luscher TF (1990) Imbalance of endothelium-derived relaxing and contracting factors. A new concept in hypertension? Am J Hypertens 3(4):317–330
3. Bianchini E, Giannarelli C, Bruno RM et al (2013) Functional and structural alterations of large arteries: methodological issues. Curr Pharm Des 19(13):2390–2400
4. Flammer AJ, Anderson T, Celermajer DS et al (2012) The assessment of endothelial function: from research into clinical practice. Circulation 126(6):753–767. doi:10.1161/CIRCULATIONAHA.112.093245
5. Bruno RM, Taddei S (2011) Nitric Oxide. In: Skinner FCMJS (ed) Encyclopedia of exercise medicine in health and disease. Springer, Berlin
6. Taddei S, Ghiadoni L, Virdis A et al (2003) Mechanisms of endothelial dysfunction: clinical significance and preventive non-pharmacological therapeutic strategies. Curr Pharm Des 9(29):2385–2402

7. Munzel T, Gori T, Bruno RM, Taddei S (2010) Is oxidative stress a therapeutic target in cardiovascular disease? Eur Heart J 31(22):2741–2748. doi:10.1093/eurheartj/ehq396
8. Jameson M, Dai FX, Luscher T et al (1993) Endothelium-derived contracting factors in resistance arteries of young spontaneously hypertensive rats before development of overt hypertension. Hypertension 21(3):280–288
9. Mordi I, Mordi N, Delles C, Tzemos N (2016) Endothelial dysfunction in human essential hypertension. J Hypertens 34(8):1464–1472
10. Panza JA, Quyyumi AA, Brush JE Jr, Epstein SE (1990) Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. N Engl J Med 323(1):22–27. doi:10.1056/NEJM199007053230105
11. Taddei S, Virdis A, Ghiadoni L et al (1998) Vitamin C improves endothelium-dependent vasodilation by restoring nitric oxide activity in essential hypertension. Circulation 97(22):2222–2229
12. Virdis A, Bacca A, Colucci R et al (2013) Endothelial dysfunction in small arteries of essential hypertensive patients: role of cyclooxygenase-2 in oxidative stress generation. Hypertension 62(2):337–344. doi:10.1161/HYPERTENSIONAHA.111.00995
13. Li Q, Yon JY, Cai H (2015) Mechanisms and consequences of eNOS dysfunction in hypertension. J Hypertens 33(6):1128–1136
14. Taddei S, Versari D, Cipriano A et al (2006) Identification of a cytochrome P450 2C9-derived endothelium-derived hyperpolarizing factor in essential hypertensive patients. J Am Coll Cardiol 48(3):508–515. doi:10.1016/j.jacc.2006.04.074
15. John S, Schmieder RE (2000) Impaired endothelial function in arterial hypertension and hypercholesterolemia: potential mechanisms and differences. J Hypertens 18(4):363–374
16. Benjamin EJ, Larson MG, Keyes MJ et al (2004) Clinical correlates and heritability of flow-mediated dilation in the community: the Framingham Heart Study. Circulation 109(5):613–619. doi:10.1161/01.CIR.0000112565.60887.1E
17. Hamburg NM, Palmisano J, Larson MG et al (2011) Relation of brachial and digital measures of vascular function in the community: the Framingham Heart Study. Hypertension 57(3):390–396. doi:10.1161/HYPERTENSIONAHA.110.160812
18. Schnabel RB, Schulz A, Wild PS et al (2011) Noninvasive vascular function measurement in the community: cross-sectional relations and comparison of methods. Circ Cardiovasc Imaging 4(4):371–380. doi:10.1161/CIRCIMAGING.110.961557
19. Juonala M, Viikari JS, Ronnemaa T et al (2006) Elevated blood pressure in adolescent boys predicts endothelial dysfunction: the cardiovascular risk in young Finns study. Hypertension 48(3):424–430. doi:10.1161/01.HYP.0000237666.78217.47
20. Taddei S, Virdis A, Mattei P et al (1996) Defective L-arginine-nitric oxide pathway in offspring of essential hypertensive patients. Circulation 94(6):1298–1303
21. Ehret GB, Caulfield MJ (2013) Genes for blood pressure: an opportunity to understand hypertension. Eur Heart J 34(13):951–961. doi:10.1093/eurheartj/ehs455
22. Ghiadoni L, Taddei S, Virdis A et al (1998) Endothelial function and common carotid artery wall thickening in patients with essential hypertension. Hypertension 32(1):25–32
23. Yan RT, Anderson TJ, Charbonneau F et al (2005) Relationship between carotid artery intima-media thickness and brachial artery flow-mediated dilation in middle-aged healthy men. J Am Coll Cardiol 45(12):1980–1986. doi:10.1016/j.jacc.2004.12.079
24. Rossi R, Nuzzo A, Olaru AI et al (2011) Endothelial function affects early carotid atherosclerosis progression in hypertensive postmenopausal women. J Hypertens 29(6):1136–1144. doi:10.1097/HJH.0b013e328345d950
25. Koivistoinen T, Virtanen M, Hutri-Kahonen N et al (2011) Arterial pulse wave velocity in relation to carotid intima-media thickness, brachial flow-mediated dilation and carotid artery distensibility: the cardiovascular risk in young Finns study and the Health 2000 survey. Atherosclerosis 220(2):387–393. doi:10.1016/j.atherosclerosis.2011.08.007
26. Bruno RM, Penno G, Daniele G et al (2012) Type 2 diabetes mellitus worsens arterial stiffness in hypertensive patients through endothelial dysfunction. Diabetologia 55(6):1847–1855. doi:10.1007/s00125-012-2517-1

27. Treasure CB, Klein JL, Vita JA et al (1993) Hypertension and left ventricular hypertrophy are associated with impaired endothelium-mediated relaxation in human coronary resistance vessels. Circulation 87(1):86–93
28. Muiesan ML, Salvetti M, Monteduro C et al (2001) Flow-mediated dilatation of the brachial artery and left ventricular geometry in hypertensive patients. J Hypertens 19(3 Pt 2):641–647
29. Taddei S, Virdis A, Mattei P et al (1995) Lack of correlation between microalbuminuria and endothelial function in essential hypertensive patients. J Hypertens 13(9):1003–1008
30. Ghiadoni L, Taddei S, Virdis A (2012) Hypertension and endothelial dysfunction: therapeutic approach. Curr Vasc Pharmacol 10(1):42–60
31. Ghiadoni L, Magagna A, Versari D et al (2003) Different effect of antihypertensive drugs on conduit artery endothelial function. Hypertension 41(6):1281–1286. doi:10.1161/01.HYP.0000070956.57418.22
32. Ried K, Sullivan TR, Fakler P et al (2012) Effect of cocoa on blood pressure. Cochrane Database Syst Rev 8:CD008893. doi:10.1002/14651858.CD008893.pub2
33. Bruno RM, Daghini E, Ghiadoni L et al (2012) Effect of acute administration of vitamin C on muscle sympathetic activity, cardiac sympathovagal balance, and baroreflex sensitivity in hypertensive patients. Am J Clin Nutr 96(2):302–308. doi:10.3945/ajcn.112.035022
34. Savvidou MD, Hingorani AD, Tsikas D et al (2003) Endothelial dysfunction and raised plasma concentrations of asymmetric dimethylarginine in pregnant women who subsequently develop pre-eclampsia. Lancet 361(9368):1511–1517. doi:10.1016/S0140-6736(03)13177-7
35. Yeboah J, McClelland RL, Polonsky TS et al (2012) Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA 308(8):788–795. doi:10.1001/jama.2012.9624
36. Bruno RM, Gori T, Ghiadoni L (2014) Endothelial function testing and cardiovascular disease: focus on peripheral arterial tonometry. Vasc Health Risk Manag 10:577–584. doi:10.2147/VHRM.S44471
37. Muiesan ML, Salvetti M, Paini A et al (2008) Prognostic role of flow-mediated dilatation of the brachial artery in hypertensive patients. J Hypertens 26(8):1612–1618. doi:10.1097/HJH.0b013e328304b083
38. Ghiadoni L, Tani C, Bruno RM et al (2014) Prognostic value of flow-mediated dilation in patients with systemic lupus erythematosus: a pilot prospective cohort study. Atherosclerosis 236(2):381–384. doi:10.1016/j.atherosclerosis.2014.07.023
39. Kitta Y, Obata JE, Nakamura T et al (2009) Persistent impairment of endothelial vasomotor function has a negative impact on outcome in patients with coronary artery disease. J Am Coll Cardiol 53(4):323–330. doi:10.1016/j.jacc.2008.08.074
40. Modena MG, Bonetti L, Coppi F et al (2002) Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. J Am Coll Cardiol 40(3):505–510
41. Zuchi C, Ambrosio G, Luscher TF, Landmesser U (2010) Nutraceuticals in cardiovascular prevention: lessons from studies on endothelial function. Cardiovasc Ther 28(4):187–201. doi:10.1111/j.1755-5922.2010.00165.x

# Genetics of Blood Pressure and Hypertension

# 10

Sandosh Padmanabhan, Li-En Tan, and Anna F. Dominiczak

The role of genetics in blood pressure regulation and hypertension is established through multiple strands of evidence. Family and twin studies have shown that BP is a heritable trait, with heritability ranging from 15 to 40% for the clinic SBP and from 15 to 30% for clinical DBP; a higher heritability was noted for the ABPM (sleep) around 69% and 51% for SBP and DBP, respectively [1–3]. The risk of hypertension is significantly increased in subjects with one or two hypertensive parents, and BP levels correlate more in monozygotic twins than dizygotic twins [4, 5]. Secondly, the existence of rare monogenic forms of hypertension and the identification of their underlying causal mutations have enhanced our understanding of molecular pathways that regulate BP regulation [6]. Finally, accruing evidence from genome-wide association studies (GWAS) highlights the role of common variants in BP regulation and points to novel pathways that may lead to novel therapies [7].

## 10.1 Monogenic Forms of Hypertension

Discovery of the monogenic Mendelian forms of hypertension has mainly been through positional cloning using large family pedigrees, with multiple members of the family showing a clear inheritance pattern. Patients with these types of disorders represent less than 1% of the hypertensive population and are considered to have secondary hypertension. Mutations causing monogenic hypertension are characterised by being rare with a major defect that usually disrupts a single pathway. Given the complexity and the presence of several systems and physiological pathways that control BP, it is surprising that most of the identified monogenic hypertension

S. Padmanabhan • L.-E. Tan • A.F. Dominiczak (✉)
BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Wolfson Medical School Building, University Avenue, Glasgow G12 8QQ, UK
e-mail: Anna.Dominiczak@glasgow.ac.uk



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_10

syndromes are due to mutation in genes that play key roles in renal sodium handling [6, 7]. Table 10.1 summarises the different forms of monogenic hypertension and their key features and causal genes.

## 10.2 Polygenic Pathways of BP Regulation and Hypertension

Several GWAS have been conducted using BP as a quantitative trait or by using a binary definition of hypertension. All the significant GWAS signals are summarised in Table 10.2. The first GWAS was a case-control design from the Wellcome Trust Case Control Consortium (WTCCC), published in 2007 [8]. The study examined 7 common complex diseases using 2000 cases each and 3000 shared controls. The study genotyped approximately 500,000 SNPs using the 500 K Affymetrix SNP chip and reported a total of 24 significant disease-SNP association signals ($p < 5.0 \times 10^{-7}$). Hypertension was the only trait without any significant association signal across the genome. Similarly, in the first GWAS that analysed BP as a quantitative trait in the Framingham Heart Study using almost 71,000 SNPs, 1400 related individuals revealed no significant results [9]. This study used six primary phenotypes for BP derived from single and long-term averaged (LTA) SBP and DBP. These two studies represent the first attempts at applying the GWAS approach for hypertension and BP, and the important lessons taken from these two attempts influenced the study designs of future studies that yielded strong signals. The key message was the complexity of hypertension and the need for having much larger sample size to discover association signals for genetic marker with low effect sizes.

The first two successful GWAS for BP were reported in 2009 by two large consortia, the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) study [10] and the Global Blood Pressure Genetic (Global BPgen) study [11]. Both studies analysed BP as a quantitative trait. The CHARGE consortium included six population-based cohorts of European ancestry with a total sample size of 29,000 individuals, and the Global BPgen consisted of 17 cohorts with a total sample size of 34,000 at the discovery phase. The two consortia tested the association of SBP and DBP as the primary phenotypes, using a cross-sectional measurement with addition of a fixed value of 15/10 mmHg or 10/5 mmHg for individuals taking antihypertensive therapies in CHARGE and Global BPgen, respectively. In order to combine the results from different cohorts, genotype imputation, using linkage disequilibrium patterns, was used to fill in missing markers across all the included cohorts, thus allowing merger of genotypes from different genotyping chips and platforms. The final association tests were performed in almost 2.5 million genotyped or imputed SNPs and discovered 13 loci independently associated with SBP or DBP at a level of genome-wide significance ($p < 5.0 \times 10^{-8}$) [10, 11]. Each study reported eight loci with three loci overlapping in both studies. These two studies have been followed by further GWAS, and the results of these studies are summarised in Table 10.2. In addition, most of the loci reported in these two studies were novel except for some loci such as *CYP17A1-NT5C2* and *MTHFR-NPPB*, the former has been associated with a rare Mendelian

**Table 10.1** Monogenic disorders of blood pressure regulation with characteristic clinical features and treatment

| Syndrome | Subtypes | Inheritance | Locus | Gene | BP | Renin | Aldosterone | Serum $K^+$ | Catecholamines | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|
| Liddle syndrome MIM 177200 | | AD | 16p12.2 | *SCNN1B – SCNN1G* | ↑↑ | ↓↓ | ↓↓ | ↓↓ | – | Amiloride or triamterene |
| Gitelman's syndrome MIM 263800 | | AR | 16q13 | *SLC12A3* | ↓↓ | ↑↑ | – | ↓↓ | – | Oral potassium and magnesium supplementation with adequate salt and water |
| Bartter's syndrome | Type 1 "antenatal" MIM 601678 | AR | 15q21.1 | *SLC12A1* | ↓↓ | ↑↑ | ↑↑ | ↓↓ | – | Potassium supplementation and the use of cyclooxygenase inhibitors, angiotensin-converting enzyme (ACE) inhibitors, and potassium-sparing diuretics |
| | Type 2 "antenatal" MIM 241200 | AR | 11q24.3 | *KCNJ1* | | | | | | |
| | Type 3 "antenatal" | AR | 1p36.13 | *CLCNKB* | | | | | | |
| | Type 4a MIM 602522 | AR | 1p32.3 | *BSND* | | | | | | |
| | Type 4b (digenic) MIM 613090 | AR | 1p36.13 | *CLCNKA CLCNKB* | | | | | | |
| | Type 5 antenatal MIM 300971 | AR | Xp11.21 | *MAGED2, MAGED, BARTS5* | | | | | | |
| Familial hyperaldosteronism (FH) | FH type 1 or glucocorticoid remediable aldosteronism MIM 103900 | AD | 8q24.3 | *CYP11B1* | ↑↑ | ↓↓ | ↑↑ | ↓ | – | Dexamethasone |
| | FH type 2 MIM 605635 | AD | 7p22.3-7p22.1 | | | | | | | |
| | FH type 3 MIM 613677 | AD | 11q24.3 | *KCNJ5* | | | | | | |

(continued)

**Table 10.1** (continued)

| Syndrome | Subtypes | Inheritance | Locus | Gene | BP | Renin | Aldosterone | Serum $K^+$ | Catecholamines | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|
| Apparent mineralocorticoid excess (AME) MIM 218030 | | AR | 16q22.1 | *HSD11B2* | ↑↑ | ↓↓ | ↓↓ | ↓↓ | – | Low-sodium diet and spironolactone |
| Pseudohypoaldosteronism (PHA) | PHA1A MIM 177735 | AD | 4q31.2 | *NR3C2* | ↓↓ | ↑↑ | ↑↑ | ↑↑ | – | Thiazide diuretics, prostaglandin inhibitors, alkalising agents, and potassium-binding resins |
| | PHA2B "Gordon's syndrome" MIM 614491 | AD | 17q21.2 | *WNK4* | ↑↑ | ↓↓ | ↑ | ↑ | – | |
| | PHA2C "Gordon's syndrome" MIM 614492 | AD | 12p12.3 | *WNK1* | | | | | | |
| | PHA2D "Gordon's syndrome" MIM 614495 | AD/AR | 5q31.2 | *KLHL3* | | | | | | |
| | PHA2E "Gordon's syndrome" MIM 614496 | AD | 2q36.2 | *CUL3* | | | | | | |
| Sporadic aldosterone-producing adenoma (APA) or primary aldosteronism | | AD | 11q24.3 | *KCNJ5* | ↑↑ | ↓↓ | ↑↑ | ↓ | – | Surgery, aldosterone antagonists |
| | | AD | 1p31.1 | *ATP1A1* | | | | | | |
| | | AD | 3p21.3 | *CACNA1D* | | | | | | |
| | | AD | Xq28 | *ATP2B3* | | | | | | |
| Hypertension exacerbation in pregnancy MIM 605115 | | AD | 4q31.2 | *NR3C2* | ↑↑ | ↓↓ | ↓↓ | ↓ | – | Spironolactone contraindicated, sodium chloride treatment |
| 11β-Hydroxylase MIM 202010 | | AR | 8q21 | *CYP11B1* | ↑↑ | ↓↓ | ↓↓ | ↓↓ | – | Glucocorticoid therapy |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 3β-Hydroxysteroid dehydrogenase OMIM 613890 | | AR | 1p12 | *HSD3B2* | ↑↑ | ↓↓ | ↓↓ | ↓↓ | – | Glucocorticoid therapy |
| 17α-Hydroxylase deficiency MIM 202110 | | AR | 10q24.3 | *CYP17A1* | ↑↑ | ↓↓ | ↓↓ | ↓↓ | – | Glucocorticoid therapy, potassium-sparing diuretics |
| 21-Hydroxylase deficiency MIM 201910 | | AR | | *CYP21A2* | ↑↑ | ↓↓ | ↓↓ | ↓↓ | – | Glucocorticoid therapy |
| Paragangliomas (PGL) | Paragangliomas 1 MIM 168000 | AD | 11q23.1 | *SDHD* | ↑↑ | – | – | – | ↑↑ | Surgery, adrenergic blockers (alpha-blockade followed by beta-blockade) |
| | Paragangliomas 2 MIM 601650 | AD | 11q12.2 | *SDHAF2* | | | | | | |
| | Paragangliomas 3 MIM 605373 | AD | 1q23.3 | *SDHC* | | | | | | |
| | Paragangliomas 4 MIM 115310 | AD | 1p36.13 | *SDHB* | | | | | | |
| | Paragangliomas 5 MIM 614165 | AD | 5p15.3 | *SDHA* | | | | | | |
| Von Hippel-Lindau syndrome MIM 193300 | | AD | 3p25.3 | *VHL* | ↑↑ | – | – | – | ↑↑ | |
| Multiple endocrine neoplasia, type IIA MIM 171400 | | AD | 10q11.2 | *RET* | ↑↑ | – | – | – | ↑↑ | |
| NOS3-pregnancy-induced hypertension MIM +163,729 | | AD | 7q36.1 | *NOS3* | ↑↑ | – | – | – | ↑↑ | |

**Table 10.2** Summary of all GWAS results for BP and hypertension in different ancestries

| Locus | SNP | Genotype | Coded allele | Coded allele freq | | | BP effect | | | Nearest gene(s) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | European | Asian | African | European | Asian | African | |
| 1p36.2 | rs880315 | C/T | C | 0.35 | 0.59 | 0.16 | ↑ | ↑ | | *CASZ1* |
| 1p36.22 | rs17367504 | A/G | G | 0.17 | 0.10 | 0.06 | ↓ | ↓ | | *MTHFR, CLCN6,* |
| | rs5068 | C/T | C | 0.07 | 0.00 | 0.01 | ↓ | | | *NPPA, NPPB* |
| 1p13.2 | rs2932538 | C/T | C | 0.73 | 0.80 | 0.85 | ↓ | | | *SLC16A1,* |
| | rs17030613 | A/C | C | 0.19 | 0.45 | 0.05 | | ↑ | | *CAPZA1, ST7L,* |
| | rs10745332 | A/G | A | 0.74 | 0.81 | 0.77 | | ↑ | | *MOV10* |
| 1q32.1 | rs2169137 | C/G | G | 0.74 | 0.94 | 0.80 | ↑ | | | *MDM4* |
| 1q42.2 | rs2004776 | A/G | A | 0.26 | 0.67 | 0.54 | ↑ | | | *AGT* |
| 2p23.2 | rs1275988 | A/G | A | 0.60 | 0.23 | 0.08 | ↓ | | | *KCNK3* |
| 2q11.2 | rs7599598 | A/G | A | 0.57 | 0.63 | 0.09 | ↓ | | | *FER1L5* |
| 2q24.3 | rs1446468 | A/G | A | 0.53 | 0.47 | 0.96 | ↓ | | | *FIGN* |
| | rs13002573 | A/G | G | 0.25 | 0.40 | 0.11 | ↓ | | | *FIGN* |
| | rs16849225 | C/T | C | 0.75 | 0.59 | 0.94 | | ↑ | | *FIGN* |
| | rs6749447 | G/T | G | 0.28 | 0.72 | 0.58 | ↑ | | | *STK39* |
| 2q32.1 | rs16823124 | A/G | A | 0.23 | 0.51 | 0.10 | ↑ | | | *PDE1A* |
| 3p25.3 | rs347591 | G/T | G | 0.33 | 0.23 | 0.51 | ↓ | | | *HRH1-ATG7* |
| 3p24.1 | rs13082711 | C/T | T | 0.80 | 0.94 | 0.96 | ↓ | | | *SLC4A* |
| | rs820430 | C/T | T | 0.64 | 0.40 | 1.00 | ↑ | | | |
| 3p22.1 | rs9815354 | A/G/T | A | 0.23 | 0.12 | 0.17 | ↑ | ↑ | | *ULK4* |
| | rs3774372 | C/T | T | 0.77 | 0.87 | 0.81 | ↓ | | | |
| | rs1717027 | C/T | T | 0.22 | 0.12 | 0.66 | ↑ | | | |
| 3p21.31 | rs319690 | A/G | A | 0.51 | 0.75 | 0.41 | ↑ | | | *MAP4* |
| | rs7651237 | A/G | G | 0.64 | 0.94 | 0.88 | ↑ | | | |
| 3p21.1 | rs9810888 | G/T | G | 0.53 | 0.59 | 0.46 | | ↑ | | *CACNA1D* |
| 3q26.1 | rs16833934 | A/G | G | 0.37 | 0.17 | 0.65 | ↓ | | | *MIR1263* |
| 3q26.2 | rs419076 | G/T | T | 0.48 | 0.13 | 0.57 | ↑ | | | *MECOM* |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 4q12 | rs871606 | A/G | A | 0.87 | 0.78 | 0.76 | ↑ | ↑ | | *CHIC2* |
| 4q21.21 | rs16998073 | A/T | T | 0.19 | 0.30 | 0.05 | ↑ | ↑ | | *FGF5* |
| | rs1458038 | A/G | A | 0.27 | 0.34 | 0.05 | ↑ | | | |
| 4q24 | rs13107325 | A/C/T | T | 0.10 | 0.00 | 0.00 | ↓ | | | *SLC39A8* |
| 4q25 | rs6825911 | C/T | C | 0.20 | 0.48 | 0.54 | | ↑ | | *ENPEP, PITX2* |
| 4q32.1 | rs13139571 | A/C | C | 0.74 | 0.68 | 0.88 | ↑ | | | *GUCY1A3-GUCY1B3* |
| 5p13.3 | rs1173771 | C/T | C | 0.51 | 0.57 | 0.81 | ↑ | | | *NPR3-C5orf23* |
| | rs7733331 | C/T | T | 0.50 | 0.42 | 0.42 | ↓ | | | |
| | rs1173766 | C/T | C | 0.52 | 0.59 | 0.62 | | ↑ | | |
| 5q33.3 | rs11953630 | A/C/T | T | 0.34 | 0.06 | 0.15 | ↓ | | | *EBF1* |
| 6p22.2 | rs1799945 | C/G | G | 0.18 | 0.04 | 0.00 | ↑ | ↑ | | *HFE* |
| | rs198823 | G/T | T | 0.65 | 0.23 | 0.60 | ↓ | | | |
| 6p21.33 | rs805303 | C/T | C | 0.70 | 0.57 | 0.30 | ↑ | | | *BAG1* |
| | rs2021783 | C/T | C | 1.00 | 0.81 | 1.00 | | ↑ | | *CYP21A2* |
| 6p21.32 | rs2854275 | G/T | T | 0.08 | 0.03 | 0.08 | ↓ | | | *HLA-DQB1* |
| 6p21.1 | rs10948071 | C/T | T | 0.70 | 0.67 | 0.05 | ↓ | | | *CRIP3* |
| 6q22.33 | rs13209747 | C/G/T | T | 0.45 | 0.48 | 0.12 | ↑ | ↑ | ↑ | *RSPO3* |
| 6q25.1 | rs17080102 | C/G | C | 0.06 | 0.01 | 0.09 | ↓ | ↓ | ↓ | *PLEKHG1* |
| 7p15.2 | rs17428471 | G/T | T | 0.08 | 0.05 | 0.14 | ↑ | ↑ | ↑ | *EVX1-HOXA* |
| 7p12.3 | rs2949837 | A/T | A | 0.23 | 0.61 | 0.00 | ↑ | | | *IGFBP3* |
| 7q21.2 | rs2282978 | C/T | C | 0.36 | 0.06 | 0.43 | ↑ | | | *CDK6* |
| 7q22.3 | rs17477177 | C/T | T | 0.72 | 0.91 | 0.93 | ↓ | | | *PIK3CG* |
| | rs12705390 | A/G | G | 0.72 | 0.91 | 0.93 | ↓ | | | |
| 7q36.1 | rs3918226 | C/T | T | 0.10 | 0.00 | 0.00 | ↑ | | | *NOS3* |
| 8p23.1 | rs4841569 | A/G | G | 0.57 | 1.00 | 0.89 | ↑ | | | *BLK-GATA4* |
| | rs2898290 | C/T | C | 0.58 | 0.02 | 0.55 | NR | | | |
| 8q24.12 | rs2071518 | C/T | T | 0.20 | 0.19 | 0.60 | ↑ | | | *NOV* |

(continued)

**Table 10.2** (continued)

| Locus | SNP | Genotype | Coded allele | Coded allele freq | | | BP effect | | | Nearest gene(s) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | European | Asian | African | European | Asian | African | |
| 10p12.31 | rs11014166 | A/T | A | 0.63 | 0.97 | 0.89 | ↑ | ↓ | | *CACNB2* |
| | rs1813353 | A/G | A | 0.65 | 0.92 | 0.85 | ↑ | | | |
| | rs4373814 | C/G | G | 0.63 | 0.53 | 0.43 | ↓ | | | |
| | rs12258967 | C/G | C | 0.64 | 1.00 | 0.73 | ↑ | | | |
| 10q21.2 | rs1530440 | C/T | T | 0.16 | 0.20 | 0.02 | ↓ | | | *c10orf107* |
| | rs4590817 | C/G | G | 0.82 | 1.00 | 0.82 | ↑ | | | |
| | rs12244842 | G/T | T | 0.25 | 0.19 | 0.35 | ↓ | | | |
| | rs7070797 | A/G | A | 0.15 | 0.00 | 0.00 | ↓ | | | |
| 10q22.2 | rs4746172 | C/T | C | 0.23 | 0.56 | 0.19 | ↑ | | | *VCL* |
| 10q23.33 | rs932764 | A/G | G | 0.43 | 0.58 | 0.15 | ↑ | | | *PLCE1* |
| 10q24.32 | rs1004467 | C/T | T | 0.92 | 0.67 | 0.81 | ↑ | | | *CYP17A1-NT5C2* |
| | rs11191548 | C/T | T | 0.92 | 0.72 | 0.99 | ↑ | ↑ | | |
| | rs12413409 | A/G | G | 0.92 | 0.72 | 0.98 | | ↑ | | |
| | rs4409766 | C/T | T | 0.93 | 0.78 | 0.82 | | ↑ | | |
| | rs3824755 | C/G | C | 0.07 | 0.23 | 0.17 | ↓ | | | |
| 10q25.3 | rs2782980 | C/T | T | 0.27 | 0.15 | 0.44 | ↓ | | | *ADRB1* |
| | rs7076938 | C/T | C | 0.33 | 0.17 | 0.45 | ↓ | | | |
| | rs1801253 | C/G | G | 0.32 | 0.15 | 0.41 | ↓ | | | |
| 11p15.5 | rs661348 | C/T | C | 0.45 | 0.58 | 0.11 | ↑ | | | *LSP1-TNNT3* |
| 11p15.4 | rs7129220 | A/G | G | 0.89 | 1.00 | 0.95 | ↓ | | | *ADM* |
| 11p15.1 | rs381815 | A/C/T | T | 0.30 | 0.25 | 0.18 | ↑ | | | *PLEKHA7* |
| | rs757081 | C/G | G | 0.63 | 0.66 | 1.00 | ↑ | | | *PIK3C2A, NUCB2, NCR3LG1* |
| 11p15.2 | rs2014408 | C/T | T | 0.20 | 0.21 | 0.03 | ↑ | ↑ | ↑ | *SOX6* |
| | rs4757391 | C/T | C | 0.18 | 0.17 | 0.23 | | ↑ | | |
| 11q13.1 | rs4601790 | A/G | G | 0.25 | 0.42 | 0.07 | ↑ | | | *EHBP1L1* |
| | rs3741378 | A/G | A | 0.15 | 0.38 | 0.36 | ↓ | | | *RELA* |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 11q22.1 | rs633185 | C/G | G | 0.68 | 0.55 | 0.82 | ↓ | | | *FLJ32810-TMEM133* |
| 11q24.3 | rs11222084 | A/T | T | 0.40 | 0.07 | 0.26 | ↑ | | | *ADAMTS8* |
| 12q13.13 | rs7297416 | A/C | C | 0.25 | 0.62 | 0.38 | ↓ | | | *HOXC4* |
| 12q21.33 | rs11105354 | A/G | G | 0.12 | 0.42 | 0.11 | ↓ | | | *ATP2B1* |
| | rs2681492 | A/G | A | 0.88 | 0.58 | 0.84 | ↑ | | | |
| | rs2681472 | C/T | T | 0.88 | 0.58 | 0.89 | ↑ | ↑ | | |
| | rs17249754 | A/G | G | 0.88 | 0.59 | 0.84 | ↑ | ↑ | | |
| 12q24.12 | rs3184504 | C/T | T | 0.45 | 0.00 | 0.00 | ↑ | | | *SH2B3* |
| | rs653178 | A/G | A | 0.56 | 1.00 | 1.00 | ↓ | | | |
| 12q24.13 | rs11066280 | A/T | T | 1.00 | 0.75 | 1.00 | | ↑ | | *RPL6-ALDH2* |
| 12q24.21 | rs35444 | C/T | T | 0.59 | 0.73 | 0.55 | ↑ | | | *TBX5-TBX3* |
| | rs2384550 | A/G | A | 0.37 | 0.09 | 0.34 | ↓ | | | |
| | rs10850411 | C/T | T | 0.72 | 0.46 | 0.66 | ↑ | | | |
| | rs1991391 | C/T | C | 0.64 | 0.91 | 0.58 | ↑ | | | |
| | rs11067763 | A/G | A | 0.89 | 0.61 | 0.65 | | ↑ | | *MED13L* |
| 15q21.1 | rs1036477 | A/G | G | 0.10 | 0.42 | 0.61 | ↓ | | | *FBN1* |
| 15q24.1 | rs6495122 | A/C | A | 0.38 | 0.78 | 0.78 | ↑ | | | *CYP1A1-ULK3* |
| | rs1378942 | G/T | G | 0.32 | 0.79 | 1.00 | ↑ | | | |
| 15q24.2 | rs11072518 | C/T | T | 0.34 | 0.42 | 0.44 | ↑ | | | *COX5A* |
| | rs1133323 | A/G | A | 0.59 | 0.17 | 0.00 | ↓ | | | |
| 15q26.1 | rs2521501 | A/T | T | 0.63 | 0.93 | 0.80 | ↑ | | | *FURIN-FES* |
| 16p12.3 | rs13333226 | A/G | G | 0.18 | 0.05 | 0.38 | ↑ | | | *UMOD* |
| 16q22.1 | rs33063 | A/G | A | 0.19 | 0.15 | 0.00 | ↑ | | | *NFAT5* |
| 17q21.31 | rs12946454 | C/T | T | 0.71 | 0.62 | 0.80 | ↑ | | | *PLCD3* |
| 17q21.32 | rs17608766 | C/T | T | 0.91 | 1.00 | 1.00 | ↓ | | | *GOSR2* |
| 17q21.33 | rs12940887 | C/T | T | 0.41 | 0.09 | 0.03 | ↑ | | | *ZNF652* |
| | rs16948048 | A/G | G | 0.42 | 0.09 | 0.42 | ↑ | | | |
| 20p12.2 | rs1327235 | A/G | G | 0.52 | 0.48 | 0.53 | ↑ | | | *JAG1* |
| | rs1887320 | A/G | A | 0.58 | 0.43 | 0.54 | | ↑ | | |
| 20q13.32 | rs6015450 | A/G | G | 0.07 | 0.00 | 0.22 | ↑ | | | *GNAS-EDN3* |
| | rs6092743 | A/G | A | 0.06 | 0.00 | 0.06 | ↑ | | | *C20orf174* |

form of hypertension, and the latter lies in a region that has previously been associated with BP and hypertension [12].

In 2011, the International Consortium for Blood Pressure Genome-wide Association Studies (ICBP-GWAS) published the largest meta-analysis for systolic and diastolic blood pressure in >69,899 European individuals, followed by validation in 132,000 individuals [13]. The SNP association analyses were performed under an additive genetic model, which assumes that the effect conferred by an allele is increased by r-fold for heterozygotes and 2r-fold for homozygotes. The model was adjusted for sex, BMI, age, and age$^2$ (to account for the middle-age plateau of DBP). Also, a fixed value of 15/10 mmHg was added to individuals taking antihypertensive treatment to account for treatment effect. The study identified 29 independent SNPs at 28 loci, of which 16 loci were novel and the remaining 13 loci were a replication of the previously reported loci in CHARGE or Global BPgen. Although the majority of SNPs identified by ICBP were intragenic, some loci were in gene desert regions or in genomic regions that have no gene encoding protein with a biological plausible effect on BP.

A second study was also carried out by the ICBP consortium using mean arterial pressure (MAP) and pulse pressure (PP) as primary phenotypes with the addition of further six studies in the consortia, increasing the total discovery sample size to more than 74,000 individuals [14]. The study identified four novel loci associated with PP and two loci associated with MAP, with one locus associated with both traits near *FIGN*. The important finding of this study was that three of the four loci associated with PP were found to have an opposite effect in SBP and DBP, unlike the majority of BP variants that exerts effect in the same direction on SBP and DBP, which suggests the presence of genetic pathways that may differentially influence SBP and DBP. The study has also showed that most of MAP variants were also associated with both SBP and DBP, suggesting a high correlation between these three BP traits.

Whilst most of the GWAS for BP have taken the quantitative route studying BP as a continuous variable, two studies analysed hypertension as a binary trait [15, 16]. The first study identified a novel locus located in the promoter region of uromodulin gene (*UMOD)*, which is exclusively expressed in the kidney and may influence BP by a novel sodium homeostatic pathway [15]. This study employed an alternative strategy to minimise misclassification bias and increase statistical power by selecting individuals from the extreme of the BP distribution; this strategy has allowed a sharper contrast between cases and controls. The second study used a classical case-control approach using the HYPERGENES Project and identified a new locus in the promoter region of the endothelial NO synthase gene, which is a critical mediator for cardiovascular homeostasis and BP control via vascular tone regulation [16].

GWAS for populations other than European descent were also performed with the aim of replicating the variants identified in European populations and also finding new population-specific loci. The Asian Genetic Epidemiology Network Blood Pressure (AGEN-BP) was the largest non-European GWAS that included more than 30,000 individuals in the discovery stage and 20,000 for replication [17]. AGEN-BP

identified six novel loci and confirmed seven loci previously reported in CHARGE and Global BPgen. The Continental Origins and Genetic Epidemiology Network (COGENT) study performed trans-ethnic meta-analysis GWAS with a discovery sample size of 29,000 individuals of African-American (AA) origin [18]. The replication sample included a mixed ethnic background of European and East Asian origins due to a lack of sufficient samples from AA. The COGENT study reported five loci associated with SBP or DBP, three of which were not previously reported to be associated with BP. A Chinese GWAS reported three novel loci and replicated 14 previously reported BP loci [19]. The success of replicating the previously reported loci for European population in the other population suggests that the physiologic effects of these loci may be generalised across populations with diverse genetic backgrounds. Yet, identifying novel loci also suggests that populations with different genetic backgrounds may have a unique genetic factor as a result of differences in allele frequencies or population-specific factors that interact with genes to influence BP.

Long-term averaging (LTA) of repeated BP measures has been used within longitudinal cohorts rather than analysing single BP measurement to improve the phenotype precision [20]. This identified 39 association signals at 19 loci and two novel gene loci *KCNK3* and *CRIP3*. The study has also estimated a 20% improvement in statistical power with using the LTA approach over the single-visit method. Modelling gene x age interactions to detect SNPs with age-specific genetic effects on BP which would otherwise have been missed from a standard main-effect model identified a variant near *MIR126* [21]. The SNPs with the largest age-gene interaction in three loci (*CASZ1*, *EHBP1L1*, and *GOSR2*) displayed opposite directions of effect by increasing BP in the young and decreasing BP in the old, by a difference in the effect size that can reach up to 1.58 mmHg [21]. An important message from this study is that pooling data from different studies with a wide range of age distribution may obscure genetic effects that are age dependent.

Gene × environmental interaction was assessed in two other studies with smaller sample sizes; gene-alcohol interaction analysis in one study [22] identified a SNP rs10826334 near *SLC16A9* whose effect was modulated by both the number of alcoholic drinks and the ounces of alcohol consumed per week. SBP decreased by 3.8 mmHg in those consuming 14 drinks/week compared to only 0.46 in non-drinkers. Gene × smoking and gene x education interactions were explored in two other studies but these await replication [23, 24].

## 10.3 Genetic Mechanisms of BP Regulation and Dysregulation

We now have a greater understanding of the pathways of BP regulation that are influenced by genes (Fig. 10.1). Whilst most of these pathways have emerged from studies of rare monogenic syndromes, GWAS studies are slowly revealing novel pathways. An outline of the molecular pathways of these variants that affect blood pressure and lead to disease is summarised below and in Table 10.1.

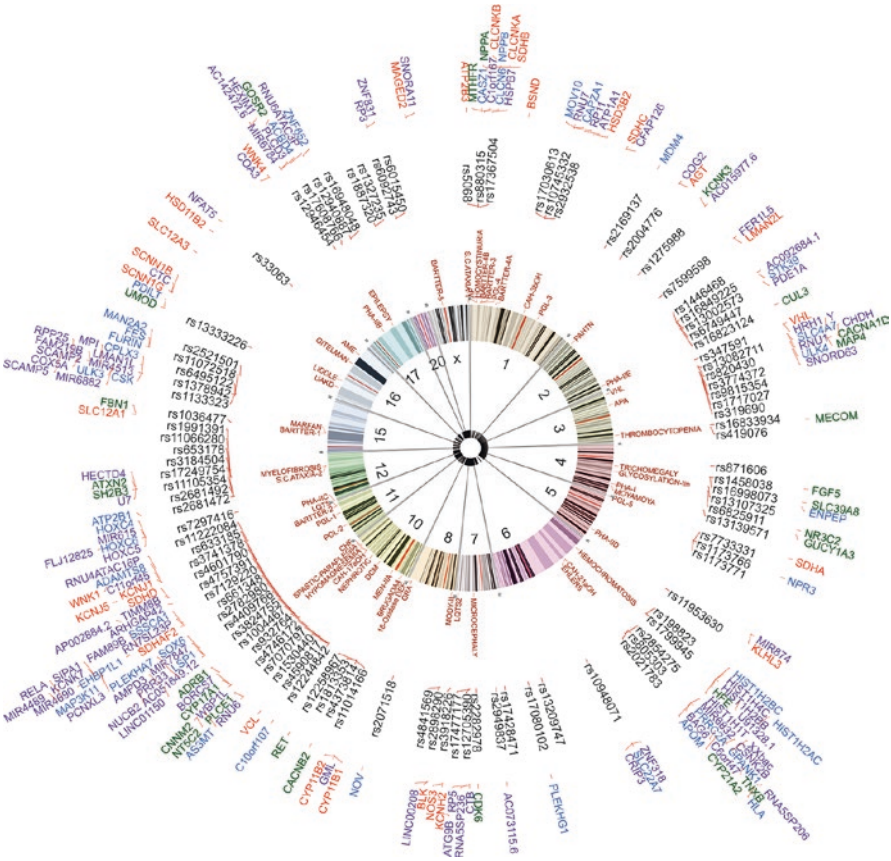


**Fig. 10.1** Genetic landscape of monogenic and polygenic blood pressure/hypertension syndromes, causal genes, and GWAS loci. Tracks from outside-in are sequential genes within BP loci (*blue,* genes in GWAS loci; *red,* monogenic genes; *green,* monogenic genes and with SNPs in blood pressure GWAS); monogenic blood pressure syndromes

## 10.4 Glucocorticoid-Remediable Aldosteronism or Familial Hyperaldosteronism Type 1

This is a rare autosomal dominant disorder caused by a chimeric gene containing the 5′ regulatory sequences of 11β-hydroxylase (CYP11B1, which confers ACTH responsiveness) fused with the distal coding sequences of aldosterone synthase (CYP11B2) leading to ACTH rather than angiotensin II or potassium as the main controller of aldosterone secretion [25]. The specific treatment for hypertension in these individuals is low-dose glucocorticoids to suppress ACTH secretion or amiloride, which directly blocks the epithelial sodium channel (ENaC), or spironolactone, which blocks binding of aldosterone to the mineralocorticoid receptor (MCR).

## 10.5 Apparent Mineralocorticoid Excess

The main defect in AME is absence or reduced activity of 11β-hydroxysteroid dehydrogenase (HSD11B2), resulting in hypertension in which cortisol acts as if it were a potent mineralocorticoid [26]. Normally, both cortisol and aldosterone have MCR agonist activity, and HSD11B2 is protective by metabolising cortisol to prevent its binding to the MCR. Acquired deficiency of this enzyme may result from its inhibition by glycyrrhizic acid (the active metabolite from licorice, certain brands of chewing tobacco, and carbenoxolone). Patients diagnosed with AME syndrome respond well to low-sodium diet and spironolactone, which blocks binding of both cortisol and aldosterone to the MCR.

## 10.6 Pseudohypoaldosteronism Type II (Gordon's Syndrome)

This is a form of hypertension associated with hyperkalaemia, nonanion gap metabolic acidosis, and increased salt reabsorption by the kidney. The WNK (with no lysine [K]) kinases play central roles in regulating mammalian BP by initiating a signalling pathway that controls the activity of critical ion cotransporters in the kidney NCC ($Na^+/Cl^-$ ion cotransporter) and NKCC2 ($Na^+/K^+/2Cl^-$ cotransporter 2). Gordon's syndrome is caused by mutations in WNK1, WNK4, Kelch-like 3 (KLHL3), and Cullin 3 (CUL3) genes. CUL3 and KLHL3 mutations putatively inhibit the ubiquitylation of WNK4 and probably other WNK isoforms, resulting in the overactivation of NCC/NKCC2 ion cotransporters and consequently increased salt retention and hypertension [27, 28]. Treatment consists of either a low-salt diet or thiazide diuretics, aimed at decreasing chloride intake and blocking $Na^+$-$Cl^-$ cotransporter activity, respectively.

## 10.7 Liddle Syndrome

This is an autosomal dominant condition with a clinical picture of hypertension and aldosterone excess but with low aldosterone and renin levels. It is caused by mutations in the genes coding the β or γ subunits of ENaC (*SCNN1B*, *SCNN1G*), resulting in deletions of proline-rich regions which are essential for binding of Nedd4-2 (NEDD4L), a regulatory repressor that promotes channel degradation [29]. The inability of β and γ subunits to bind Nedd4 results in constitutive expression of sodium channels and prolongation of the half-life of ENaCs at the renal distal tubule apical cell surface, leading to increased rates of sodium reabsorption, volume expansion, and hypertension. Treatment of Liddle syndrome with amiloride or triamterene lowers BP and corrects the hypokalaemia and acidosis.

## 10.8 Bartter's Syndrome

This is a salt-losing condition characterised by hypokalaemic metabolic alkalosis and normal or low blood pressure with increased renin activity and high aldosterone levels. The defective mechanism is located in the thick ascending limb (TAL) of Henle's loop and comprises loss of function of NKCC2 or a group of other proteins which lead to secondary loss of function of NKCC2-ROMK channel, chloride channel Kb (ClC-Kb), Bartin, and calcium-sensing receptor (CaSR) [30]. Clinical and laboratory findings among patients with Bartter's syndrome resemble those of chronic abuse of loop diuretics. Patients with Bartter's syndrome, especially those with antenatal manifestation, exhibit increased urine levels of prostaglandin E2 (PGE2) and diminished susceptibility to the pressor effect of Ang II and norepinephrine. Patients with Bartter's syndrome are more prone to life-threatening complications, especially during the postnatal period, such as volume depletion, diarrhoea, spasm, fever, and dangerous hypokalaemia. Chronic therapy of underlying abnormalities such as increased prostaglandin synthesis and RAAS activity, which aggravate electrolyte and acid-base disturbances, includes potassium supplementation and the use of cyclooxygenase inhibitors, angiotensin-converting enzyme (ACE) inhibitors, and potassium-sparing diuretics.

## 10.9 Gitelman's Syndrome

In Gitelman's syndrome, the defective mechanism is located in the distal convoluted tubule and comprises loss of function of the sodium chloride cotransporter (NCC) [31]. Clinical and laboratory findings among patients with Gitelman's syndrome resemble those of chronic abuse of thiazide diuretics. The prevalence of Gitelman's syndrome is estimated to be 1:40,000 in the general population, and the prevalence of heterozygotes in the Caucasian population is approximately 1%. Chronic treatment of patients with Gitelman's syndrome comprises oral potassium and magnesium supplementation with adequate salt and water consumption in order to maintain effective extracellular volume. Indomethacin, amiloride, and eplerenone have been used to treat hypokalaemia.

## 10.10 Primary Aldosteronism

Individuals with primary aldosteronism constitutively produce aldosterone from the adrenal gland, resulting in hypertension with variable hypokalaemia and a suppressed circulating renin. It is estimated that ≤40% of aldosterone-producing adenomas (APAs) harbour a gain-of-function somatic mutation in a $K^+$ channel, KCNJ5, which results in membrane depolarization and enhanced aldosterone production. Mutations in three other genes have been discovered in a further 7% of APAs-ATP1A1, encoding the α1 subunit of $Na^+/K^+$-ATPase itself; ATP2B3, encoding a plasma membrane $Ca^{2+}$-ATPase 3 homologous to the sarcoplasmic

endoplasmic reticulum $Ca^{2+}$-ATPases (SERCA); and CACNA1D, encoding an L-type $Ca^{2+}$ channel, CaV1.3 [32]. A substantial proportion of APAs resembling adrenal zona glomerulosa cells harbour gain-of-function mutations in genes important for the regulation of $Na^{+}$ and $Ca^{2+}$, ATP1A1, and CACNA1D, respectively, whereas KCNJ5 mutations are common in APAs resembling cortisol-secreting cells of the adrenal zona fasciculate [33]. The distinction between APA and bilateral hyperplasia is clinically important because removal of the affected adrenal gland in APAs cures or ameliorates hypertension in the majority of patients, whereas bilateral adrenal hyperplasia requires lifelong treatment with an aldosterone antagonist and bilateral adrenalectomy not indicated.

## 10.11 Phaeochromocytomas and Paragangliomas

Phaeochromocytomas and paragangliomas are rare neuroendocrine tumours of the adrenal glands and the sympathetic and parasympathetic paraganglia. Autosomal dominantly inherited phaeochromocytomas are caused by a variety of RET proto-oncogene mutations. Other pheochromocytoma susceptibility genes include the tumour suppressor gene *VHL* observed in families with von Hippel-Lindau syndrome and the gene that encodes succinate dehydrogenase subunits A, B, C, and D (*SDHA*, *SDHB*, *SDHC*, and *SDHD*, respectively) with heterozygous germline mutations of *SDHB*, *SDHC*, and *SDHD* causing the well-characterised familial pheochromocytoma-paraganglioma syndromes known, respectively, as paraganglioma 4, paraganglioma 3, and paraganglioma 1 [34]. Newer predisposing genes for pheochromocytoma/paraganglioma include *KIF1Bbeta*, *PHD2*, and *SDHAF2* [34].

## 10.12 Uromodulin

A GWAS of BP extremes showed the minor G allele of a UMOD promoter SNP, rs13333226, and was associated with a lower risk of hypertension and reduced urinary UMOD excretion [15]. Uromodulin gene expression is exclusively localised to the thick ascending limb of the loop of Henle (TAL) in the kidney where 25% of the filtered sodium is reabsorbed. UMOD knockout mice demonstrated an increased localization of the salt-retaining NKCC2 (sodium-potassium-chloride cotransporter 2) in subapical vesicles of TAL cells with reduced phosphorylation, both resulting in reduced cotransporter activity [35]. This results in greater sodium excretion as compared to wild-type mice, translating to 20 mmHg lower BP in the knockout mice at baseline, as measured by radiotelemetry [36]. Notably, this difference in BP was exacerbated with salt loading, where the knockout mice were resistant to its hypertensive effects [36]. Conversely, UMOD overexpression caused a dose-dependent increase in UMOD expression and excretion, associated with an increase in BP [37]. The main sodium transporter in TAL is NKCC2 which is blocked by the commonly used loop diuretic furosemide. Trudu et al. [37] showed furosemide treatment significantly enhanced natriuresis and reduced BP levels both in the transgenic mice and in

the hypertensive individuals homozygous for the UMOD increasing allele. Thus GWAS has directed focus on a novel pathway of BP regulation involving altered expression of uromodulin which appears to influence sodium homeostasis and opens an avenue for translational studies to discover or repurpose drugs for treatment of hypertension.

## 10.13 Natriuretic Peptide

Common SNPs in the chromosomal region containing NPPA and NPPB, the genes encoding the ANP and BNP pro-peptides, are associated with circulating levels of the natriuretic peptides and also associated with BP [11, 12]. The GWAS SNP rs5068 lies in the 3′-UTR of the *NPPA* gene which encodes the pro-peptide of ANP, NT-proANP. Healthy volunteers, which were homozygous for the risk allele of rs5068, showed lower NT-proANP expression possibly mediated through a microRNA miR-425 and provide a putative mechanism to explain how the risk allele reduces ANP level and consequently increases BP [38]. The genetic effect of rs5068 on circulating NT-proANP levels is comparable with the environmental change induced by switching from an extremely low-salt diet (230 mg/d) to a diet with salt content typical of a Western diet (4600 mg/d) [38].

## 10.14 Missing Heritability

Despite the identification of numerous SNPs associated with hypertension and BP traits, the proportion of phenotypic variance that is explained by all of these loci together is less than 2.5%. This phenomenon has been described as the problem of "missing heritability" and is not restricted to BP traits [39]. For instance, a classic complex trait such as height which has a very large heritability estimate from family studies (about 80%) has less than 10% of the phenotypic variance explained from the SNPs identified using very large sample sizes (>180,000 individuals). A different way of estimating heritability using SNP data of unrelated individuals is the GCTA approach introduced by Yang et al. ($h^2_{SNP}$) [40]. This is based on estimating the heritability from unrelated individuals using common SNPs with the assumption that heritability estimates in unrelated individuals are only attributable to the common SNPs, whilst the estimation in related individuals is attributed to the entire genome. Applying this method to systolic blood pressure has shown that $h^2_{SNP}$ was about 24%, which is approximately 50% of the heritability estimates from other twin studies, and about 80% of the same study heritability estimate ($h^2$ = 30%) [41]. Furthermore, the number of independent variants with similar effect size to those reported in the ICBP study was estimated to be 116 (95% CI, 57–174), which can collectively explain around 2.2% of the phenotypic variance for BP phenotypes, compared with only 0.9% explained by the 29 SNPs identified by ICBP [13]. These findings indicate that a large proportion of the heritability of BP is "hidden" rather than "missing"

because of large number of common variants, each of which has too small an effect to be detected at the stringent genome-wide significance level using current sample sizes.

## 10.15 Emerging Insights from Other Omics: Metabolomics

Other omic technologies such as metabolomics are potentially powerful tools to identify molecular pathways. They can capture both intrinsic and extrinsic factors, and their dynamic nature makes them ideal for measuring physiological response to external stimuli or the development of pathogenic processes. Metabolomics is the systematic study of metabolites, which are small molecules, generated by the process of metabolism, and has been important in elucidating the pathways underlying metabolic disorders. Small molecule metabolites have an important role in biological systems and can help define candidate systems in the pathogenesis of hypertension. Furthermore, metabolomic markers are closer to the phenotype of interest in contrast to the genotype which is static and unchanged throughout life. Metabolomic profiling of over 3000 adult twins identified a putative novel pathway for BP regulation involving a dicarboxylic acid (hexadecanedioate) with a causal role supported by in vivo studies in rats [42]. The role of hexadecanedioate in a vascular mechanism for hypertension is supported by evidence from a study of pulmonary hypertension, indicating a disruption of β-oxidation and an increase of ω-oxidation in this condition and pointing to a putative role in elevating pressure in both the systemic and the pulmonary circulations [43]. The strongest genetic association seen with hexadecanedioate maps to SLCO1B1, an association previously reported in a metabolome-wide genetic study in Caucasians [44]. Targeted metabolomic profiling in the European Prospective Investigation Into Cancer and Nutrition (EPIC)-Potsdam study showed higher concentrations of serine and glycine, and acyl-alkyl-phosphatidylcholines C42:4 and C44:3 tended to be associated with higher and diacyl-phosphatidylcholines C38:4 and C38:3 with lower predicted 10-year hypertension-free survival [45]. Other metabolite associations with incident hypertension and blood pressure come from two US studies which found 4-hydroxyhippurate, a metabolic sex steroid pattern, and two diacylglycerols 16:0/22:5 and 16:0/22:6 to be associated with blood pressure and incident hypertension [46, 47]. Finally, Menni et al. showed 12 metabolites to be strongly associated with pulse wave velocity with uridine and phenylacetylglutamine, and serine appears strongly correlated with PWV in women [48].

**Conclusions**

Genomics has provided us with a deep understanding of the genetic architecture of hypertension and blood pressure regulation. The studies of monogenic disorders have resulted in a catalogue of critical genes involved in blood pressure regulation, whilst genome-wide association studies are just beginning to yield insights into common variants that affect blood pressure. The emerging encouraging results from metabolomic profiling in hypertension indicate that these signals will be more tractable, and integrating genomics and metabolomics may

accelerate functional studies. The full promise of genetic studies will be realised when these results translate into clinical benefit either in terms of risk prediction, treatment stratification, or new drug discovery.

## References


1. Kotchen TA, Kotchen JM, Grim CE et al (2000) Genetic determinants of hypertension: identification of candidate phenotypes. Hypertension 36:7–13
2. Havlik RJ, Garrison RJ, Feinleib M et al (1979) Blood pressure aggregation in families. Am J Epidemiol 110:304–312
3. Kupper N, Willemsen G, Riese H et al (2005) Heritability of daytime ambulatory blood pressure in an extended twin design. Hypertension 45:80–85
4. Wang NY, Young JH, Meoni LA et al (2008) Blood pressure change and risk of hypertension associated with parental hypertension: the Johns Hopkins Precursors Study. Arch Intern Med 168:643–648
5. Luft FC (2001) Twins in cardiovascular genetic research. Hypertension 37:350–356
6. Lifton RP, Gharavi AG, Geller DS (2001) Molecular mechanisms of human hypertension. Cell 104:545–556
7. Padmanabhan S, Caulfield M, Dominiczak AF (2015) Genetic and molecular aspects of hypertension. Circ Res 116:937–959
8. Weelcome Trust Case Control Consortium (2007) Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 447:661–678
9. Levy D, Larson MG, Benjamin EJ et al (2007) Framingham Heart Study 100K Project: genome-wide associations for blood pressure and arterial stiffness. BMC Med Genet 8(Suppl 1):S3
10. Levy D, Ehret GB, Rice K et al (2009) Genome-wide association study of blood pressure and hypertension. Nat Genet 41:677–687
11. Newton-Cheh C, Johnson T, Gateva V et al (2009) Genome-wide association study identifies eight loci associated with blood pressure. Nat Genet 41:666–676
12. Newton-Cheh C, Larson MG, Vasan RS et al (2009) Association of common variants in NPPA and NPPB with circulating natriuretic peptides and blood pressure. Nat Genet 41:348–353
13. Ehret GB, Munroe PB, Rice KM et al (2011) Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature 478:103–109
14. Wain LV, Verwoert GC, O'Reilly PF et al (2011) Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure. Nat Genet 43:1005–1011
15. Padmanabhan S, Melander O, Johnson T et al (2010) Genome-wide association study of blood pressure extremes identifies variant near UMOD associated with hypertension. PLoS Genet 6:e1001177
16. Salvi E, Kutalik Z, Glorioso N et al (2012) Genomewide association study using a high-density single nucleotide polymorphism array and case-control design identifies a novel essential hypertension susceptibility locus in the promoter region of endothelial NO synthase. Hypertension 59:248–255
17. Kato N, Takeuchi F, Tabara Y et al (2011) Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians. Nat Genet 43:531–538
18. Franceschini N, Fox E, Zhang Z et al (2013) Genome-wide association analysis of blood-pressure traits in African-ancestry individuals reveals common associated genes in African and non-African populations. Am J Hum Genet 93:545–554
19. Lu X, Wang L, Lin X et al (2015) Genome-wide association study in Chinese identifies novel loci for blood pressure and hypertension. Hum Mol Genet 24:865–874
20. Ganesh SK, Chasman DI, Larson MG et al (2014) Effects of long-term averaging of quantitative blood pressure traits on the detection of genetic associations. Am J Hum Genet 95:49–65

21. Simino J, Shi G, Bis JC et al (2014) Gene-age interactions in blood pressure regulation: a large-scale investigation with the CHARGE, Global BPgen, and ICBP Consortia. Am J Hum Genet 95:24–38
22. Simino J, Sung YJ, Kume R et al (2013) Gene-alcohol interactions identify several novel blood pressure loci including a promising locus near SLC16A9. Front Genet 4:277
23. Sung YJ, de Las FL, Schwander KL et al (2015) Gene-smoking interactions identify several novel blood pressure loci in the Framingham Heart Study. Am J Hypertens 28:343–354
24. Basson J, Sung YJ, Schwander K et al (2014) Gene-education interactions identify novel blood pressure loci in the Framingham Heart Study. Am J Hypertens 27:431–444
25. Lifton RP, Dluhy RG, Powers M et al (1992) A chimaeric 11 beta-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. Nature 355:262–265
26. Cerame BI, New MI (2000) Hormonal hypertension in children: 11beta-hydroxylase deficiency and apparent mineralocorticoid excess. J Pediatr Endocrinol Metab 13:1537–1547
27. Wilson FH, Disse-Nicodeme S, Choate KA et al (2001) Human hypertension caused by mutations in WNK kinases. Science 293:1107–1112
28. Boyden LM, Choi M, Choate KA et al (2012) Mutations in kelch-like 3 and cullin 3 cause hypertension and electrolyte abnormalities. Nature 482:98–102
29. Shimkets RA, Warnock DG, Bositis CM et al (1994) Liddle's syndrome: heritable human hypertension caused by mutations in the beta subunit of the epithelial sodium channel. Cell 79:407–414
30. Simon DB, Karet FE, Hamdan JM et al (1996) Bartter's syndrome, hypokalaemic alkalosis with hypercalciuria, is caused by mutations in the Na-K-2Cl cotransporter NKCC2. Nat Genet 13:183–188
31. Simon DB, Nelson-Williams C, Bia MJ et al (1996) Gitelman's variant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. Nat Genet 12:24–30
32. Zennaro MC, Boulkroun S, Fernandes-Rosa F (2015) An update on novel mechanisms of primary aldosteronism. J Endocrinol 224:R63–R77
33. Brown MJ (2014) Ins and outs of aldosterone-producing adenomas of the adrenal: from channelopathy to common curable cause of hypertension. Hypertension 63:24–26
34. Fishbein L (2016) Pheochromocytoma and Paraganglioma: genetics, diagnosis, and treatment. Hematol Oncol Clin North Am 30:135–150
35. Mutig K, Kahl T, Saritas T et al (2011) Activation of the bumetanide-sensitive Na+, K+, 2Cl- cotransporter (NKCC2) is facilitated by Tamm-Horsfall protein in a chloride-sensitive manner. J Biol Chem 286:30200–30210
36. Graham LA, Padmanabhan S, Fraser NJ et al (2014) Validation of uromodulin as a candidate gene for human essential hypertension. Hypertension 63:551–558
37. Trudu M, Janas S, Lanzani C et al (2013) Common noncoding UMOD gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression. Nat Med 19:1655–1660
38. Arora P, Wu C, Khan AM et al (2013) Atrial natriuretic peptide is negatively regulated by microRNA-425. J Clin Invest 123:3378–3382
39. Manolio TA, Collins FS, Cox NJ et al (2009) Finding the missing heritability of complex diseases. Nature 461:747–753
40. Yang J, Benyamin B, McEvoy BP et al (2010) Common SNPs explain a large proportion of the heritability for human height. Nat Genet 42:565–569
41. Vattikuti S, Guo J, Chow CC (2012) Heritability and genetic correlations explained by common SNPs for metabolic syndrome traits. PLoS Genet 8:e1002637
42. Menni C, Graham D, Kastenmuller G et al (2015) Metabolomic identification of a novel pathway of blood pressure regulation involving hexadecanedioate. Hypertension 66:422–429
43. Zhao Y, Peng J, Lu C et al (2014) Metabolomic heterogeneity of pulmonary arterial hypertension. PLoS One 9:e88727

44. Suhre K, Shin SY, Petersen AK et al (2011) Human metabolic individuality in biomedical and pharmaceutical research. Nature 477:54–60
45. Dietrich S, Floegel A, Weikert C et al (2016) Identification of serum metabolites associated with incident hypertension in the European prospective investigation into cancer and nutrition-Potsdam Study. Hypertension 68:471–477
46. Kulkarni H, Meikle PJ, Mamtani M et al (2013) Plasma lipidomic profile signature of hypertension in Mexican American families: specific role of diacylglycerols. Hypertension 62:621–626
47. Zheng Y, Yu B, Alexander D et al (2013) Metabolomics and incident hypertension among blacks: the atherosclerosis risk in communities study. Hypertension 62:398–403
48. Menni C, Mangino M, Cecelja M et al (2015) Metabolomic study of carotid-femoral pulse-wave velocity in women. J Hypertens 33:791–796

# Part III

# Hypertension Phenotypes: Monogenic Syndromes

# Monogenic Forms of Hypertension

# 11

Hakan R. Toka

## 11.1 Introduction

Hypertension is a significant risk factor for cardiovascular morbidity, affecting more than 25% of the adult population, and a worldwide leading cause for cardiovascular mortality [1–3]. Blood pressure goals and treatment strategies remain debated despite numerous clinical hypertension trials and development of more efficient drugs during the last few decades. Ethnic background and comorbidities play a role in achieving adequate blood pressure control.

Since the human genome project [4], advances in nucleotide sequencing and computing have led to identification of allelic gene variation among various populations, predisposing to disease susceptibility. One of the first to notice inheritance of hypertension was the German physician Wilhelm Weitz (1881–1969), who reported that family members of hypertensive individuals were more likely to have elevated blood pressure themselves [5]. The British physician Sir George Pickering reported that blood pressure variation in the general population follows a Gaussian distribution and that the etiology of hypertension is multifactorial, caused by multiple genes and environmental factors [6]. The role of genetic factors on blood pressure was demonstrated by extensive twin studies, which made remarkable contributions. Monozygotic twins have high concordance of blood pressure levels ranging from ~48 to ~60% for systolic and ~34–67% for diastolic blood pressure [7]. In addition, the identification of single genes with large effects on blood pressure variation helped tremendously to define primary physiologic mechanisms, revealing previously unknown disease mechanisms [8, 9]. Initially large families with noticeable blood pressure variation were studied with microsatellite marker and linkage analysis. In some instances, candidate gene analysis was utilized in conditions that had been previously studied in great detail. Next-generation sequencing and advanced

H.R. Toka, M.D., Ph.D., FASN.
Manatee Memorial Hospital, Graduate Medical Education, Bradenton, FL, USA
e-mail: hrtoka@gmail.com



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_11

computational tools have made it possible to identify more disease genes in small pedigrees and individuals with extremes of blood pressure variation [10, 11]. The relevance of recognizing rare diseases caused by single-gene defects has been substantiated by studies in the general population; rare allelic variation in Mendelian disease genes has been shown to affect blood pressure variation in the Framingham population, supporting that the same genes contribute to common phenotypes [12].

Monogenic hypertension and syndromes of renal salt wasting associated with lower blood pressure are reviewed here, comparing distinct molecular pathways of blood pressure regulation.

## 11.2 Monogenic Hypertension

### 11.2.1 Increased Sodium Reabsorption in the Distal Nephron

#### 11.2.1.1 Glucocorticoid-Remediable Aldosteronism (Familial Hyperaldosteronism Type 1; OMIM #103900)

Glucocorticoid-remediable aldosteronism (GRA) is an autosomal disorder with variable increase in aldosterone secretion in response to ACTH. Affected individuals are often suspected of having primary hyperaldosteronism; however computerized tomography scanning of the adrenal glands will be negative for adrenal adenoma. GRA features salt-sensitive hypertension, associated with low renin levels, mild hypokalemia, and metabolic alkalosis (Table 11.1). A distinguishing biochemical feature is the presence of abnormal urinary steroid metabolites (18-hydroxycortisol and 18-oxocortisol), which helped recognizing the etiology of this condition. Linkage analysis of a large kindred with GRA localized the responsible gene to chromosome 8q21. At this locus resides aldosterone synthase (encoded by the gene *CYP11B2* – cytochrome P450, family 11, subfamily B, polypeptide 2), which produces aldosterone in the zona glomerulosa via regulation by angiotensin 2. The neighboring gene at this locus, *CYP11B1* (11β-hydroxylase), has a highly similar nucleotide sequence (~95%) and is regulated by ACTH, participating in the final steps of glucocorticoid production. An unequal crossing-over at this chromosomal location, consisting of the regulatory region of the 11β-hydroxylase gene and the main structural portion of aldosterone synthase gene (Fig. 11.1), leads to the formation of a chimeric gene *CYP11B1/CYP11B2*. The protein of this chimera performs all of the same actions of the aldosterone and however is regulated by ACTH. Glucocorticoid steroid treatment ameliorates hypertension via suppression of the chimeric gene in the adrenal zona fasciculata, giving this condition its name [13, 14].

#### 11.2.1.2 Apparent Mineralocorticoid Excess Syndrome (AME; OMIM #218030)

The clinic presentation of apparent mineralocorticoid excess (AME) can be similar to GRA (Table 11.1); however, contrary to GRA, the inheritance is autosomal recessive and the urine analysis is negative for abnormal steroid metabolites. Instead, urinary free cortisol-to-cortisone ratio is elevated (ratio >0.5) in the

**Table 11.1** Monogenic hypertension syndromes associated with increased sodium reabsorption in the kidney

| Syndrome | Inheritance | Serum $K^+$ | Serum pH | Renin | Aldosterone | Treatment | Locus | Disease gene |
|---|---|---|---|---|---|---|---|---|
| Liddle's syndrome | AD | ↓ | ↑ | ↓ | ↓ | ENaC inhibitors | 16p12 | ENaC (epithelial sodium channel) |
| Glucocorticoid-remediable aldosteronism (GRA) | AD | ↓ | ↑ | ↓ | N (↑) | Corticosteroid therapy | 8q24 | Chimeric gene: 11β-hydroxylase/aldosterone synthase |
| Apparent mineralocorticoid excess (AME) | AR | ↓ | ↑ | ↓ | ↓ | Spironolactone (ENaC inhibitors) | 16q22 | 11β-Hydroxysteroid dehydrogenase |
| Mineralocorticoid receptor (MR)-activating mutation | AD | ↓ | ↑ | ↓ | ↓ | ENaC inhibitors | 4q31 | NR3C2 |
| Aldosterone-producing adrenal adenomas (APA) | De novo[a] | ↓ | ↑ | ↓ | ↑ | Spironolactone (adrenal adenomectomy) | 11q24<br>3p21<br>1p13<br>Xq28 | KCNJ5, CACNA1D, ATP1A1, ATP2B3 |
| Congenital adrenal hyperplasia (CAH) | AR<br>AR | ↓ | ↑ | ↓ | ↓ | Corticosteroid therapy | 10q24<br>8q24 | 17α-Hydroxylase,<br>11β-Hydroxylase |
| Pseudohypoaldosteronism type II (PAH II) | AD<br>AD<br>AR/de novo | ↑ | ↓ | ↓ | N (↑) | Thiazide diuretics | 12p13<br>17q21<br>5q31<br>2q36 | WNK1, WNK4, Kelch-like3, Cullin3 |

*AD* autosomal dominant; *AR* autosomal recessive; *N* normal; *KCNJ5* $K^+$ inwardly rectifying channel, subfamily J, member 5; *CACNA1D* calcium channel, voltage-dependent, L type, α-1D subunit; *ATP1A1* $Na^+/K^+$ ATPase α-1 subunit; *ATP2B3* ATPase, Ca++ transporting, plasma membrane 3

[a]Can be inherited in autosomal-dominant fashion (rare)

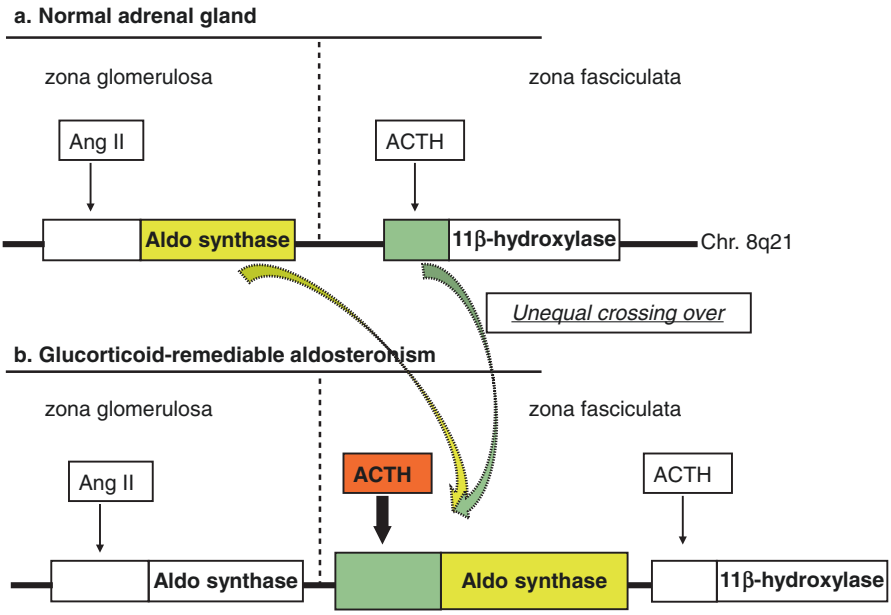



**Fig. 11.1** In glucocorticoid-remediable aldosteronism (GRA), an unequal crossing-over of two neighboring genes, *CYP11B1* (11β-hydroxylase) and *CYP11B2* (aldosterone synthase), leads to a gene fusion. The resulting chimeric gene product consists of the regulatory 5′ region of the 11β-hydroxylase and the structural portion of aldosterone synthase, performing all of the same functions as aldosterone, however being regulated by ACTH (adrenocorticotropic hormone) instead of angiotensin 2

setting of normal serum cortisol levels. Severe nephrocalcinosis and bilateral renal cysts have been reported in some cases; the etiology is not entirely clear but may be related in part due to chronic, long-standing hypokalemia. The elevated urinary cortisol-to-cortisone ratio was useful in identifying the gene defect, because cortisol can bind and activate the mineralocorticoid receptor (MR). This activation is inhibited by the 11β-hydroxysteroid dehydrogenase enzyme (11β-HSD), which rapidly oxidizes cortisol to the inactive metabolite cortisone. This mechanism is important, because at baseline circulating concentrations of cortisol are several orders of magnitude higher than aldosterone. Candidate gene analysis in individuals with AME identified bi-allelic loss-of-function mutations in the kidney isoform of 11β-HSD, rendering 11β-HSD2 incapable of converting cortisol to cortisone [15]. Low-sodium diet, MR antagonists, and ENaC blockers are used to treat patients with AME. Individuals ingesting large amounts of licorice or other glycyrrhetinic acid-containing substances (e.g., certain liquors, chewing tobaccos, etc.) can develop the features of AME due to inhibition of 11β-HSD2 by glycyrrhetinic acid [16].

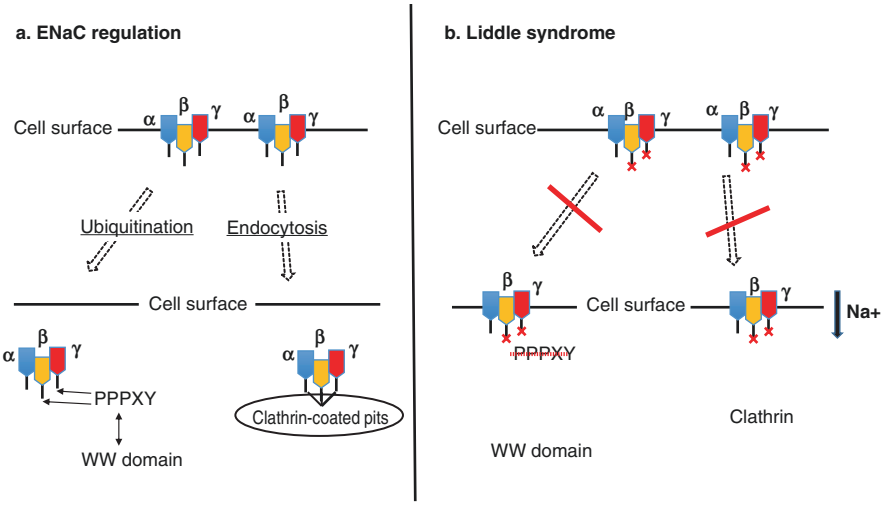



**Fig. 11.2** (**a**) The epithelial sodium channel ENaC is a membrane protein consisting of three subunits (α, β, and γ) forming a heteromeric channel, whose surface expression (activity) is regulated by ubiquitination and clathrin-dependent endocytosis. A peptide sequence—PPPXY—in the cytoplasmic tails of the ENaC subunits interacts with tryptophan-rich WW-domains of ubiquitin-protein ligase such as NEDD4-2 (not shown), degrading cell surface proteins. (**b**) Missense mutations or deletions in PPPXY of either the β- or the γ-subunit lead to impaired deactivation of ENaC from the cell surface, leading to increased sodium reabsorption by a constitutively active ENaC

### 11.2.1.3 Liddle Syndrome (OMIM #218030)

Grant Liddle was the first to describe this autosomal dominant condition, in which affected individuals feature early, and frequently severe, hypertension associated with metabolic alkalosis and hypokalemia [17]. Both renin and aldosterone levels are suppressed. Hypertension is not responsive to spironolactone treatment, however improves with ENaC blockers [18]. Candidate gene analysis identified gain-of-function mutations in two out of its three ENaC subunits as causes for this syndrome (Fig. 11.2). Missense mutations or deletions in the cytoplasmic tails of the β- or the γ-subunit lead to impaired deactivation of ENaC from the tubular cell surface in the renal collecting duct [19, 20]. The mutations are reported in a proline-rich PY motif (also called PPPXY), which interact with tryptophan-rich WW-domains of proteins that are known for ubiquitination and degradation of cell surface proteins. The cytoplasmic tails of ENaC are also believed to play an important role for endocytosis via clathrin-coated pits [21]. In Liddle syndrome, internalization of the ENaC channels from the cell surface is impaired, leading to constitutively active sodium reabsorption (Fig. 11.2), which explains the extraordinary efficacy of ENaC blockers in the treatment of this syndrome (Table 11.1). Treatment with amiloride is preferred over triamterene due to a longer half-life and decreased risk of crystallizing in acidic urine, which can lead to irreversible renal tubular injury in rare cases [22].

#### 11.2.1.4 Activating Mutation in the Mineralocorticoid Receptor (Autosomal Dominant Hypertension with Severe Exacerbation in Pregnancy; OMIM #605115)

Candidate gene screening in individuals with features resembling Liddle's syndrome, who tested negative for ENaC mutations, led to the identification of a gain-of-function mutation in the MR gene *NR3C2* [23]. The heterozygous mutation in one affected family was found at codon 810 of *NR3C2*, resulting in a leucine (L) amino acid substitution for serine (S). The mode of transmission is autosomal dominant (Table 11.1). Affected females exhibited severe gestational hypertension, which suggested that other steroids may act as agonists of mutated MR-S810L. Structural protein analysis revealed that the mutation allowed for activation by steroids lacking the 21-hydroxyl group such as progesterone. This modification also explains why in *in vitro* studies spironolactone acts as an agonist of mutated MR-S810L [23].

#### 11.2.1.5 Aldosterone-Producing Adrenal Adenomas (Familial Hyperaldosteronism Type III; OMIM #613677)

Aldosterone-producing adrenal adenomas (APAs) are a frequent cause for secondary hypertension due to renin-independent excess production of aldosterone in the adrenal gland [24]. Individuals with APA have typically negative family history (Table 11.1). Patients are identified due to hypokalemia and feature a characteristic unilateral adrenal mass on computerized tomography. Adrenal vein sampling demonstrates predominant aldosterone secretion from the gland harboring the tumor and is crucial for the diagnosis, allowing to distinguish APA from idiopathic hyperaldosteronism (bilateral adrenal hyperplasia).

A rare monogenic form of primary hyperaldosteronism with autosomal-dominant mode of inheritance was identified in one family with bilateral familial adrenal adenomas associated with severe hypertension [25]. Mutational analysis revealed a novel germline mutation (T158A) within a highly conserved residue of *KCNJ5*, encoding for the inwardly rectifying potassium channel Kir3.4. Structural proteomics and in vitro experiments suggest that *KCNJ5* mutations can lead to chronic depolarization of zona glomerulosa cells in the adrenal glands and thereby increase cell proliferation and aldosterone production [26, 27]. Independently performed exome sequencing studies from APA tissues revealed that ~30–40% harbor somatic mutations at highly conserved residues on *KCNJ5* (either G151R or L168R) [28, 29].

Since the discovery of *KCNJ5* as the main mechanism for the etiology of APA, somatic mutations in other, less frequently affected genes have been recognized. These include somatic gain-of-function in *CACNA1D*, encoding a voltage-gated calcium channel [30]; loss-of-function in *ATP1A1*, encoding the Na/K-ATPase α1-subunit [31]; and loss-of-function in *ATP2B3*, encoding a calcium ATPase [32]. Primary hyperaldosteronism due to somatic *CACNA1D* mutations affect ~12% of individuals, who can feature seizures and neurological abnormalities (OMIM #615474). Interestingly, there is a gender discrepancy in the frequency of APA gene mutations; at least twice as many more females than males carry somatic mutations

in *KCNJ5* (29), whereas mostly males will have somatic mutations in *ATP1A1* and *ATP2B3* [32]. The frequency of ATP1A1 and ATP2B3 as cause for APA has been estimated ~5% and 1–2%, respectively [32].

#### 11.2.1.6 Congenital Adrenal Hyperplasia (CAH; OMIM #202110, #202010)

Congenital adrenal hyperplasia (CAH) syndromes are autosomal recessive inherited conditions, resulting from mutations in genes that facilitate biochemical steroidogenesis in the adrenal glands. In this condition, the adrenal glands produce deficient amounts of cortisol while secreting either excessive or deficient amounts of sex hormones and mineralocorticoid steroids during prenatal development [33]. The CAH syndromes are classified into common, so-called salt-wasting or simple-virilizing CAH, mostly due to 21α-hydroxylase deficiency, and the rarer, non-classical forms, which cause ~5–10% of CAH cases. Only nonclassical CAH is associated with hypertension, which is caused by increased production of mineralocorticoid precursors (11-deoxy corticosterone and corticosterone). The cause is loss-of-function mutations in *CYP11B1* (enzyme 11β-hydroxylase, OMIM #202010) or *CYP17A1* (enzyme 17α-hydroxylase, OMIM #202110) [33]. While ACTH and mineralocorticoids are increased, both cortisol and sex steroids are decreased. Hypertension can develop in childhood due to volume expansion and is associated with hypokalemia and metabolic alkalosis (Table 11.1). Treatment with glucocorticoids suppresses ACTH, thereby decreasing mineralocorticoid precursor production and alleviating hypertension [34]. Other features in CAH include female virilization (*CYP11B1* mutations) and ambiguous genitalia in genetic males or ovarian dysfunction at puberty in genetic females (*CYP17A1 mutations*).

#### 11.2.1.7 Pseudohypoaldosteronism Type II (Hypertension Hyperkalemia Syndrome; OMIM #614491, #614492, #614495, #614496)

Pseudohypoaldosteronism type II (PHA II) is a unique form of rare hypertension syndromes associated with hyperkalemia and metabolic acidosis [35] (Table 11.1). Hypercalciuria has been reported in some cases, making this syndrome a near mirror image of Gitelman syndrome [36]. Renin is typically suppressed whereas aldosterone levels can be elevated due to hyperkalemia. The hypertension is chloride-dependent because the exchange of bicarbonate or citrate infusions instead of chloride can ameliorate blood pressure elevation [37]. To date, four genes have been identified causing this heterogeneous syndrome, including intronic deletions in the With-No-Lysine(K) kinase *WNK1* (PHA type IIB) and missense mutations in *WNK4* (PHA type IIC). Both were discovered by linkage analysis of large pedigrees with autosomal dominant inheritance of PHA II [38]. The WNK mutation leads to increased sodium reabsorption via activation of the sodium-chloride cotransporter (NCC) in the distal convoluted tubule (DCT), regardless of volume status; simultaneously renal tubular potassium excretion is decreased in PHA II (via inhibition of ROMK, the apical renal outer medullary potassium channel) despite hyperkalemia [39].

Since the discovery of the WNKs, various functions in the kidney have been identified. WNK4 is regulated by intracellular chloride concentration [Cl]i. In conditions of high [Cl]i, WNK4 seems to act as an inhibitor of NCC via heterodimer formation with other WNKs. In contrast, when [Cl]i is low, WNK4 can activate NCC. This modulation of WNK4 by [Cl]i has been shown to account for the potassium-sensing properties of the distal convoluted tubule [40]. Besides NCC and ROMK regulation in the distal convoluted tubule, a WNK kinase cascade including the SGK1 (serum/glucocorticoid regulated kinase 1)/Nedd4-2 complex is believed to regulate ENaC in the cortical collecting duct [41]. Interestingly, the modulation of all channels and transporter by WNKs occurs via the phosphorylation of other serine-threonine kinases such as the SPAK (Ste20-related proline-alanine-rich kinase)/OSR1 (oxidative stress-responsive kinase) complex, which regulates NCC [42]. In addition, extrarenal WNK kinases have been identified in numerous other tissues, making them a potential drug target not only for blood pressure regulation and potassium handling but also for cystic fibrosis (WNK4) and central nervous system disorders (WNK2 and WNK3), including autism, epilepsy, and stroke [43–45].

Other gene defects causing PHA II have been identified by exome sequencing: *KLHL3* (Kelch-like 3, PHA type IID) and *CUL3* (Cullin3, PHA type IIE) genes form a RING-type E3 ligase ubiquitination system, which regulates the abundance of WNKs in the distal nephron [46]. Impaired ubiquitination of NCC from the luminal cell surface is the speculated mechanism for PHA type IID and IIE [42, 46].

All PHA II genes lead to increased stability and/or function of NCC at the cell surface, resulting in hyperkalemic hypertension; however the PHA II phenotype can vary greatly. Patients affected by *de novo CUL3* mutations are more severely affected as they develop PHA II at younger age and present with more severe hyperkalemia and acidosis. In contrast, patients with *WNK1* mutations feature typically mild hyperkalemia with hypertension occurring at later age. Nevertheless, thiazide diuretics are a very effective treatment for all forms of PHA II, regardless of gene defect and severity of presenting features [36].

### 11.2.2 Sympathetic Nervous System Hyperactivity: Hereditary Familial Pheochromocytoma (OMIM #171300)

Pheochromocytomas (PCCs) are rare catecholamine-producing tumors, associated with variable symptoms depending on type and secretory pattern of produced catecholamine(s). Hypertension in PCC is elicited by increased sympathetic activity and can present as labile or paroxysmal, frequently complicated by orthostatic hypotension. Plasma renin activity and aldosterone levels are both elevated due to decreased intravascular volume and increased renin secretion; hypokalemia can be seen [47]. Over ~90% of PCCs occur in the adrenal gland, whereas ~10% can be found in extra-adrenal tissue (paragangliomas). PCC can be malignant and metastasize (~10%) and also occur bilaterally (~10%).

Overall, known genetic mutations may account for the pathogenesis of ~60% of PCCs and paragangliomas [48]. PCCs can present as part of hereditary syndromes, which include the phakomatosis von Hippel-Lindau syndrome (OMIM #193300), multiple endocrine neoplasia (MEN) types IIA (#171400) and IIB (#162300), and neurofibromatosis I (#162200). The most frequent cause of inherited PCC is gain-of-function mutation in the *RET* proto-oncogene causing MEN type II [49], which can feature medullary thyroid cancer (types IIA and IIB), hyperparathyroidism (type IIA), and mucosal neuromas (type IIB). Mutations in genes encoding for the subunits of the succinate dehydrogenase (SDH) protein complex are frequently the cause for paragangliomas [50]. A recent exome sequencing study from non-syndromic PCC tissues identified novel, amino acid-changing somatic mutations in genes associated with apoptosis-related pathways. Particularly, mutations in the "cancer" gene *KMT2D* (lysine (K)-specific methyltransferase 2D) were discovered more frequently (~14%) [51].

The treatment of choice for PCCs is surgical resection of the affected adrenal gland(s) or the catecholamine-producing paraganglioma, respectively. Irreversible alpha-blockade prior to surgery and use of beta-blockers is mandatory to prevent life-threatening hypertensive complications [47].

### 11.2.3 Pathway Affecting Vascular Resistance: Hypertension Brachydactyly Syndrome (HBS; OMIM #112410)

A hypertension syndrome associated with brachydactyly was first described in 1973 in a large Turkish kindred [52]. The condition has autosomal dominant pattern of inheritance and has 100% penetrance of all features. Affected individuals are of short stature, develop hypertension in early childhood, and have decreased life expectancy when untreated [53]. Hand X-rays show shortened metacarpal bones (brachydactyly type E), cone-shaped epiphysis, and short end phalanx of the thumb (brachydactyly type B) [54]. Blood pressure in HBS is not salt-sensitive; the renin-angiotensin-aldosterone and catecholamine axis function normally. Left ventricular cardiac hypertrophy or retinopathy despite severe hypertension are absent [55, 56]. Affected individuals require two or more antihypertensive drugs to lower blood pressure [57]. Baroreceptor reflex response is abnormal, resulting in an excessive increase of blood pressure with sympathetic stimuli [58]. In addition, neurovascular anomalies at the left ventrolateral medulla oblongata can be found on MRI in all affected individuals [59]. The significance of this finding is unclear.

The gene locus was mapped to chromosome 12p [53], containing a complex chromosomal rearrangement of unclear significance [54, 60]. The disease gene for this condition was discovered by utilizing genome sequencing in affected individuals from six unrelated families; all displayed novel gain-of-function mutations in highly conserved residues in exon 4 of the phosphodiesterase 3A gene *PDE3A* [61]. In vitro analyses of mesenchymal stem cell-derived vascular smooth muscle cells (VSMCs) and chondrocytes obtained from affected individuals suggested increased protein kinase A-mediated PDE3A phosphorylation as disease mechanism. The

mutations lead to increase in PDE3A's cAMP-hydrolytic activity and thereby enhance cell proliferation. The level of phosphorylated vasodilator-stimulated phosphoprotein is diminished in VSMCs, suggesting altered vascular smooth muscle function. Cell-based studies demonstrated that available PDE3A inhibitors suppress the mutant isoforms [62]. Although the exact molecular mechanisms for this syndrome are still being investigated, VSMC-expressed PDE3A is an interesting therapeutic target for the treatment of hypertension.

### 11.2.4 Pathway with Unclear Mechanism: Mitochondrial Hypomagnesemia, Hypertension, and Hypercholesterolemia Syndrome (OMIM #500005)

A hypercholesterolemia, hypertension, and hypomagnesemia syndrome was described in a family with 142 members [63]. Sequencing of the mitochondrial genome identified a homoplasmic mutation substituting cytidine for uridine immediately 5-prime to the mitochondrial tRNA anticodon for isoleucine (Ile) in all members of the maternal lineage, indicating mitochondrial inheritance. *In silico* analysis showed that uridine at this position is nearly invariant among tRNAs stabilizing the tRNA anticodon loop. Hypertension, hypomagnesemia, and hypercholesterolemia each showed ~50% penetrance among adults on the maternal lineage. The prevalence of hypertension showed marked age dependence, increasing from ~5% in subjects under age of 30 years to ~95% in those over the age of 50 years. In vivo NMR (nuclear magnetic resonance) spectroscopy of striated muscle in one affected individual showed decrease in ATP production [63]. Given the loss of mitochondrial function with aging due to increased defects in the mitochondrial genome, increased blood pressure could be explained by loss of ATP production, which has been associated with hypertension in the animal model (63). The increased presence of reactive oxygen species (ROS) secondary to mitochondrial dysfunction is also a possible mechanism for hypertension [64]. In addition, epidemiological studies have shown that children of hypertensive mothers are more likely to develop hypertension, suggesting that the mitochondrial genome could be associated with inheriting hypertension [65]. The exact mechanism(s) of this mitochondrial syndrome remain unknown.

## 11.3 Genetic Syndromes of Decreased Blood Pressure

### 11.3.1 Renal Sodium Wasting in the Thick Ascending Limb: Bartter Syndrome (OMIM #601678, #241200, #607364, #602522)

Bartter syndrome refers to a heterogeneous group of disorders that are unified by autosomal recessive transmission of pronounced renal salt wasting, hypokalemic

**Table 11.2** Bartter's syndrome: salt-wasting nephropathies due to abnormal function of the thick ascending limb (TAL)

| Type | Inheritance | Serum $K^+$ | Serum pH | Renin | Aldosterone | Treatment | Locus | Disease gene (protein) |
|---|---|---|---|---|---|---|---|---|
| 1 | AR | ↓ | ↑ | ↑ | ↑ | Increase salt intake (for all types) | 15q21 | SLC12A1 (NKCC2) |
| 2 | AR | ↓ | ↑ | ↑ | ↑ | | 11q24 | KCNJ1 (ROMK) |
| 3 | AR | ↓ | ↑ | ↑ | ↑ | | 1p36 | CLCNKB |
| 4 | AR | ↓ | ↑ | ↑ | ↑ | | 1p32 | BSND |

*AR* autosomal recessive; *AD* autosomal dominant; *SLC12A1* solute carrier family 12, member 1; *KCNJ1* potassium inwardly rectifying channel, subfamily J, member 1; *CLCNKB* chloride channel, voltage-sensitive Kb; *BSND* barttin

metabolic alkalosis, and hypercalciuria (Table 11.2). The mechanism is a defect in the reabsorption of sodium chloride in the thick ascending limb (TAL), where ~30% of filtered salt is normally reabsorbed via coordinated operation of apical and basolateral transporters and channels that generate a lumen-positive electrical potential across the epithelial layer (Fig. 11.3). Reduced function of TAL transporters or channels, secondary either to pharmacological inhibition (loop diuretics) or genetic mutations (i.e. Bartter syndrome), is associated with renal salt wasting [65].

Neonatal (also known as antenatal) Bartter syndrome is the most common form and is associated with polyhydramnios during pregnancy. Newborn infants feature polyuria and polydipsia, requiring parenteral fluid administration for severe volume contraction. Frequently hypercalciuria is present and nephrocalcinosis will develop, leading to renal failure. Neonatal Bartter syndrome is caused by homozygous or compound heterozygous loss-of-function mutations in the sodium-potassium-2chloride cotransporter (NKCC2) gene (Bartter type 1) or in the renal outer medullary potassium channel (ROMK) gene (Bartter type 2) [66, 67]. In comparison, type 3 or "classic" Bartter is caused by loss-of-function mutations in the voltage-gated chloride channel Kb (CLCNKB) gene and is usually diagnosed at school age or later [68]. In type 3, increased urinary calcium excretion is significantly milder and nephrocalcinosis is not present; however kidney stones can develop later in life. Renal function is typically normal; however, progression to end-stage renal disease has been described in some cases [69]. Bartter type 4 is caused by mutations in barttin (*BSND*), an accessory β-subunit for CLCNKB in the TAL [70]. Because barttin is also expressed in stria vascularis cells of the inner ear, where it serves as β-subunit of a highly similar chloride channel (CLCNKA), affected individuals typically feature sensorineural hearing loss.

Gain-of-function mutations in the calcium-sensing receptor gene (*CASR*) can feature renal salt wasting and hypercalciuria, thereby mimicking Bartter syndrome [71]. PTH levels are severely suppressed in this syndrome, which is known as autosomal dominant hypocalcemia (OMIM #601198); by some this syndrome is classified as Bartter type 5 due to the presence of renal salt wasting, hypokalemia, and hypercalciuria.

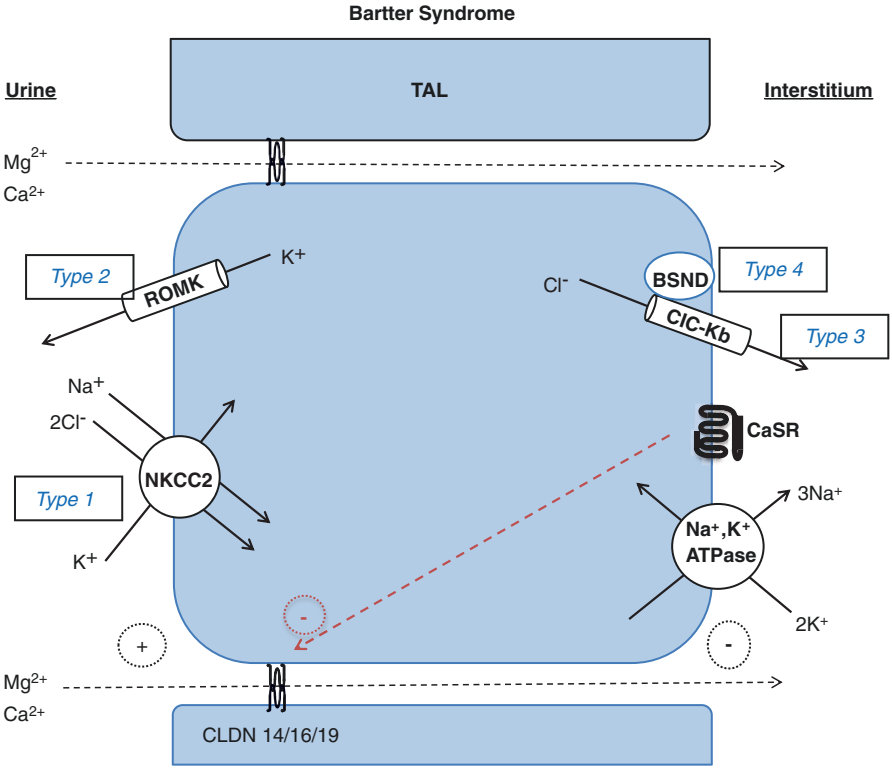



**Fig. 11.3** Schematic illustration of a tubular epithelial cell in the thick ascending limb (TAL). Loss of function of the apical sodium-potassium-2 chloride cotransporter (NKCC2) or the renal outer medullary potassium channel (ROMK) cause neonatal Bartter type 1 or type 2, respectively. Classic Bartter or type 3 is caused by loss of function of the voltage-gated chloride channel Kb (CLCNKB), located at the basolateral membrane. A defect in CLCNKB's β-subunit barttin causes a similar phenotype and however is associated with sensorineural deafness due to barttin's presence in the inner ear (type 4). A phenocopy of Bartter (by some classified as type 5) is caused by gain-of-function mutations in the calcium-sensing receptor (CASR), which is a negative regulator of paracellular calcium and magnesium transport (modulating a tight junctional claudin complex, illustrated by red arrow). Altered electrochemical driving forces in the TAL may explain the Bartter features observed. Abbreviations: *BSND* barttin; *CLDN* claudin

## 11.3.2 Renal Sodium Wasting in the Distal Convoluted Tubule and/or Collecting Duct

### 11.3.2.1 Gitelman Syndrome (OMIM #263800)

Gitelman syndrome is an autosomal recessive condition, in which affected individuals present with symptoms identical to those who are on thiazide diuretics, featuring hypokalemia, hypomagnesemia, metabolic alkalosis, and associated renal sodium wasting (Table 11.3). Linkage analysis in several unrelated families identified the thiazide-sensitive sodium chloride cotransporter (NCC) gene *SLC12A3* as cause for this disease. Both homozygous and compound heterozygous loss-of-function

**Table 11.3** Monogenic forms of salt-wasting nephropathies associated with low(er) blood pressure

| Syndrome | Inheritance | Serum $K^+$ | Serum pH | Renin | Aldosterone | Therapy | Locus | Disease gene (protein) |
|---|---|---|---|---|---|---|---|---|
| Gitelman | AR | ↓ | ↑ | ↑ | ↑ | Increase salt intake | 16q13 | SLC12A3 (NCCT) |
| EAST | AR | ↓ | ↑ | ↑ | ↑ | Increase salt intake | 1q23 | KCNJ10 (Kir4.1) |
| Pseudohypoaldosteronism type I (PHA I) | AD<br>AR<br>AR<br>AR | ↑ | ↓ | ↑ | ↑ | Increase salt intake | 4q31<br>12p13<br>16p13<br>16p13 | NR3C2<br>SCNN1A<br>SCNN1B<br>SCNN1G |
| Renal tubular dysgenesis (RTD) | AR | ↑ | ↓ | ↑ or ↓ | ↓ | Vasopressors | 1q32<br>1q42<br>3q24<br>17q23 | REN<br>AGT<br>ACE<br>AGT1R |

*AR* autosomal recessive; *AD* autosomal dominant; *EAST* epilepsy, ataxia, sensorineural deafness, tubulopathy; *Kir 4.1* inward rectifier-type $K^+$-channel, member 4.1; *NR3C2* nuclear receptor subfamily 3, group C, member 2; *SCNN1A, 1B or 1C* sodium channel, non-voltage gated 1, α-subunit, β-subunit or γ-subunit (genes encoding for ENaC subunits); *REN* renin; *AGT* angiotensinogen; *ACE* angiotensin-converting enzyme; *AGT1R* angiotensin 2 type 1 receptor

mutations have been reported [72]. Affected individuals can be asymptomatic; however, muscular cramps, weakness, and irritability related to hypomagnesemia and hypokalemia can occur. More severe symptoms such as paralysis and cardiac arrest are rare but have been reported [73]. Interestingly, individuals with heterozygous loss-of-function mutation, with only one mutated NCC allele (estimated prevalence ~0.5–1% in Caucasian population), may have a survival benefit due to lower blood pressure levels and increased bone mineral density [12, 74].

#### 11.3.2.2 Pseudohypoaldosteronism Type I (OMIM #177735, #264350)

Pseudohypoaldosteronism (PHA) type I is a salt-wasting nephropathy characterized by unresponsiveness to mineralocorticoids [75, 76]. Affected individuals present with hyperkalemic acidosis despite high aldosterone levels and show significant improvement with high-salt diet (Table 11.3). Two genetic subtypes can be distinguished, type IA, inherited in an autosomal dominant fashion, and type IB, transmitted in autosomal recessive pattern. Type IA is caused by mutations in the mineralocorticoid receptor gene *NR3C2* and has a milder phenotype [75]. In infancy, affected children display frequent vomiting, failure to thrive, and short stature; labs feature hyponatremia, hyperkalemia, and urinary salt wasting. PHA type IA improves with age, and affected individuals can be asymptomatic when they reach adulthood and however remain susceptible to volume depletion. The recessive form, type IB, is caused by loss-of-function mutations in any one of the three genes encoding for the α-, β-, or γ-subunits of ENaC, leading to decreased channel activity and thereby severe renal salt wasting [76]. PHA type IB presents a near mirror image of Liddle syndrome. Sodium content is also increased in saliva, sweat, and stool. Multiple organ systems are affected and the mortality is high in the neonatal period. Respiratory failure is a frequent complication, sometimes leading to misdiagnosis of cystic fibrosis.

#### 11.3.2.3 Epilepsy, Ataxia, Sensorineural Deafness, and Tubulopathy (EAST Syndrome; OMIM #612780)

EAST syndrome features salt-wasting tubulopathy associated with neurological abnormalities [77, 78]. The mode is autosomal recessive and consanguinity has been described in some families. The responsible gene was mapped by linkage analysis to chromosome 1q23 (*KCNJ10*) and encodes for the inwardly rectifying potassium channel Kir4.1. It is expressed in the basolateral membranes of the distal convoluted tubule (DCT), connecting tubule (CNT), and also collecting duct epithelia. The electrolyte and acid-base abnormalities in EAST are similar to Gitelman syndrome, featuring hypokalemia, hypomagnesemia, and metabolic alkalosis (Table 11.3). Renin and aldosterone levels are both elevated. Affected individuals compensate for renal salt losses with increased salt consumption, thereby typically maintaining normal blood pressure [77]. The proposed mechanism is that *KCNJ10* loss-of-function mutations impair the activity of the Na/K-ATPase at the basolateral membrane, thereby decreasing transepithelial sodium transport in the DCT, CNT, and CD [78]. Due to expression of Kir4.1 in neuronal tissue, including the inner ear,

various additional features are present. Mice deficient in *KCNJ10* exhibit striking pathology of the entire central nervous system and display renal salt wasting and volume contraction as well [79].

#### 11.3.2.4 Renal Tubular Dysgenesis (RTD; 267,430)

Autosomal recessive transmitted RTD is a heterogeneous developmental disorder, characterized by abnormal renal tubular formation associated with persistent fetal oligoanuria and severe hypotension. In utero or perinatal death is frequently observed in affected children [80]. Parental consanguinity has been reported in ~1/3 of cases [81]. Infants surviving the neonatal period display severe and refractory hypotension requiring vasopressors, respiratory assistance, and kidney replacement therapy. Death at birth occurs frequently due to pulmonary hypoplasia and respiratory failure. Only few individuals with RTD survive after days or weeks of intensive care [81]. Kidney histopathology showed absence of differentiated proximal tubular cells, which is the pathological hallmark of this disorder. All renal tubules appear abnormally developed, primitive, and reminiscent of collecting tubules. Postnatal skull ossification defects (so-called hypocalvaria) are often seen. RTD is caused by loss-of-function mutations in four genes, all encoding for proteins of the renin-angiotensin system (RAS). The genes shown in Table 11.3 include REN (renin), AGT (angiotensinogen), ACE (angiotensin-converting enzyme), and AGT1R (angiotensin II receptor type 1). A similar phenotype can be seen in children whose mothers were exposed to RAS blockers during pregnancy (known as ACEi fetopathy) [82].

**Conclusion**

Research on rare monogenic hypertension and its counterpart, syndromes with lower blood pressure, has been insightful to understanding disease mechanisms affecting blood pressure variation. It is likely that the combined effects of rare allelic variation in the described genes and others regulate blood pressure variation in the general population [12]. Studies on monogenic hypertension along with blood pressure genomics described elsewhere in this textbook will advance our understanding of hypertension, define new drug targets, and improve treatment and prevention.

## References

1. Mosterd A, D'Agostino RB, Silbershatz H et al (1999) Trends in the prevalence of hypertension, antihypertensive therapy, and left ventricular hypertrophy from 1950 to 1989. N Engl J Med 340(16):1221–1227
2. WHO (2009) Global health risks: mortality and burden of disease attributable to selected major risks. WHO Library Cataloguing-in-Publication Data
3. Kearney PM, Whelton M, Reynolds K et al (2005) Global burden of hypertension: analysis of worldwide data. Lancet 365(9455):217–223
4. Lander ES, Linton LM, Birren B et al (2001) Initial sequencing and analysis of the human genome. Nature 409(6822):860–921
5. Weitz W (1923) Zur Atiology der genuinen Hypertonie. Klin Med 96:151
6. Pickering GW (1955) The genetic factor in essential hypertension. Ann Intern Med 43(3):457–464

7. Hottenga JJ, Boomsma DI, Kupper N et al (2005) Heritability and stability of resting blood pressure. Twin Res Hum Genet 8(5):499–508
8. Lifton RP, Gharavi AG, Geller DS (2001) Molecular mechanisms of human hypertension. Cell 104(4):545–556
9. Toka HR, Koshy JM, Hariri A (2013) The molecular basis of blood pressure variation. Pediatr Nephrol 28(3):387–399
10. Bockenhauer D, Medlar AJ, Ashton E et al (2012) Genetic testing in renal disease. Pediatr Nephrol 27:873–883
11. Bailey-Wilson JE, Wilson AF (2011) Linkage analysis in the next-generation sequencing era. Hum Hered 72(4):228–236
12. Ji W, Foo JN, O'Roak BJ et al (2008) Rare independent mutations in renal salt handling genes contribute to blood pressure variation. Nat Genet 40(5):592–599
13. Lifton RP, Dluhy RG, Powers M et al (1992) A chimaeric 11 beta-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. Nature 355(6357):262–265
14. Lifton RP, Dluhy RG, Powers M et al (1992) Hereditary hypertension caused by chimaeric gene duplications and ectopic expression of aldosterone synthase. Nat Genet 2(1):66–74
15. Mune T, Rogerson FM, Nikkila H et al (1995) Human hypertension caused by mutations in the kidney isozyme of 11 beta-hydroxysteroid dehydrogenase. Nat Genet 10(4):394–399
16. White PC, Mune T, Agarwal AK (1997) 11 beta-Hydroxysteroid dehydrogenase and the syndrome of apparent mineralocorticoid excess. Endocr Rev 18(1):135–156
17. Liddle GW, Bledsoe T, Coppage WS Jr (1963) A familial renal disorder stimulating primary aldosteronism but with negligible aldosterone secretion. Trans Assoc Am Phys 76:199–213
18. Botero-Velez M, Curtis JJ, Warnock DG (1994) Brief report: Liddle's syndrome revisited—a disorder of sodium reabsorption in the distal tubule. N Engl J Med 330(3):178–181
19. Shimkets RA, Warnock DG, Bositis CM et al (1994) Liddle's syndrome: heritable human hypertension caused by mutations in the beta subunit of the epithelial sodium channel. Cell 79(3):407–414
20. Hansson JH, Nelson-Williams C, Suzuki H et al (1995) Hypertension caused by a truncated epithelial sodium channel gamma subunit: genetic heterogeneity of Liddle syndrome. Nat Genet 11(1):76–82
21. Rotin D, Kanelis V, Schild L (2001) Trafficking and cell surface stability of ENaC. Am J Physiol Renal Physiol 281(3):F391–F399
22. Roy LF, Villeneuve JP, Dumont A et al (1991) Irreversible renal failure associated with triamterene. Am J Nephrol 11(6):486–488
23. Geller DS, Farhi A, Pinkerton N et al (2000) Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. Science 289(5476):119–123
24. Rossi GP, Bernini G, Caliumi C et al (2006) A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. J Am Coll Cardiol 48(11):2293–2300
25. Geller DS, Zhang J, Wisgerhof MV et al (2008) A novel form of human mendelian hypertension featuring nonglucocorticoid-remediable aldosteronism. J Clin Endocrinol Metab 93(8):3117–3123
26. Scholl UI, Nelson-Williams C, Yue P et al (2012) Hypertension with or without adrenal hyperplasia due to different inherited mutations in the potassium channel KCNJ5. Proc Natl Acad Sci U S A 109(7):2533–2538
27. Hattangady NG, Karashima S, Yuan L et al (2016) Mutated KCNJ5 activates the acute and chronic regulatory steps in aldosterone production. J Mol Endocrinol 57(1):1–11
28. Choi M, Scholl UI, Yue P et al (2011) K+ channel mutations in adrenal aldosterone-producing adenomas and hereditary hypertension. Science 331(6018):768–772
29. Boulkroun S, Beuschlein F, Rossi GP et al (2012) Prevalence, clinical, and molecular correlates of KCNJ5 mutations in primary aldosteronism. Hypertension 59(3):592–598
30. Scholl UI, Goh G, Stolting G et al (2013) Somatic and germline CACNA1D calcium channel mutations in aldosterone-producing adenomas and primary aldosteronism. Nat Genet 45(9):1050–1054

31. Azizan EA, Poulsen H, Tuluc P et al (2013) Somatic mutations in ATP1A1 and CACNA1D underlie a common subtype of adrenal hypertension. Nat Genet 45(9):1055–1060
32. Beuschlein F, Boulkroun S, Osswald A et al (2013) Somatic mutations in ATP1A1 and ATP2B3 lead to aldosterone-producing adenomas and secondary hypertension. Nat Genet 45(4):440–444. 444e1-2
33. Speiser PW, White PC (2003) Congenital adrenal hyperplasia. N Engl J Med 349(8):776–788
34. Speiser PW (2011) Medical treatment of classic and nonclassic congenital adrenal hyperplasia. Adv Exp Med Biol 707:41–45
35. Gordon RD, Geddes RA, Pawsey CG, O'Halloran MW (1970) Hypertension and severe hyperkalaemia associated with suppression of renin and aldosterone and completely reversed by dietary sodium restriction. Australas Ann Med 19(4):287–294
36. Mayan H, Vered I, Mouallem M et al (2002) Pseudohypoaldosteronism type II: marked sensitivity to thiazides, hypercalciuria, normomagnesemia, and low bone mineral density. J Clin Endocrinol Metab 87(7):3248–3254
37. Schambelan M, Sebastian A, Rector FC Jr (1981) Mineralocorticoid-resistant renal hyperkalemia without salt wasting (type II pseudohypoaldosteronism): role of increased renal chloride reabsorption. Kidney Int 19(5):716–727
38. Wilson FH, Disse-Nicodeme S, Choate KA et al (2001) Human hypertension caused by mutations in WNK kinases. Science 293(5532):1107–1112
39. Kahle KT, Wilson FH, Lalioti M et al (2004) WNK kinases: molecular regulators of integrated epithelial ion transport. Curr Opin Nephrol Hypertens 13(5):557–562
40. Argaiz ER, Gamba G (2016) The regulation of Na+Cl- cotransporter by with-no-lysine kinase 4. Curr Opin Nephrol Hypertens 25:417–423
41. Rotin D, Staub O (2012) Nedd4-2 and the regulation of epithelial sodium transport. Front Physiol 3:212
42. Hadchouel J, Ellison DH, Gamba G (2016) Regulation of renal electrolyte transport by WNK and SPAK-OSR1 kinases. Annu Rev Physiol 78:367–389
43. Alessi DR, Zhang J, Khanna A et al (2014) The WNK-SPAK/OSR1 pathway: master regulator of cation-chloride cotransporters. Sci Signal 7(334):re3
44. Mendes AI, Matos P, Moniz S et al (2011) Antagonistic regulation of cystic fibrosis transmembrane conductance regulator cell surface expression by protein kinases WNK4 and spleen tyrosine kinase. Mol Cell Biol 31(19):4076–4086
45. Tang BL (2016) (WNK)ing at death: With-no-lysine (Wnk) kinases in neuropathies and neuronal survival. Brain Res Bull 125:92–98
46. Boyden LM, Choi M, Choate KA et al (2012) Mutations in kelch-like 3 and cullin 3 cause hypertension and electrolyte abnormalities. Nature 482(7383):98–102
47. Pacak K, Linehan WM, Eisenhofer G et al (2001) Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. Ann Intern Med 134(4):315–329
48. Pillai S, Gopalan V, Smith RA, Lam AK (2016) Updates on the genetics and the clinical impacts on phaeochromocytoma and paraganglioma in the new era. Crit Rev Oncol Hematol 100:190–208
49. Tischler AS (2006) Molecular and cellular biology of pheochromocytomas and extra-adrenal paragangliomas. Endocr Pathol 17(4):321–328
50. Baysal BE, Maher ER (2015) 15 YEARS OF PARAGANGLIOMA: Genetics and mechanism of pheochromocytoma-paraganglioma syndromes characterized by germline SDHB and SDHD mutations. Endocr Relat Cancer 22(4):T71–T82
51. Juhlin CC, Stenman A, Haglund F et al (2015) Whole-exome sequencing defines the mutational landscape of pheochromocytoma and identifies KMT2D as a recurrently mutated gene. Genes Chromosomes Cancer 54(9):542–554
52. Bilginturan N, Zileli S, Karacadag S, Pirnar T (1973) Hereditary brachydactyly associated with hypertension. J Med Genet 10(3):253–259
53. Schuster H, Wienker TE, Bahring S et al (1996) Severe autosomal dominant hypertension and brachydactyly in a unique Turkish kindred maps to human chromosome 12. Nat Genet 13(1):98–100

54. Toka HR, Bahring S, Chitayat D et al (1998) Families with autosomal dominant brachydactyly type E, short stature, and severe hypertension. Ann Intern Med 129(3):204–208
55. Schuster H, Wienker TF, Toka HR et al (1996) Autosomal dominant hypertension and brachydactyly in a Turkish kindred resembles essential hypertension. Hypertension 28(6):1085–1092
56. Hattenbach LO, Toka HR, Toka O et al (1998) Absence of hypertensive retinopathy in a Turkish kindred with autosomal dominant hypertension and brachydactyly. Br J Ophthalmol 82(12):1363–1365
57. Schuster H, Toka O, Toka HR et al (1998) A cross-over medication trial for patients with autosomal-dominant hypertension with brachydactyly. Kidney Int 53(1):167–172
58. Jordan J, Toka HR, Heusser K et al (2000) Severely impaired baroreflex-buffering in patients with monogenic hypertension and neurovascular contact. Circulation 102(21):2611–2618
59. Naraghi R, Schuster H, Toka HR et al (1997) Neurovascular compression at the ventrolateral medulla in autosomal dominant hypertension and brachydactyly. Stroke 28(9):1749–1754
60. Bahring S, Kann M, Neuenfeld Y et al (2008) Inversion region for hypertension and brachydactyly on chromosome 12p features multiple splicing and noncoding RNA. Hypertension 51(2):426–431
61. Maass PG, Aydin A, Luft FC et al (2015) PDE3A mutations cause autosomal dominant hypertension with brachydactyly. Nat Genet 47(6):647–653
62. Toka O, Tank J, Schachterle C et al (2015) Clinical effects of phosphodiesterase 3A mutations in inherited hypertension with brachydactyly. Hypertension 66(4):800–808
63. Wilson FH, Hariri A, Farhi A et al (2004) A cluster of metabolic defects caused by mutation in a mitochondrial tRNA. Science 306(5699):1190–1194
64. Mori T, Ogawa S, Cowely AW Jr, Ito S (2012) Role of renal medullary oxidative and/or carbonyl stress in salt-sensitive hypertension and diabetes. Clin Exp Pharmacol Physiol 39(1):125–131
65. Herbert SC (2003) Bartter syndrome. Curr Opin Nephrol Hypertens 12(5):527–532
66. Simon DB, Karet FE, Hamdan JM, DiPietro A, Sanjad SA, Lifton RP (1996) Bartter's syndrome, hypokalaemic alkalosis with hypercalciuria, is caused by mutations in the Na-K-2Cl cotransporter NKCC2. Nat Genet 13(2):183–188
67. Simon DB, Karet FE, Rodriguez-Soriano J et al (1996) Genetic heterogeneity of Bartter's syndrome revealed by mutations in the K+ channel, ROMK. Nat Genet 14(2):152–156
68. Simon DB, Bindra RS, Mansfield TA et al (1997) Mutations in the chloride channel gene, CLCNKB, cause Bartter's syndrome type III. Nat Genet 17(2):171–178
69. Lee SE, Han KH, Jung YH et al (2011) Renal transplantation in a patient with Bartter syndrome and glomerulosclerosis. Korean J Pediatr 54(1):36–39
70. Estevez R, Boettger T, Stein V et al (2001) Barttin is a Cl- channel beta-subunit crucial for renal Cl- reabsorption and inner ear K+ secretion. Nature 414(6863):558–561
71. Vargas-Poussou R, Huang C, Hulin P et al (2002) Functional characterization of a calcium-sensing receptor mutation in severe autosomal dominant hypocalcemia with a Bartter-like syndrome. J Am Soc Nephrol 13(9):2259–2266
72. Simon DB, Nelson-Williams C, Bia MJ et al (1996) Gitelman's variant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. Nat Genet 12(1):24–30
73. Bansal T, Abeygunasekara S, Ezzat V (2010) An unusual presentation of primary renal hypokalemia-hypomagnesemia (Gitelman's syndrome). Ren Fail 32(3):407–410
74. Nicolet-Barousse L, Blanchard A, Roux C et al (2005) Inactivation of the Na-Cl co-transporter (NCC) gene is associated with high BMD through both renal and bone mechanisms: analysis of patients with Gitelman syndrome and Ncc null mice. J Bone Miner Res 20(5):799–808
75. Geller DS, Rodriguez-Soriano J, Vallo Boado A et al (1998) Mutations in the mineralocorticoid receptor gene cause autosomal dominant pseudohypoaldosteronism type I. Nat Genet 19(3):279–281
76. Chang SS, Grunder S, Hanukoglu A et al (1996) Mutations in subunits of the epithelial sodium channel cause salt wasting with hyperkalaemic acidosis, pseudohypoaldosteronism type 1. Nat Genet 12(3):248–253

77. Reichold M, Zdebik AA, Lieberer E et al (2010) KCNJ10 gene mutations causing EAST syndrome (epilepsy, ataxia, sensorineural deafness, and tubulopathy) disrupt channel function. Proc Natl Acad Sci U S A 107(32):14490–14495
78. Scholl UI, Choi M, Liu T et al (2009) Seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME syndrome) caused by mutations in KCNJ10. Proc Natl Acad Sci U S A 106(14):5842–5847
79. Rozengurt N, Lopez I, Chiu CS et al (2003) Time course of inner ear degeneration and deafness in mice lacking the Kir4.1 potassium channel subunit. Hear Res 177(1–2):71–80
80. Schreiber R, Gubler MC, Gribouval O et al (2010) Inherited renal tubular dysgenesis may not be universally fatal. Pediatr Nephrol 25(12):2531–2534
81. Gubler MC, Antignac C (2010) Renin-angiotensin system in kidney development: renal tubular dysgenesis. Kidney Int 77(5):400–406
82. Sedman AB, Kershaw DB, Bunchman TE (1995) Recognition and management of angiotensin converting enzyme inhibitor fetopathy. Pediatr Nephrol 9(3):382–385

# Arterial Hypertension in Turner Syndrome

# 12

Katya De Groote, Laurent Demulier, Julie De Backer, and Tine De Backer

## 12.1 Turner Syndrome and Associated Cardiovascular Disease

Turner syndrome (TS) is a rare chromosomal disorder, occurring in 1 per 2000 to 1 per 5000 live-born girls [1–3]. Monosomy X is present in about half of the cases; the others present a structural X chromosome aberration or a mosaic karyotype [4, 5]. The phenotype of TS is highly variable, but short stature and gonadal failure are characteristic features. Congenital and acquired cardiovascular disease, renal abnormalities and endocrine and neurocognitive disorders are frequently associated [6].

Compared to the 'general' population, morbidity and mortality are increased, cardiovascular disease being the most important cause of premature death [7–10]: the risk to die from cardiovascular disease is four times higher in TS patients than in the general population [8], and life expectancy is reduced by a decade. Cardiovascular anomalies are found in up to half of the TS patients and mainly involve the left side of the cardiovascular system. Bicuspid aortic valve (BAV), aortic arch anomalies, including coarctation, and progressive dilation of the ascending aorta [6, 11–13] are the most frequent. Aortic dissection is a relatively rare but frequently fatal complication in TS patients that often occurs at a young age [9, 14].

In TS patients, arterial hypertension (AHT) is a highly prevalent risk factor for cerebrovascular disease and aortic dissection adding significantly to the medical

K. De Groote (✉)
Department of Paediatrics, Paediatric Cardiology and Turner Clinic, Ghent University Hospital, Ghent, Belgium
e-mail: katya.degroote@uzgent.be

L. Demulier • J. De Backer
Department of Cardiology and Turner Clinic, Ghent University Hospital, Ghent, Belgium

T. De Backer
Department of Cardiology and Clinical Pharmacology, Ghent University Hospital, Ghent, Belgium



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_12

burden of the syndrome. Compared to the general population, the relative risk for AHT-related morbidity is 2.9 [15], and the incidence of death related to hypertensive disease is sixfold increased [8].

## 12.2 Definition and Prevalence of Hypertension in Turner Syndrome

### 12.2.1 Definition of Arterial Hypertension

The definition of arterial hypertension in adults and children is presented in Table 12.1.

### 12.2.2 Prevalence of Arterial Hypertension in Adult Turner Patients

Prospective data on blood pressure measurements and the prevalence of AHT in TS are scarce [19]. Most publications report blood pressure values in TS that are higher compared to healthy age-matched controls [20–26], but this is not confirmed by all [27–29]. The prevalence of AHT in adult TS patients ranges from 15 to 58%; both systolic and diastolic hypertension are reported. This variation can be partially explained by the different definitions of AHT used and by divergence in the population characteristics (age, race and lifestyle) [19]. Data on nocturnal dipping patterns in adult TS patients are scarce; a blunted dipping (dipping <10%) is reported in 13% [23, 25].

**Table 12.1** Definition of arterial hypertension for adults and children

| | Adults | Children |
|---|---|---|
| *Hypertension* | | |
| In-office BP | SBP ≥140 mmHg and/or DBP ≥90 mmHg[16] | SBP and/or DBP >p95for age, sex and height[17] |
| 24-h ABPM 24 h | SBP ≥130 mmHg and/or DBP ≥80 mmHg[16] | SBP and/or DBP >p95for age, sex and height[18] |
| Daytime | SBP day ≥135 mmHg and/or DBP day ≥85 mmHg[16] | SBP day or DBP day >p95for age, sex and height[18] |
| *Isolated nocturnal hypertension* | | |
| Ambulatory BP | SBP night ≥120 mmHg and/or DBP night ≥70 mmHg and SBP day <135 mmHg and DBP day <85 mmHg[16] | SBP night and/or DBD night >p95for age, sex and height and SBP day and/or DBD day <p95for age, sex and height[18] |
| *Blunted nocturnal dipping* | | |
| 24-h ambulatory BP | [(1-SBP night/SBP day)*100] ≤10% | [(1-SBP night/SBP day)*100] ≤10% |

*BP* blood pressure, *ABPM* ambulatory blood pressure monitoring, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BP night* mean systolic blood pressure during night time, *SBP day* mean systolic blood pressure during daytime, *>p95* above the 95th percentile, *<p95* below the 95th percentile

### 12.2.3 Prevalence of Arterial Hypertension in Paediatric Turner Patients

The prevalence of AHT in young TS girls ranges from 0 to 40% [29–34] with a variability that cannot be explained by different definitions of AHT (all studies define hypertension as a blood pressure above the 95th percentile for sex, age and height) but rather by divergence in the population characteristics [19]. Abnormal nocturnal dipping (<10%) is found in up to 57% of paediatric TS patients [29, 31, 33].

## 12.3 Aetiology of Hypertension in Turner Syndrome

The aetiology of AHT in TS is poorly understood and presumably multifactorial [35].

### 12.3.1 Essential Hypertension

Overweight and obesity, established risk factors for AHT, are highly prevalent in TS [36], and TS patients have an increased risk for both type 1 and 2 diabetes [37]. The sympathetic nervous system—an important factor in blood pressure regulation [38]—is over-activated in TS leading to an increased BP and a higher heart rate [39, 40]. Oestrogens are involved in the regulation of the autonomous nerve system and the vascular function, the latter by modulating a variety of biological cascades (e.g. RAA system and endothelin) and by their antioxidant activity [41]. Oestrogen deficiency, characteristic for TS, is at least partially responsible for the sympathetic overstimulation seen in TS [39, 40]. In the general population, increased stiffness of the aortic wall is an important cause of increasing systolic blood pressure with advancing age [42, 43]. Interestingly, in patients with TS with and without a bicuspid aortic valve or aortic coarctation, an early increase of aortic stiffness parameters has been documented, which might contribute to the increased prevalence of hypertension [21, 44–46]. The impact of hormone replacement therapy on BP remains subject of debate, although some studies describe a lowering of diastolic blood pressure [23, 47, 48], a decrease of augmentation index [49] and a reduction in carotid intima-media thickness [50].

### 12.3.2 Secondary Hypertension

AHT can develop secondary to structural cardiovascular or renal defects. In TS, coarctation is found in 4–15% of patients [11, 13, 37, 51], and the aortic arch is often hypoplastic [11, 51]. No statistically significant association between aortic arch anomalies and elevated BP was found in TS [52, 53], but this observation could have been biased by the small number of coarctation patients included in the studies. However, other publications do describe a relationship between an elongated transverse arch with abnormal curvature and elevated BP [11, 53]. Malformations

of the kidney and the collecting system are found in 38–41% of TS girls [52, 54]. Although they can evolve towards renal scarring, there is no significant association between their presence and AHT in TS girls [52]. Also classical renovascular AHT in TS is rare.

## 12.4 Hypertension and Acquired Cardiovascular Disease in Turner Syndrome

AHT is a well-established risk factor for aortic dissection, an often fatal complication in TS patients [55]; Stanford type A aortic dissections are the most common. The incidence in TS is estimated at 36/100,000 Turner years [9] which is 12 times higher than in the general population [56]. Dissection often occurs at a young age, with a mean of 30.7 years (range, 4–64 years) [14]. Arterial hypertension is present in about half of the reported cases; other acknowledged risk markers are BAV, aortic coarctation, aortic dilation and pregnancy. However, dissection also occurs in TS patients without obvious risk factors [9, 14, 55].

Aortic dilation, which may proceed to aortic dissection, is found in 20–30% of TS patients and can present from childhood. The link between BP and aortic dilation remains a subject of debate [24, 28, 53, 57–60].

Elevated systolic blood pressure, together with advancing age and body surface area, plays a role in the development of the left ventricular hypertrophy that is found in 23% of adult TS patients [61].

## 12.5 Diagnosis of Hypertension in Turner Syndrome

### 12.5.1 Blood Pressure Measurement

Correct diagnosis of AHT requires a standardised office BP measurement with the use of an appropriate-sized cuff [16] at least once a year. At the first visit, BP should be measured at both arms in the sitting position; the arm with the higher value is taken as reference for subsequent visits. To detect obstructive aortic arch malformations, BP is also measured in a supine position at the four limbs where the value at the legs should be at least equal or higher than the one obtained at the arm, comparable to the ankle-arm index.

If the systolic office BP exceeds 130 mmHg and/or the diastolic BP 80 mmHg (or the 95th percentile for children), 24-h ambulatory blood pressure measurement (ABPM) at the arm with the highest value is recommended. In patients without office AHT, it seems appropriate to screen with a 24-h ABPM at transition from the paediatric to the adult TS clinic and from then on at least once every 5 years to detect masked hypertension or a blunted dipping pattern or nocturnal hypertension. Measurements on a more regular basis are advised in the case of concomitant BAV, coarctation, dilation of the aorta, renal abnormalities, end-organ damage or associated cardiovascular risk factors.

### 12.5.2 Elaboration After Diagnosis of Hypertension

Secondary AHT should be ruled out at the moment of a new diagnosis of AHT. Elaboration includes evaluation of renal function, ultrasound of the renal arteries and the kidneys, evaluation of the thyroid function, a cardiac ultrasound and cardiac MRI with angiography of the aorta (if not recently performed) to rule out coarctation of the aorta. If the anamnesis reveals complaints suggestive of phaeochromocytoma, measurement of catecholamines and metanephrines in 24-h urine and/or plasma should be performed. Obstructive sleep apnoea syndrome should be ruled out in patients with a history of snoring [62], in case of nocturnal hypertension or severe obesity. Drugs predisposing to hypertension should be asked for.

### 12.5.3 Screening for End-Organ Damage

Chronic AHT causes vascular changes leading to organ damage in the kidney (kidney failure), the eyes (retinopathy), the heart (left ventricular hypertrophy, ischaemic heart disease), the brain (cerebrovascular accidents) and other great vessels (aortic aneurysm and low extremity peripheral artery disease). Data on the prevalence of these complications in TS are lacking, but ischaemic heart disease and cerebrovascular disease are important contributors to the increased mortality in TS [8]. Screening for end-organ damage should therefore be performed according to the hypertension guidelines [16].

## 12.6 Treatment of Arterial Hypertension in Turner Patients

### 12.6.1 Treatment Strategy in Adult TS Patients

Cut-off values for the initiation of BP treatment in TS remain a subject of debate. There are no evidence-based guidelines, but in view of the potentially increased risk for aortic dilation and the detrimental effect of AHT in the evolution to aortic dissection, lower-than-conventional BP thresholds seem appropriate, especially in patients with associated aortic disease [63, 64]. A therapeutic flowchart based on BP and associated cardiovascular pathology is presented in Fig. 12.1 [19]. Patients with additional cardiovascular risk factors should be treated according to the international guidelines on hypertension [16].

As in the general population, treatment of AHT consists primarily of appropriate lifestyle measures. Overweight and poor physical fitness are major issues in TS, and efforts should be made to reduce weight and improve physical exercise. There are no data comparing different pharmacologic antihypertensive therapies in TS patients. Most recommendations suggest beta-blockers as first-line therapy, given their favourable effect on aortic dilation and the risk of dissection. This has been proven in patients with Marfan syndrome [39, 63–65], but clear evidence in Turner syndrome is lacking. However, beta-blockers have a positive effect on the sinus

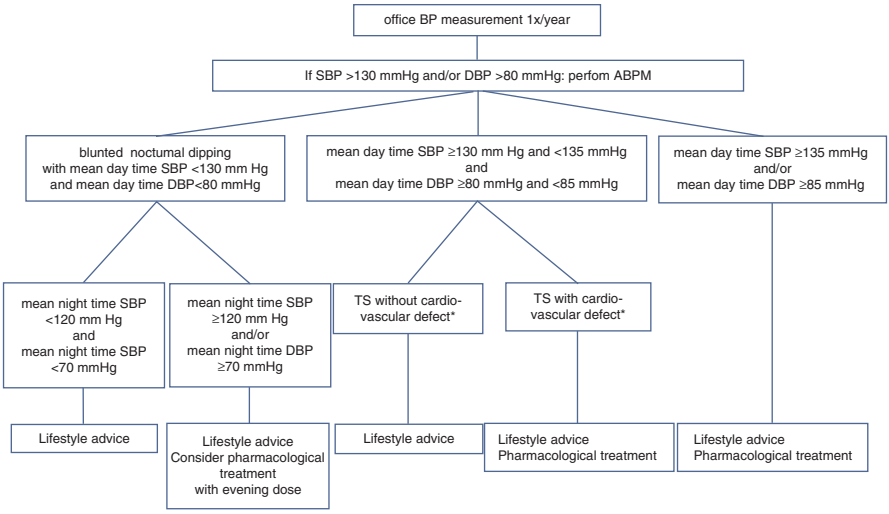



**Fig. 12.1** Treatment algorithm in adult TS patients. *Cardiovascular defects: bicuspid aortic valve, aortic coarctation or dilation of the ascending aorta >20 mm/m$^2$. TS patients with additional cardiovascular risk factors are treated according to the international guidelines on arterial hypertension (2013 ESH/ESC Guidelines for the management of arterial hypertension. Eur Heart J 2013;34:1925–1938)

tachycardia frequently encountered in TS patients [39, 40]. As studies show an increased RAA activation in Turner syndrome, ACE inhibitors (ACEI) or angiotensin receptor blockers (ARB) are a reasonable alternative, especially in the presence of left ventricular hypertrophy and diabetes or the metabolic syndrome [34]. Both ACEI and ARB have teratogenic properties and cannot be used during pregnancy. Table 12.2 presents a scheme for the initiation of pharmacological treatment, based on associated pathology.

Additional risk factors should be diagnosed and treated appropriately. This includes optimisation of thyroid function, hyperlipidemia and diabetes. The effect of treatment must be regularly checked, preferably with 24-h ABPM. If the target BP is not achieved, combination antihypertensive therapy should be considered [16].

Women with isolated insufficient nocturnal dipping should be followed more closely, and lifestyle changes should be encouraged. If isolated nocturnal AHT appears, treatment with evening administration of the medication could be considered [66].

### 12.6.2 Treatment Strategy in Paediatric TS Patients

There are no data on the optimal blood pressure treatment goals in young TS patients. It seems reasonable to use the reference values for the general paediatric population that are expressed for sex, age and height, as this probably avoids bias due to the short stature of Turner girls [17]. BP values between the 90th and 95th percentile for age and height indicate a prehypertensive state and require close follow-up. A healthier lifestyle is promoted including weight reduction, enough sleep,

**Table 12.2** Initiation of antihypertensive treatment in TS patients, based on associated pathology

| Indication | Pharmacological treatment |
|---|---|
| Isolated hypertension | Beta-blocker<br>If contraindicated or not tolerated: ACE inhibitor or angiotensin receptor blocker or calcium channel blocker |
| Associated dilation of the aorta | Beta-blocker<br>If contraindicated or not tolerated: angiotensin receptor antagonist |
| Associated systolic ventricular dysfunction | ACE inhibitor<br>Angiotensin receptor antagonist<br>Beta-blocker<br>Associate a diuretic if necessary<br>Associate a mineralocorticoid receptor blocker if necessary |
| Associated left ventricular hypertrophy | ACE inhibitor<br>Angiotensin receptor blocker<br>Beta-blocker<br>Calcium channel blocker<br>Associate a diuretic if necessary<br>Associate a mineralocorticoid receptor antagonist if necessary |
| Metabolic syndrome | ACE inhibitor<br>Angiotensin receptor blocker<br>Calcium channel blocker |
| Pregnancy | Beta-blocker (labetalol or metoprolol)<br>Methyldopa<br>Associate long-acting calcium channel blocker if necessary |

healthy diet and physical activity. Children with BP values between 95th and 99th percentile require lifestyle advice and repetitive measurements to confirm the diagnosis of AHT [17]. If the BP exceeds the 99th percentile, pharmacological treatment should be initiated. The optimal choice of treatment is similar to the one for the adult population.

### 12.6.3 Treatment Strategy in Pregnant Turner Patients

Pregnant TS patients are at an increased risk for hypertension and preeclampsia. During gestation, BP should be checked regularly and AHT treated rigorously. Even if the BP is within normal limits, preventive treatment with a beta-blocker could be considered [67]. Coarctation, severe dilation of the aorta (ASI >25 mm/m$^2$) and uncontrolled AHT are formal contraindications for pregnancy [67].

## References

1. Nielsen J, Wohlert M (1991) Chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. Hum Genet 87(1):81–83
2. Iyer NP, Tucker DF, Roberts SH et al (2012) Outcome of fetuses with Turner syndrome: a 10-year congenital anomaly register based study. J Matern Fetal Neonatal Med 25(1):68–73

3. Maeda T, Ohno M, Matsunobu A et al (1991) A cytogenetic survey of 14,835 consecutive liveborns. Jinrui Idengaku Zasshi 36(1):117–129
4. Sybert VP, McCauley E (2004) Turner's syndrome. N Engl J Med 351(12):1227–1238
5. Stochholm K, Juul S, Juel K et al (2006) Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. J Clin Endocrinol Metab 91(10):3897–3902
6. Gravholt CH (2005) Clinical practice in Turner syndrome. Nat Clin Pract Endocrinol Metab 1(1):41–52
7. Lin AE, Lippe BM, Geffner ME et al (1986) Aortic dilation, dissection, and rupture in patients with Turner syndrome. J Pediatr 109(5):820–826
8. Schoemaker MJ, Swerdlow AJ, Higgins CD et al (2008) Mortality in women with turner syndrome in Great Britain: a national cohort study. J Clin Endocrinol Metab 93(12):4735–4742
9. Gravholt CH, Landin-Wilhelmsen K, Stochholm K et al (2006) Clinical and epidemiological description of aortic dissection in Turner's syndrome. Cardiol Young 16(5):430–436
10. Lin AE, Silberbach M (2007) Focus on the heart and aorta in Turner syndrome. J Pediatr 150(6):572–574
11. Ho VB, Bakalov VK, Cooley M et al (2004) Major vascular anomalies in Turner syndrome: prevalence and magnetic resonance angiographic features. Circulation 110(12):1694–1700
12. Mazzanti L, Prandstraller D, Fattori R et al (2006) Monitoring of congenital heart disease (CHD) and aortic dilatation in Turner syndrome: Italian experience. Int Congr Ser 1298:123–130
13. Gotzsche CO, Krag-Olsen B, Nielsen J, Sorensen KE, Kristensen BO (1994) Prevalence of cardiovascular malformations and association with karyotypes in Turner's syndrome. Arch Dis Child 71(5):433–436
14. Carlson M, Silberbach M (2007) Dissection of the aorta in turner syndrome: two cases and review of 85 cases in the literature. J Med Genet 44(12):745–749
15. Gravholt CH, Juul S, Naeraa RW, Hansen J (1998) Morbidity in Turner syndrome. J Clin Epidemiol 51(2):147–158
16. Mancia G, Fagard R, Narkiewicz K et al (2013) 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 34:1925–1938
17. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 114(2 Suppl 4th Report):555–576
18. Wuhl E, Witte K, Soergel M et al (2002) Distribution of 24-h ambulatory blood pressure in children: normalized reference values and role of body dimensions. J Hypertens 20(10):1995–2007
19. De Groote K, Demulier L, De Backer J et al (2015) Arterial hypertension in Turner syndrome: a review of the literature and a practical approach for diagnosis and treatment. J Hypertens 33(7):1342–1351
20. Ostberg JE, Brookes JA, McCarthy C et al (2004) A comparison of echocardiography and magnetic resonance imaging in cardiovascular screening of adults with Turner syndrome. J Clin Endocrinol Metab 89(12):5966–5971
21. Ostberg JE, Donald AE, Halcox JP et al (2005) Vasculopathy in turner syndrome: arterial dilatation and intimal thickening without endothelial dysfunction. J Clin Endocrinol Metab 90(9):5161–5166
22. Landin-Wilhelmsen K, Bryman I, Wilhelmsen L (2001) Cardiac malformations and hypertension, but not metabolic risk factors, are common in Turner syndrome. J Clin Endocrinol Metab 86(9):4166–4170
23. Gravholt CH, Naeraa RW, Nyholm B et al (1998) Glucose metabolism, lipid metabolism, and cardiovascular risk factors in adult Turner's syndrome. Diabetes Care 21(7):1062–1070
24. Hjerrild BE, Mortensen KH, Sorensen KE et al (2010) Thoracic aortopathy in Turner syndrome and the influence of bicuspid aortic valves and blood pressure: a CMR study. J Cardiovasc Magn Reson 12(1):12
25. Giordano R, Forno D, Lanfranco F et al (2011) Metabolic and cardiovascular outcomes in a group of adult patients with Turner's syndrome under hormonal replacement therapy. Eur J Endocrinol 164(5):819–826

26. O'Gorman CS, Syme C, Lang J et al (2013) An evaluation of early cardiometabolic risk factors in children and adolescents with Turner syndrome. Clin Endocrinol 78(6):907–913
27. Pirgon O, Atabek ME, Oran B, Guclu R (2008) Atherogenic lipid profile and systolic blood pressure are associated with carotid artery intima-media thickness in children with Turner syndrome. J Clin Res Pediatr Endocrinol 1(2):62–71
28. Baguet JP, Douchin S, Pierre H et al (2005) Structural and functional abnormalities of large arteries in the Turner syndrome. Heart 91(11):1442–1446
29. Akyurek N, Atabek ME, Eklioglu BS, Alp H (2014) Ambulatory blood pressure and subclinical cardiovascular disease in children with Turner syndrome. Pediatr Cardiol 35(1):57–62
30. Cleeman L, Hjerrild B, Lauridsen A et al (2009) Long term hormone replacement therapy preserves bone mineral density in Turner syndrome. Eur J Endocrinol 161(2):251–257
31. Fudge EB, Constantacos C, Fudge JC, Davenport M (2014) Improving detection of hypertension in girls with turner syndrome using ambulatory blood pressure monitoring. Horm Res Paediatr 81(1):25–31
32. Lee SH, Jung JM, Song MS et al (2013) Evaluation of cardiovascular anomalies in patients with asymptomatic turner syndrome using multidetector computed tomography. J Korean Med Sci 28(8):1169–1173
33. Nathwani NC, Unwin R, Brook CG, Hindmarsh PC (2000) Blood pressure and Turner syndrome. Clin Endocrinol 52(3):363–370
34. Virdis R, Cantu MC, Ghizzoni L et al (1986) Blood pressure behaviour and control in Turner syndrome. Clin Exp Hypertens 8(4–5):787–791
35. Mortensen KH, Andersen NH, Gravholt CH (2012) Cardiovascular phenotype in Turner syndrome—integrating cardiology, genetics, and endocrinology. Endocr Rev 33:677–714
36. Elsheikh M, Conway GS (1998) The impact of obesity on cardiovascular risk factors in Turner's syndrome. Clin Endocrinol 49(4):447–450
37. Freriks K, Timmermans J, Beerendonk CC et al (2011) Standardized multidisciplinary evaluation yields significant previously undiagnosed morbidity in adult women with Turner syndrome. J Clin Endocrinol Metab 96(9):E1517–E1526
38. Joyner MJ, Charkoudian N, Wallin BG (2008) A sympathetic view of the sympathetic nervous system and human blood pressure regulation. Exp Physiol 93(6):715–724
39. Zuckerman-Levin N, Zinder O, Greenberg A et al (2006) Physiological and catecholamine response to sympathetic stimulation in Turner syndrome. Clin Endocrinol 64(4):410–415
40. Gravholt CH, Hansen KW, Erlandsen M et al (2006) Nocturnal hypertension and impaired sympathovagal tone in Turner syndrome. J Hypertens 24(2):353–360
41. Maric-Bilkan C, Gilbert EL, Ryan MJ (2014) Impact of ovarian function on cardiovascular health in women: focus on hypertension. Int J Womens Health 6:131–139
42. Coutinho T, Bailey KR, Turner ST, Kullo IJ (2014) Arterial stiffness is associated with increase in blood pressure over time in treated hypertensives. J Am Soc Hypertens 8(6):414–421
43. O'rourke MF, Staessen JA, Vlachopoulos C et al (2002) Clinical applications of arterial stiffness; definitions and reference values. Am J Hypertens 15(5):426–444
44. Lawson SA, Urbina EM, Gutmark-Little I et al (2014) Vasculopathy in the young Turner syndrome population. J Clin Endocrinol Metab 99(10):E2039–E2045
45. De Groote K, Devos D, Van Herck K et al (2017) Increased aortic stiffness in prepubertal girls with Turner syndrome. J Cardiol 69(1):201–207. doi:10.1016/j.jjcc.2016.03.006
46. Sharma J, Friedman D, Dave-Sharma S, Harbison M (2009) Aortic distensibility and dilation in Turner's syndrome. Cardiol Young 19(6):568–572
47. Langrish JP, Mills NL, Bath LE et al (2009) Cardiovascular effects of physiological and standard sex steroid replacement regimens in premature ovarian failure. Hypertension 53(5):805–811
48. Mortensen KH, Hansen KW, Erlandsen M et al (2009) Ambulatory arterial stiffness index in Turner syndrome: the impact of sex hormone replacement therapy. Horm Res 72(3):184–189
49. Elsheikh M, Bird R, Casadei B et al (2000) The effect of hormone replacement therapy on cardiovascular hemodynamics in women with Turner's syndrome. J Clin Endocrinol Metab 85(2):614–618

50. Ostberg JE, Storry C, Donald AE et al (2007) A dose-response study of hormone replacement in young hypogonadal women: effects on intima media thickness and metabolism. Clin Endocrinol 66(4):557–564
51. Kim HK, Gottliebson W, Hor K et al (2011) Cardiovascular anomalies in Turner syndrome: spectrum, prevalence, and cardiac MRI findings in a pediatric and young adult population. Am J Roentgenol 196(2):454–460
52. Nathwani NC, Unwin R, Brook CG, Hindmarsh PC (2000) The influence of renal and cardiovascular abnormalities on blood pressure in Turner syndrome. Clin Endocrinol 52(3):371–377
53. De Groote K, Devos D, Van Herck K et al (2015) Abnormal aortic arch morphology in Turner syndrome patients is a risk factor for hypertension. Heart Vessel 30(5):618–625
54. Bilge I, Kayserili H, Emre S et al (2000) Frequency of renal malformations in Turner syndrome: analysis of 82 Turkish children. Pediatr Nephrol 14(12):1111–1114
55. Carlson M, Airhart N, Lopez L, Silberbach M (2012) Moderate aortic enlargement and bicuspid aortic valve are associated with aortic dissection in Turner syndrome: report of the international turner syndrome aortic dissection registry. Circulation 126(18):2220–2226
56. Meszaros I, Morocz J, Szlavi J et al (2000) Epidemiology and clinicopathology of aortic dissection. Chest 117(5):1271–1278
57. Elsheikh M, Casadei B, Conway GS, Wass JA (2001) Hypertension is a major risk factor for aortic root dilatation in women with Turner's syndrome. Clin Endocrinol 54(1):69–73
58. Lopez L, Arheart KL, Colan SD et al (2008) Turner syndrome is an independent risk factor for aortic dilation in the young. Pediatrics 121(6):e1622–e1627
59. Mortensen KH, Hjerrild BE, Stochholm K et al (2011) Dilation of the ascending aorta in Turner syndrome—a prospective cardiovascular magnetic resonance study. J Cardiovasc Magn Reson 13:24
60. Mortensen KH, Erlandsen M, Andersen NH, Gravholt CH (2013) Prediction of aortic dilation in Turner syndrome—enhancing the use of serial cardiovascular magnetic resonance. J Cardiovasc Magn Reson 15(1):47–58
61. Mortensen KH, Gravholt CH, Hjerrild BE et al (2012) Left ventricular hypertrophy in Turner syndrome: a prospective echocardiographic study. Echocardiography 29(9):1022–1030
62. Eklund M, Kotilainen J, Evalahti M, Waltimo-Siren J (2012) Cephalometric analysis of pharyngeal airway space dimensions in Turner syndrome. Eur J Orthod 34(2):219–225
63. Conway GS, Band M, Doyle J, Davies MC (2010) How do you monitor the patient with Turner's syndrome in adulthood? Clin Endocrinol 73(6):696–699
64. Turtle EJ, Sule AA, Bath LE et al (2013) Assessing and addressing cardiovascular risk in adults with Turner syndrome. Clin Endocrinol 78(5):639–645
65. Bondy CA (2007) Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab 92(1):10–25
66. Vij R, Peixoto AJ (2009) Management of nocturnal hypertension. Expert Rev Cardiovasc Ther 7(6):607–618
67. Cabanes L, Chalas C, Christin-Maitre S et al (2010) Turner syndrome and pregnancy: clinical practice. Recommendations for the management of patients with Turner syndrome before and during pregnancy. Eur J Obstet Gynecol Reprod Biol 152(1):18–24

# Part IV

# Hypertension Phenotypes: The Heart

# Hypertensive Heart Disease

# 13

Fabio Angeli, Gianpaolo Reboldi, Monica Trapasso, Adolfo Aita, Dario Turturiello, and Paolo Verdecchia

## Abbreviations

| | |
|---|---|
| ACE-I | ACE inhibitor |
| AF | Atrial fibrillation |
| ARB | Angiotensin II receptor blocker |
| BMI | Body mass index |
| BP | Blood pressure |
| BSA | Body surface area |
| CCB | Calcium channel blocker |
| CI | Confidence interval |
| CV | Cardiovascular |
| CVD | Cardiovascular disease |
| ECG | Electrocardiogram |
| HDL | High-density lipoprotein |
| HF | Heart failure |
| HHD | Hypertensive heart disease |
| LIFE | Losartan Intervention for Endpoint Reduction |
| LV | Left ventricular |

F. Angeli, M.D. • M. Trapasso, M.D.
Division of Cardiology and Cardiovascular Pathophysiology, Hospital "Santa Maria della Misericordia" and University of Perugia, Perugia, Italy
e-mail: angeli.internet@gmail.com; montrapasso@gmail.com

G. Reboldi, M.D., Ph.D., M.Sc.
Department of Medicine, University of Perugia, Perugia, Italy
e-mail: paolo.reboldi@unipg.it

A. Aita, M.D. • D. Turturiello, M.D. • P. Verdecchia, M.D., F.A.C.C., F.E.S.C. (✉)
Department of Internal Medicine, Hospital of Assisi, Assisi, Italy
e-mail: adolfo.aita@gmail.com; dario.turturiello@gmail.com; verdec@tin.it



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_13

LVH LV hypertrophy
OR Odds ratio
PIUMA Progetto Ipertensione Umbria Monitoraggio Ambulatoriale
RAAS Renin-angiotensin-aldosterone system
RES Reliability of M-mode Echocardiographic Study
RR Relative risk
RWT Relative wall thickness

## 13.1 Introduction

Hypertensive heart disease (HHD) encompasses a wide spectrum of abnormalities that represent the accumulation of a lifetime of functional and structural adaptations to increased blood pressure (BP) load (Fig. 13.1). The clinical presentation of HHD is dependent on some demographic factors (including age, sex, and race), comorbid conditions (including obesity, diabetes mellitus, or peripheral arterial disease), and duration and severity of hypertension [1–3].

Hypertensive patients may develop a variety of cardiac structural and functional changes, including increased left ventricular (LV) mass, LV systolic and diastolic dysfunction, impairment of coronary reserve, arrhythmias, and enlargement of left atrial and aortic root [4].

Of the several adverse changes in cardiovascular (CV) morphology and function that occur in association with hypertension, most attention has been focused on LV hypertrophy (LVH) for its detrimental impact on CV morbidity and mortality [4].

This chapter summarizes the present state of knowledge in this active area of broad interest. Specifically, we aimed to provide an overview of recent contributions on the mechanisms and prognostic impact of HHD.

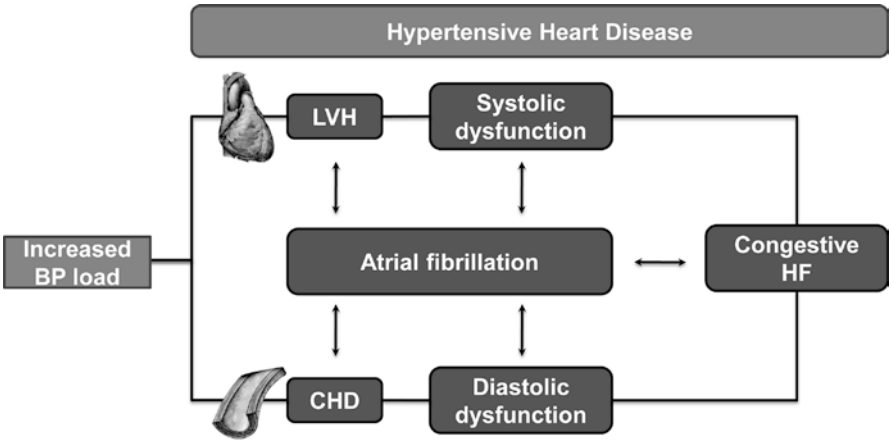



**Fig. 13.1** The wide spectrum of hypertensive heart disease. *BP* blood pressure, *LVH* left ventricular hypertrophy, *CHD* coronary heart disease, *HF* heart failure

To this purpose, we searched for experimental, clinical studies and systematic overviews using research methodology filters [5]. The following research terms were used: "hypertension," "hypertensive heart disease," "heart," "left ventricular hypertrophy," "left ventricular mass," and "prognosis." We also checked the reference list of identified articles and previous systematic reviews to find other relevant studies.

## 13.2 Mechanisms

Hemodynamic load is the fundamental stimulus to begin the sequence of biological events ultimately leading to development of HHD [4, 6].

Early in the development of HHD, cardiac involvement may be manifested by findings associated with a hyperdynamic circulation. These may include a faster heart rate, greater cardiac output than normal, an increased myocardial contractility with increased oxygen consumption, and increased circulating catecholamine or responsiveness of the myocardial and vascular beta-adrenergic receptor sites [7].

Arterial pressure rises in parallel with total peripheral resistance, the classic hemodynamic hallmark of hypertension. This increased pressure overload imposed on the left ventricle results in a structural hypertrophic adaptation [7]. Increased wall stress and strain provide a stimulus for signaling to cause mRNA transcription to increase muscular proteins [8–10]. This prompt nuclear reaction is finalized to protect the myocardium from excessive wall tension by minimizing oxygen consumption and simultaneously producing sufficient strength to provide the body tissue with the required nutriment by maintaining or even increasing cardiac output [8–10].

The development of HHD, however, may not be totally explained by hemodynamic pressure overload. Recognizable non-hemodynamic factors such as genotype, gender, and body size eventually regulate the growth of LV mass by at least in part influencing loading conditions [4, 8].

Of note, adiposity may induce important structural and functional alterations in the heart [11]. The likelihood of LVH is greater in either obese normotensive or hypertensive individuals than in their nonobese counterparts. Interestingly, besides the growth and the changes in the composition of motor units (cardiomyocytes), interstitial fat infiltration and triglyceride accumulation in the contractile elements importantly contribute to LV mass accrual, hypertrophy, and geometric pattern [11–13].

Other non-hemodynamic factors may contribute to generate the cascade of molecular changes that eventually triggers the increase in LV mass and the development of HDD.

In this context, insulin and insulin growth factors may stimulate the growth of LV mass [14–16]: it has been recently proposed that insulin resistance contributes to the development of LVH through multiple mechanisms including the accentuation of sympathetic nervous system activity, the disordered sodium reabsorption in the kidney, the growth of smooth muscle cells in blood vessels, and the generation of insulin growth factor-1 [4, 14–18].

The renin-angiotensin-aldosterone system (RAAS), an important control system for BP and intravascular volume, may also induce LVH and fibrosis [19]. The main causal mechanism is the increase in BP, which leads to increased LV wall stress. However, some of the RAAS components (including aldosterone and angiotensin II) play direct effects on the cardiomyocytes. Angiotensin II not only activates intracellular reactions which ultimately increase LV mass but also promotes atherosclerosis through proliferation of vascular smooth muscle cells and production of extracellular matrix protein [20].

Endothelin, a potent vasoconstrictor, stimulates both vascular cell growth and migration [21] and myocyte growth [22]. In a landmark study investigating the role of endogenous endothelin-1 in the development of cardiac hypertrophy in vivo, Ichikawa and coworkers [22] examined the effect of an endothelin-A receptor antagonist on the development of ventricular hypertrophy in rats with monocrotaline-induced pulmonary hypertension. Briefly, they demonstrated that blocking the action of endothelin-1 with a receptor antagonist ameliorates cardiac hypertrophy and that this action is not mediated by ameliorating hemodynamic changes [22].

There also is evidence of an inverse association, independent of BP levels, between high-density lipoprotein (HDL) cholesterol and LV mass [23]. In a cross-sectional analysis of the "*Progetto Ipertensione Umbria Monitoraggio Ambulatoriale*" (PIUMA) study, we investigated the association between HDL cholesterol and echocardiographic LV mass in 1306 never-treated subjects with essential hypertension [23]. HDL cholesterol showed an inverse association with LV mass ($r = -0.30$, $p < 0.001$). No association was found between LV mass and other lipoprotein components. In a multivariable analysis, we also demonstrated that low HDL cholesterol ($p < 0.001$) was an independent predictor of LV mass after the significant contribution of average 24-h BP, body mass index (BMI), height, stroke volume, and age [23].

As a possible explanation for the effects of low HDL-C on cardiac structural and functional alterations, therefore, the involvement of insulin resistance and hyperinsulinemia should be considered [23]. In fact, the serum levels of HDL cholesterol are inversely correlated with serum insulin levels, and some studies have reported that hyperinsulinemia is related to LVH in hypertensive patients [23]. Another possible mechanism is the detrimental effect of low HDL cholesterol levels on endothelial function, which has been associated, in turn, with LVH in hypertensive patients [23].

## 13.3 Microcirculation

The presence of LVH reflects a network of functional and structural changes in the myocardium: impaired coronary hemodynamics with reduced coronary blood flow and reserve [24], myocardial interstitial adaptations, and cardiomyocyte changes (Fig. 13.2) [25].

Atherosclerosis of large arteries and increased resistance of muscular arterioles increase the afterload leading to hypertrophy of cardiomyocytes [26]. Concurrently,

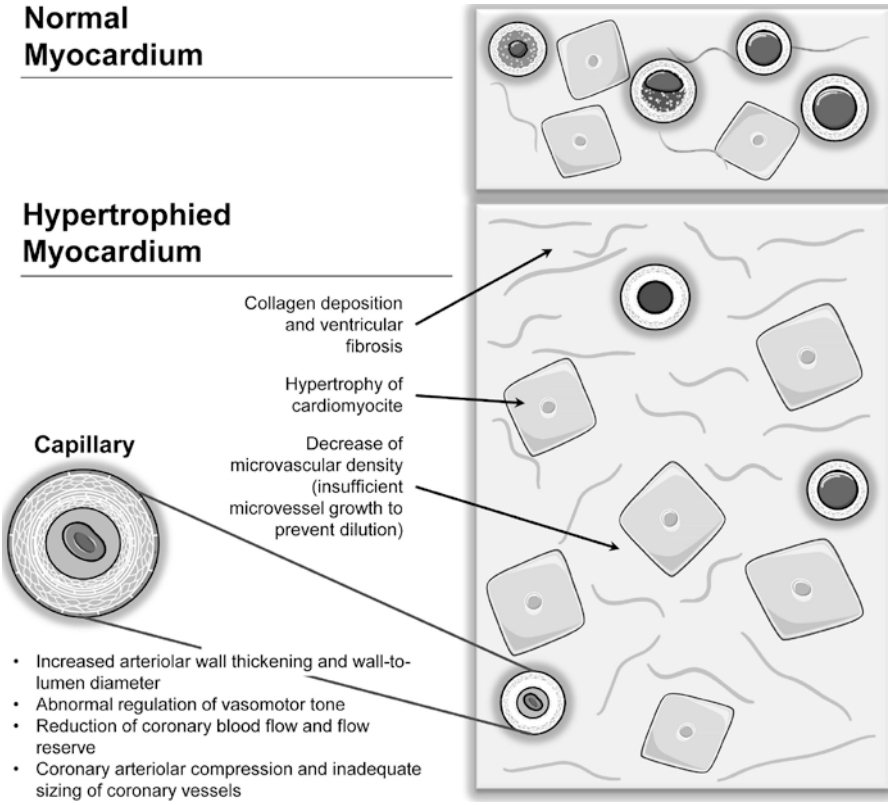



**Fig. 13.2** Main effects of chronic pressure overload on left ventricle, including impaired coronary hemodynamics with reduced coronary blood flow and reserve, myocardial interstitial adaptations, and cardiomyocyte changes

collagen deposition promotes abnormal fibrosis within the myocardial interstitium. Ventricular fibrosis hinders the elasticity of myocardium and systolic function [27–29].

Additional mechanisms which may account for impaired coronary hemodynamics include [17]: (1) coronary arteriolar compression by the hypertrophied and stiffer left ventricle produced by ventricular fibrosis, (2) inadequate sizing of coronary vessels [30], (3) increased arteriolar wall thickening and arteriolar wall-to-lumen diameter [31], (4) insufficient microvessel growth to prevent dilution because of the greater increase in other myocardial components with a consequent decrease of microvascular density [32, 33], and (5) increased LV chamber diameter reflecting myocyte hypertrophy and collagen deposition (Fig. 13.2) [26].

In this context, results of some experimental studies clearly supported the notion that LVH involves changes in myocardial tissue architecture consisting of perivascular and myocardial fibrosis and medial thickening of intramyocardial coronary arteries, in addition to myocyte hypertrophy.

Breisch and coworkers [34] analyzed the effects of pressure overload hypertrophy in the LV myocardium of adult cats after 4, 7, 30, 120, and 248 days of 90% constriction of the ascending aorta. Analysis of the microvasculature at different times after constriction of the aorta showed that capillary density and coronary reserve decreased with increasing time of hypertrophy. The combination of such alterations in flow reserve and capillary density might play an important role in the transition from a compensated to a failing heart.

Similarly, Tomanek and coworkers [35] analyzed the adverse effects on the coronary microvasculature of late-onset hypertension in middle-aged and senescent rats with renal wrap hypertension of 3-month duration. Compared with control rats, wall-to-lumen ratios of arterioles with lumen diameters less than 25 μm were higher in the hypertensive groups by some 30%, whereas larger arterioles did not show consistent intergroup differences. Capillary numerical density was markedly reduced in the hypertensive animals of both age groups. The observed microvascular alterations occurred in the absence of an absolute increase in LV mass, but in presence of cardiocyte hypertrophy. Thus, decrements in capillary numerical density were not only due to inadequate growth but reflected an absolute reduction in the number of these vessels associated with cardiocyte loss. The authors concluded that late-onset hypertension in middle-aged and senescent rats is characterized by LV wall remodeling that includes microvascular alterations that would be expected to limit maximal myocardial flow and $O_2$ supply to the cardiomyocyte [35].

## 13.4 Diagnosis of Left Ventricular Hypertrophy

LVH is a common finding in patients with CV disease (CVD) and CVD risk factors. In the clinical practice, it is generally diagnosed by electrocardiogram (ECG) or by echocardiography [1]. Echocardiography is generally preferred for confirming the presence of LVH since the sensitivity of the different ECG criteria may be as low as 7–35% with mild LVH and only 10–50% with moderate to severe disease [36]. Nevertheless, ECG is more readily available and easy to perform and interpret and is less expensive than echocardiography. Thus, if echocardiography is unavailable or too expensive, appropriate ECG criteria can be used to detect increased LV mass.

### 13.4.1 Electrocardiography

The principal ECG changes associated with LVH are increased QRS voltage and duration, left axis deviation, changes in instantaneous and mean QRS vectors, repolarization abnormalities (ST segment and T wave changes), and abnormalities in the P wave (Fig. 13.3).

These changes have been correlated with direct or indirect assessments of ventricular size or mass to establish electrocardiographic criteria for the diagnosis of hypertrophy [36].

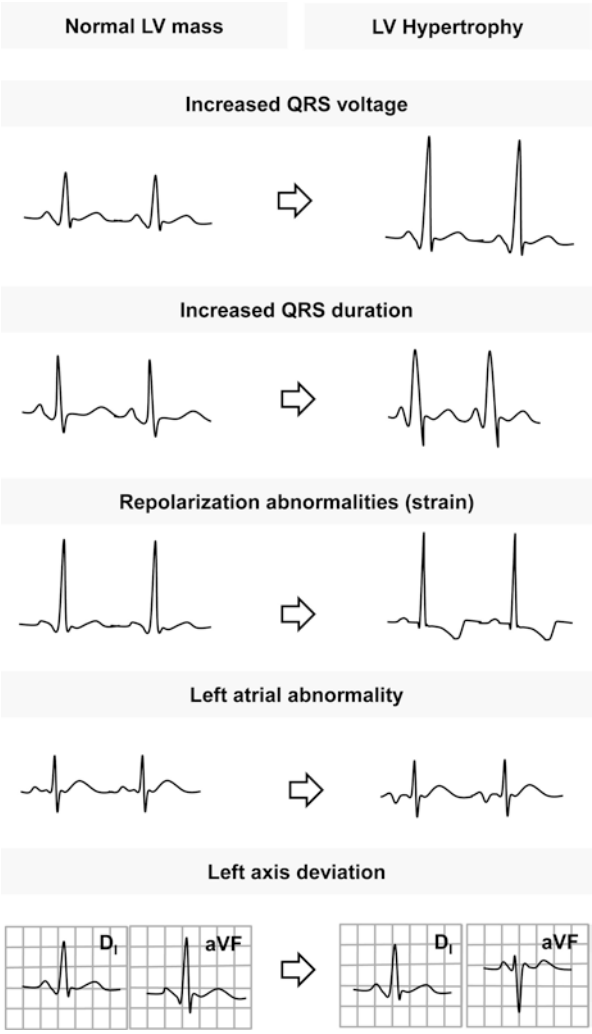



**Fig. 13.3** Major electrocardiogram findings induced by left ventricular hypertrophy. An increase in left ventricular mass augments the amplitude of voltage generated by these fibers and is usually associated with widening of the QRS duration and leftward QRS axis. Furthermore, severe left ventricular hypertrophy is associated with ST depressions and T wave inversions due to alteration in repolarization of hypertrophied muscle and relative subendocardial ischemia. Patients with LVH may also develop abnormalities in left atrial depolarization due to conduction delay or actual atrial enlargement. *LV* left ventricular

Many criteria have been developed to diagnose LVH on an ECG. Commonly used criteria for the ECG diagnosis of LVH are given below:

- Cornell voltage [37]
- Sokolow-Lyon index [38]
- Romhilt-Estes score ≥5 [39]
- Typical strain [40]
- Perugia score [41]

Briefly, the Sokolow-Lyon index [38] is defined by the sum of the S wave in lead $V_1$ plus the tallest R wave in leads $V_5$ and $V_6 \geq 3.5$ mV (35 mm); the Cornell voltage

[37] is defined by the sum of the S wave in lead $V_3$ plus the R wave lead in aVL > 2.8 mV (28 mm) in men and >2.0 mV (20 mm) in women; the Romhilt-Estes point score system [39] is computed giving different weights to specific findings (a score of 5 or more indicates "definite" LVH; a score of 4 indicates "probable" LVH); the Perugia score [41] is defined by the presence of a typical strain pattern and/or a modified Cornell voltage (sum of the S wave in $V_3$ plus the R wave in aVL > 2.0 mV in women and >2.4 mV in men); typical strain pattern [40] was defined by $a \geq 0.5$ mm depression of the J point, T wave inversion with asymmetric branches and rapid return to baseline.

Several approaches have been recently proposed in order to improve the diagnostic performance of ECG for LVH. Since most ECG criteria for LV hypertrophy are poorly sensitive, but highly specific, combination of different ECG criteria and anthropometric measures in a single index allowed improvement in sensitivity with preservation of specificity.

In this context, a recent analysis of the PIUMA study demonstrated that amplification of Cornell voltage by BMI improves performance of ECG for diagnosis of LVH [36].

LVH at ECG by the new score (BMI-corrected Perugia score) is defined by typical strain pattern or a Cornell-BMI product >604 mm kg/m$^2$, according to the following formula:

Cornell-BMI product (mm kg/m$^2$) = ((R wave amplitude in lead aVL + S wave depth in lead $V_3$) × BMI)

Of note, this new criterion allows immediate diagnosis of LVH with a rapid visual inspection of the traditional ECG (measurement of Cornell voltage and assessment of strain pattern) combined with calculation of BMI [36].

In terms of sensitivity, the new score performed better than traditional criteria widely used in clinical practice (namely, Romhilt-Estes point score, presence of typical strain, Sokolow-Lyon and Cornell voltages, and Perugia score) [36].

By the comparison of receiver operating characteristic (ROC) curve areas between the different ECG criteria for LVH, the BMI-corrected Perugia score was associated with significantly higher area under the curve (AUC) values when compared with other ECG criteria of LVH, whatever the echocardiographic reference (all $p$ <0.0001) [36].

### 13.4.2 Prognosis of ECG Left Ventricular Hypertrophy

The Framingham Heart Study [42] first showed that subjects with ECG evidence of LVH at entry and a serial increase in ECG voltage over time were twice as likely to suffer a major CV event over the subsequent years when compared with subjects with a serial decrease in voltage.

More recently, other studies have confirmed the association between LVH defined at ECG and increased CV risk [41, 43–47]. However, the magnitude of such association has varied widely among the studies [41, 45–48]. Aside from differences in patient population and adjustment for different confounders, the use of different

ECG criteria in these studies may account for a significant part of the variability in risk prediction [49].

In particular, LVH defined by the presence of a LV strain pattern on the ECG confers a worse prognosis than LVH by an increased voltage pattern alone [50].

Rautaharju and coworkers [51] compared the relative risks (RRs) of some ECG criteria, including both voltage-only criteria (Sokolow-Lyon and Cornell voltage) and criteria incorporating repolarization abnormalities. When adjusted for several confounders, they found that LVH by the Sokolow-Lyon criterion was a not significant predictor of CV mortality.

Similarly, Larsen and coworkers [50] studied the relative prognostic values of different combinations of Minnesota code pertaining to LVH. Specifically, they compared codes that identified LVH by voltage only with codes incorporating voltage and various repolarization changes, including ST depression, T inversions, and LV strain pattern. After adjustment for covariates (including age, BP, heart rate, BMI, cholesterol levels, physical exercise, history of smoking, diabetes, alcohol, and family history of ischemic heart disease), voltage-only LVH was the only pattern of LVH that was not found to be significantly associated with CV mortality.

### 13.4.3 Echocardiography

Echocardiography is one of the most important noninvasive imaging methods in the evaluation of cardiac morphology and dynamics.

Although echocardiography is more sensitive than ECG for diagnosis of LVH, health professionals need to consider some critical issues in the echocardiographic estimation of LV mass, definition of the cutoff values for diagnosis of LVH, and clinical implications of serial changes in LV mass [52]. In other words, the apparent simplicity in LV mass evaluation by echocardiography conceals several critical aspects that may limit its clinical validity [52].

Serial echocardiographic estimates of LV mass may be associated with disturbing variability [53, 54]. In the Reliability of M-mode Echocardiographic Study (RES), two M-mode tracings were recorded in the same session and after 3–10 days in the absence of treatment, and the tracings were read by two observers in each center [53]. Results showed that serial changes in LV mass by 15%, 13%, and 10% have a probability of 90%, 80%, and 75%, respectively, of representing a true biological variation and not a chance effect. Thus, a reduction of LV mass by 10% or less in a follow-up study has one probability over four of being solely a chance effect, not a true biological phenomenon [35]. Conversely, a reduction of LV mass by 15% or more has only one probability over ten of being a chance effect [53].

Furthermore, reproducibility of LV mass estimation and body size indexing and other adjustments may influence both the clinical and epidemiologic use of echocardiography in the investigation of the LV structure.

Although LV mass calculations derived from the available formulas [55–58] (Table 13.1) are strictly and linearly correlated, the final crude estimations may

**Table 13.1** Formulas to estimate left ventricular mass by echocardiography

| LV mass formulas (g) |
|---|
| LV mass (Troy [55]) = 1.05 × ([LVIDD + PWTD + IVSTD]$^3$ – [LVIDD]$^3$) |
| LV mass (Devereux [56]) = 1.04 × ([LVIDD + PWTD + IVSTD]$^3$ – [LVIDD]$^3$) – 13.6 |
| LV mass (Devereux [57]) = 0.8 × (1.04 × ([LVIDD + PWTD + IVSTD]$^3$ – [LVIDD]$^3$)) + 0.6 |
| Linear predictor of LV mass ([58]) = LVED + IVSTD + PWTD |

*LV* left ventricular, *LVIDD* LV internal diameter in diastole, *PWTD* posterior wall thickness in diastole, *IVSTD* interventricular septum thickness in diastole, *LVED* LV external diameter

**Table 13.2** Echocardiographic cut points to define left ventricular hypertrophy

| Cutoff points for LV hypertrophy | Ref. | Men | Women |
|---|---|---|---|
| LV mass/BSA (g/m$^{2.0}$) | [60] | >116 | >104 |
| LV mass/BSA (g/m$^{2.0}$) | [61] | >125 | >110 |
| LV mass/BSA (g/m$^{2.0}$) | [59] | >131 | >100 |
| LV mass/BSA (g/m$^{2.0}$) | [62] | >125 | >125 |
| LV mass/height (g/m) | [59] | >143 | >102 |
| LV mass/height (g/m) | [63] | >126 | >105 |
| LV mass/height$^{2.7}$ (g/m$^{2.7}$) | [63] | >51.0 | >51.0 |
| LV mass/height$^{2.7}$ (g/m$^{2.7}$) | [63] | >49.2 | >46.7 |
| Linear predictor (cm) | [58] | >9.8 | >9.8 |

*LV* left ventricular, *BSA* body surface area

differ by more than 20% [59]. In addition, different formulas may yield distinct cut point values for the diagnosis of LVH (Table 13.2).

Specifically, several indexes for body size correction have been proposed, such as height, allometric height adjustments, weight, body surface area (BSA), BMI, and fat-free mass (Table 13.2). The best way for normalization of LV mass is still controversial. Different adjustment criteria and their standard cut points may result in a different prevalence of LVH [59].

### 13.4.4 Prognosis of Echocardiographic Left Ventricular Hypertrophy

With the advent of echocardiography, it has been recognized that electrocardiography may be relatively insensitive for detecting prognostically important increases in LV mass [45, 64]. In particular, milder increases in LV mass could be detected only by echocardiography, and additional epidemiological data have demonstrated that a strong gradient exists between increased echocardiographic LV mass and increased CV risk [62, 65, 66].

Levy and colleagues demonstrated a progressive increase in risk associated to LV mass, even at levels not considered as "hypertrophic" [66]; more recently, in a subset of 1925 Italian hypertensive patients [67], CVD increased monotonically with more than a fourfold increase in risk between the lowest and highest LV mass quintiles. Notably, clinically relevant increment in CV risk was identified in patients with LV mass below the limits usually employed for LVH definition.

These findings have been subsequently confirmed in a prespecified analysis of the Losartan Intervention for Endpoint Reduction (LIFE) study [68], carried out in patients with essential hypertension, electrocardiographic evidence of LVH at entry, and availability of LV echocardiographic study at randomization and during follow-up. In that study, lower values of LV mass during treatment were associated with lower rates of CVD, and such an effect was additional to the benefit provided by BP-lowering and treatment modality [68].

However, it is still unclear whether different criteria for definition of LVH exert a different prognostic impact. Addressing this topic, Liao and colleagues [69] compared the predictive value of echocardiographic LVH using various methods of indexation of LV mass. They observed that an increase in any LV mass index was associated with similar risk of death from all causes and cardiac diseases. Although LVH assessed by mass indexed for BSA using conventional partition values provided somewhat better prediction, the adjusted relative risk was in general not significantly different from LVH based on other indexes [69].

Similar results were obtained by Gosse and coworkers [70]. In their analysis, they documented that different indexations of LV mass (height, height$^{2.7}$, or BSA) had similar predictive values for CV complications [70].

## 13.5 Reversal of Left Ventricular Hypertrophy

The hypothesis that a reduction of LV mass in hypertensive patients was linked with a better outcome generated a great interest from researchers and clinicians. In this context, a recent analysis by Gosse and coworkers [70] highlighted the prognostic implications of serial changes in LV mass during pharmacological treatment for hypertension. In their registry, a prospective sub-study cohort was assembled in which echocardiography was obtained at baseline and after an average follow-up of 5 years. Increasing reductions in echocardiographic LV mass were associated with greater reductions in CV event rates, independently of the baseline LV mass. In addition, patients with LVH regression showed similar survival than patients with persistence of normal LV mass [70].

The results of this study are impressive for the concordance with other echocardiographic prospective studies, with respect to the link between regression of LVH and reduction of major CV events in essential hypertension.

In a study from France [71], the incidence of CV events was 4.8% in hypertensive subjects without LVH, 9.6% in those with regression of LVH, and 15% in those without regression of LVH.

Similar data have been also reported by Koren et al. [72]. CV event rate during a 5-year follow-up was 9.2 and 28.6% for patients with regression of LVH (or persistence of normal LV mass) and with new development (or persistence of LVH), respectively.

In a long-term Italian study [73], hypertensive patients underwent a LV echocardiographic study before therapy and after 10 years of treatment. The rate of CV events was higher in the patients who had not achieved regression of LVH at

follow-up compared with those with persistently normal LV mass. Furthermore, patients with regression of LVH showed an event rate similar to those with persistently normal LV mass [73].

In a subsequent analysis of the PIUMA study [74], the lesser CV risk associated with regression of LVH (1.58 events per 100 person-years in subjects with LVH regression vs. 6.27 in those with persistent LVH) remained significant in a multivariable analysis which included BP changes as assessed by 24-h ambulatory monitoring.

A pooled analysis [75] of four studies (including 1064 hypertensive subjects aged 45–51 and 106 major CV events) showed that compared to subjects with lack of regression or new development of LVH, those who achieved regression of LVH showed a 59% lesser risk of subsequent CV disease (95% confidence intervals [CI], 22–79; $p = 0.007$). The lesser risk of events associated with regression of LVH was consistent across the individual studies. Compared to subjects with regression of LVH, those with persistently normal LV mass showed a similar risk of subsequent events (odds ratio [OR] 0.64, 95% CI, 0.31–1.30; $p = 0.21$).

However, since the event risk was 36% lower among the subjects who never experienced LVH compared to those with regression and the confidence intervals were wide, the meta-analysis did not provide definite evidence that regression of LVH reduces the risk of subsequent events to the same level as that of subjects who never experienced LVH [75].

To further clarify these aspects, a cumulative meta-analysis of seven studies for a total of 2954 patients and 339 CV events recently investigated how evidence progressed in this field.

Results support the hypothesis that a persistently normal LV mass is thus the most favorable prognostic phenotype (Fig. 13.4). Patients with persistently normal LV mass showed a markedly lower risk of CV events when compared with those with persistence or new development of LVH (OR, 0.28; 95% CI, 0.20 to 0.39; $p < 0.0001$, $I^2 = 26.1\%$). In terms of absolute risk difference, a persistently normal LV mass was associated with a significant 15% reduction in the risk of CV events (Fig. 13.4). Regression of LVH was associated with a cumulative 58% lower risk of CV events when compared to persistence or new development of LVH during follow-up (OR, 0.42; 95% CI, 0.23 to 0.77; $p = 0.0048$, $I^2 = 59.6\%$; absolute risk difference, −13%). However, and most importantly, patients with LVH regression still had a 56% higher risk of CV events than those with persistently normal LV mass (OR, 1.56; 95% CI, 1.04 to 2.36; $p = 0.033$, $I^2 = 1.2\%$; absolute risk difference, +3%) (Fig. 13.4).

## 13.6 Left Ventricular Geometry

Usually, four distinct LV geometric patterns are considered to stratify patients with hypertension: normal geometry, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy (Fig. 13.5).

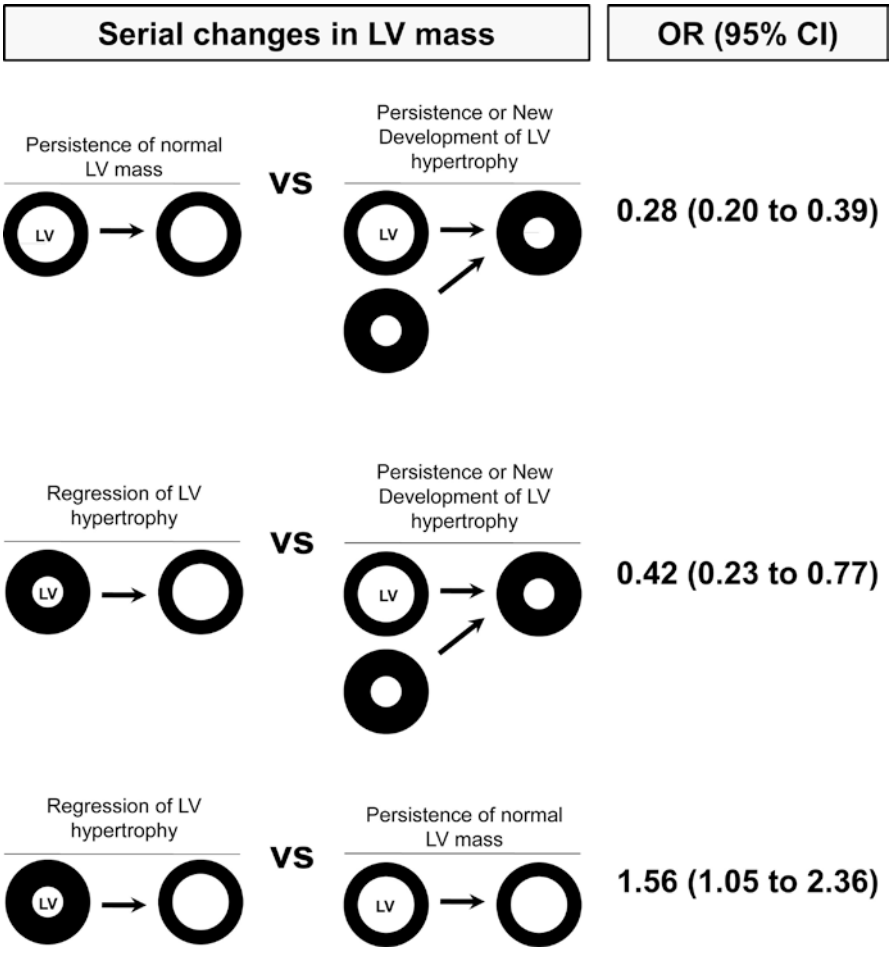



**Fig. 13.4** Results of a cumulative meta-analysis of seven clinical studies comparing cardiovascular outcome in patients with persistently normal left ventricular mass versus those with persistence or new development of left ventricular hypertrophy (upper panel), patients with LVH regression versus those with persistence or new development of LVH (middle panel), and patients with regression of left ventricular hypertrophy versus those with persistently normal LV mass (lower panel). The figure reports the risk (odds ratio) for cardiovascular events. *LV* left ventricular, *CV* cardiovascular, *OR* odds ratio

LV geometry can be described by calculating the relative wall thickness (RWT) as a function of septum or posterior wall thickness divided by the internal diameter at tele-diastole [77]. Arbitrary threshold values for RWT are generally used to differentiate normal geometry from concentric remodeling in subjects with normal LV mass and eccentric hypertrophy from concentric hypertrophy in subjects with increased LV mass [77]. While the typical feature of concentric LV hypertrophy is the increase in wall thickness, eccentric LVH describes a pattern in which both LV internal diameter and wall thickness are increased (Fig. 13.5).

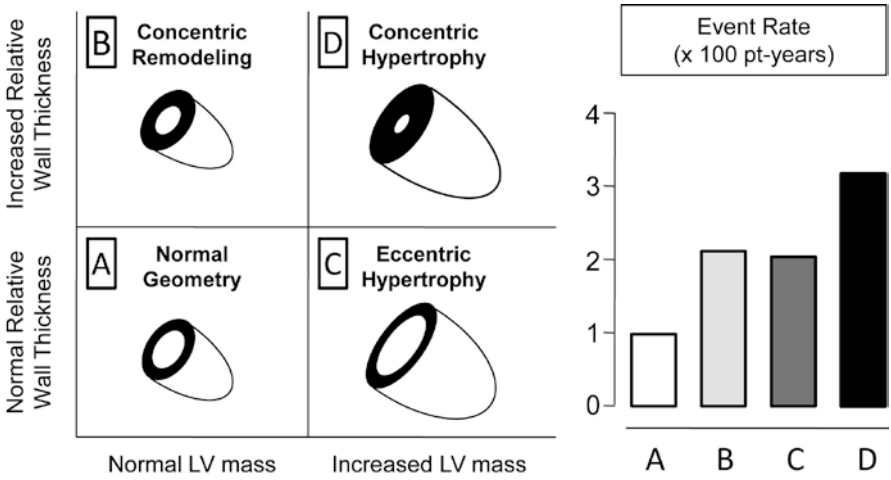



**Fig. 13.5** Prognostic value of the four different patterns of left ventricular geometry in the PIUMA study (data from [76]). *LV* left ventricular, relative wall thickness = [(2 × posterior wall thickness)/LV diastolic diameter] or [(septal wall thickness + posterior wall thickness)/LV diastolic diameter]

Although this classification permits identification of determined adaptive processes, cohort studies evaluating geometric patterns impact on the incidence of CV events provided mixed results showing that the additional prognostic role of geometric patterns over LVH was lesser than initially supposed [62, 76, 78, 79].

In general, in longitudinal studies, the risk of CV disease seems to be higher in subjects with concentric remodeling than in those with normal LV geometry and also greater in subjects with concentric LVH than in those with eccentric LVH (Fig. 13.5) [62, 71, 76, 79–81].

Koren and coworkers [62] found a 10-year incidence of CV events of 31% in patients with concentric hypertrophy compared to 11% in those with normal geometry; an Italian study [76] found a relative risk of 2.6 in patients with concentric remodeling compared to normal geometry patients; Krumholz and coworkers [79] showed a relative risk of 2.1 for all-cause mortality with concentric hypertrophy, but not additional risk in those classified as concentric remodeling.

However, since LV mass tends to be greater in subjects with concentric remodeling than in those with normal geometry, and even greater in subjects with concentric LVH than in those with eccentric LVH, the independent prognostic value of LV geometry tends to be reduced or abolished because of the overwhelming prognostic value of LV mass itself [62, 71, 76, 79–81].

## 13.7 Coronary Heart Disease

The increased CV risk associated with HDD is due in part to myocardial ischemia that can be induced by a variety of factors [82]. They include a reduced density of capillaries, medial wall thickening of arterioles, perivascular fibrosis, endothelial

dysfunction with the limited ability of the coronary arteries to dilate in response to decreased perfusion or during vasodilatory stress, and the direct compression of the endocardial capillaries by the enlarged muscle mass [1, 82].

In this context, some experimental and epidemiological data support the evidence that all these factors decrease coronary reserve and have important clinical implications [1].

Briefly, the hypertrophied myocardium is more susceptible than normal myocardium to the effects of ischemia, increased heart weight is an independent predictor of plaque rupture with superimposed thrombus [83], the increase in cardiovascular risk is directly related to the degree of increase in LV mass, and coronary occlusion is associated with a greater degree of infarction and a higher mortality rate than seen in the absence of LVH [1, 62, 66, 84].

## 13.8 Arrhythmias

HHD has been associated with both ventricular and supraventricular arrhythmias [85–87]. Although a link between arrhythmias and HHD is clearly documented in observational study, potential mechanisms explaining such association are not completely understood.

### 13.8.1 Ventricular Arrhythmias

The increased risk for arrhythmias and sudden cardiac death in HHD has been associated with increased ventricular ectopic activity [86]. Experimental models showed increased vulnerability to inducible polymorphic ventricular fibrillation in the presence of LVH induced by aortic band. Notably, these abnormalities disappeared with LVH regression after removal of the aortic band [88].

Moreover, myocardial fibrosis could cause local variations in the conduction velocities precipitating ventricular arrhythmias. Specifically, the irregular hypertrophy pattern and local areas of fibrosis in LVH can impede the homogeneous propagation of the electric impulse throughout the myocardium and its subsequent recovery [89].

Other proposed mechanisms of ventricular arrhythmias include lengthening of the action potential duration, reduced action potential upstroke velocity, slower membrane repolarization, the generation of early and delayed after-depolarizations, and beat-to-beat changes in repolarization [90, 91].

Messerli and coworkers [87] found that patients with HHD had higher-grade ventricular ectopic activity, such as coupled premature ventricular contractions and multifocal premature ventricular contractions, than those without LVH or than normotensive subjects. More recently, reports from Framingham showed that electrocardiographic LVH is a BP-independent risk factor for sudden cardiac death [48, 92].

### 13.8.2 Supraventricular Arrhythmias

Supraventricular arrhythmias are commonly associated with HHD. LVH (both concentric and eccentric types) seems to have a greater impact on the frequency of atrial arrhythmias (primarily atrial fibrillation [AF]), with the concentric type being more closely associated with supraventricular premature beats and AF [93].

The importance of LVH in the development AF was illustrated in a study of 2482 subjects with essential hypertension followed for up to 16 years [94]. During follow-up, advancing age and increased LV mass were the only independent predictors of developing AF. For every one standard deviation increase on LV mass, the risk of AF increased by 20% [94].

LVH identified by cardiac magnetic resonance imaging has also been shown to be associated with AF. In a cohort of 4942 patients followed for a median of 6.9 years, the risk of AF was significantly higher in patients with LVH identified by either magnetic resonance imaging or ECG-derived voltage measurements of LVH [95].

In a meta-analysis of ten studies involving 27,141 patients, the risk of supraventricular arrhythmias was significantly higher in patients with LVH (OR 3.4 compared with no LV hypertrophy; 95% CI 1.67.3), although there was significant heterogeneity among the baseline covariates in the included studies [85].

Electrical and structural remodeling of the left atrium is a key step in the progression from hypertension to AF. Two distinct abnormalities in atrial electrical properties occur early in HDD and are associated with the development and maintenance of AF: the prolongation of atrial conduction velocity as assessed by the signal-averaged p-wave duration and the decrease in atrial refractoriness [96, 97]. There is also accumulation of calcium within atrial myocytes, leading to a reduction of the inward L-type $Ca^{2+}$ current, which in turn contributes to the shortening of the atrial effective refractory period and the promotion and maintenance of multiple wavelet-reentry circuits [98]. In addition, structural remodeling of the atria occurs in parallel with the changes of electrical remodeling. These structural changes include dilatation and increasing atrial fibrosis [99]. Key to this fibrotic process is the deposition of increased amounts of connective tissue between individual cells and with the deposition of large amounts of collagen and fibronectin [100]. This leads to separation of myocytes from one another and subsequent impairment of atrial conduction at the microscopic level. These changes culminate in alterations in the biophysical properties of atrial tissue, allowing the initiation and perpetuation of AF [17, 18, 101].

## 13.9 Heart Failure

The physiologic alterations which occur as a result of anatomical changes in HHD include disturbances of myocardial blood flow, the development of an arrhythmogenic myocardial substrate, and diastolic dysfunction. The latter is directly related to the degree of myocardial fibrosis and is the hemodynamic hallmark of HDD.

When diastolic dysfunction is present, LV end-diastolic pressure increases out of proportion to volume and may be elevated at rest or with exertion leading to clinical heart failure (HF).

Although it has been assumed that LVH may lead to systolic dysfunction [102], it is not well known whether LVH resulting from hypertension is a major risk factor for systolic HF independent of coronary artery disease [103].

To date, hypertension may lead to HF due to systolic dysfunction in association with underlying coronary heart disease. If atherosclerotic epicardial coronary disease is present, then there may be areas of intermittent segmental flow compromise. With coronary occlusion and myocardial infarction, regional myofibrillar dropout leads to segmental wall motion abnormalities and maladaptive ventricular remodeling, usually with ventricular dilation, interstitial fibrosis, and hypertrophy of surviving myocytes.

From an epidemiological standpoint, in the Framingham Heart Study, hypertension accounted for 39% of HF cases in men and 59% in women [6, 16–19]. Overall, about 20% of individuals with HF have antecedent ECG-LVH and 60% to 70% demonstrate echo-LVH [32].

## 13.10 Therapeutic Implications

HHD includes LVH, ventricular stiffness, and systolic and diastolic dysfunction. In addition, this syndrome operates in parallel with ischemic heart disease and ultimately causes HF, if inadequately treated.

BP control and therapeutic strategies aimed to reverse HHD is associated with a reduction in CV risk. Nevertheless, in everyday practice and clinical trials, it is quite difficult to establish whether a given antihypertensive drug is superior to another in treating HHD.

Indeed, hypertensive subjects have often to combine several drugs with different mechanisms of action (i.e., diuretics, ACE inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs)) in order to achieve an adequate control of BP. Subjects with LVH, who generally have higher BP levels than those without, frequently need treatment with multiple drugs. As a result, the merit of LVH regression cannot be precisely attributed to a specific drug class in clinical trials.

In a meta-analysis of 80 trials [104] that included 146 and 17 active treatment and placebo arms, ACE-Is, ARBs, and calcium channel blockers CCBs were more potent than diuretics and beta-blockers in reducing LV mass. Specifically, after adjustments for length of therapy and degree of BP lowering, the relative reductions in LV mass index were 13%, 11%, 10%, 8%, and 6% for ARBs, CCBs, ACE inhibitors, diuretics, and beta-blockers, respectively [104]. However, some of these trials were small and of short duration. It has been suggested that clinical trials testing differences between different drugs on LVH should have a randomized double-blind design and should last 1 year minimum. Subjects of both genders should be enrolled

and there should be at least 150 to 200 patients per treatment arm. In addition, an anatomically validated method of cardiac imaging should be used [48].

The *Studio Italiano Sugli Effetti CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica* (Cardio-Sis) [105] showed that a tight BP control beyond currently recommended levels reduces the risk for LVH (primary outcome) and major CV events (secondary outcome), when compared with a usual BP control. Cardio-Sis involved a total of 1111 nondiabetic individuals aged 55 years or older with systolic BP ≥ 150 mmHg who were randomly assigned to a target systolic BP < 140 mmHg ("usual" BP control) or <130 mmHg (tight BP control) [105]. By the end of the study, 17.0% of the usual-control group had ECG-documented LVH compared with 11.4% of the tight-control group (OR 0.63; 95% CI 0.43–0.91; $p = 0.013$) [105].

## 13.11 Perspectives

In this overview, we have summarized the currently available experimental and clinical data on HHD. It is worth noting that the potential mechanisms linking increased LV mass to the risk of major CV disease are still uncertain. Several factors seem to exert a sort of "two-way effect" by increasing LV mass and, in the same time, promoting development and progression of atherosclerotic lesions [106–108]. Elevated BP stimulates both LVH and atherosclerosis [109]. LV mass, intima-media thickness [110], and carotid atherosclerosis [110, 111] progress in parallel, and arterial stiffness, expressed by the pulse wave velocity and partly reflecting generalized atherosclerosis at the level of large elastic arteries, is associated with LVH independently of BP [4, 112]. Similarly, the mechanisms through which regression of LVH reduces the risk of CV disease in hypertensive subjects are still unclear [113]. Regression of LVH is associated with numerous cardiac benefits, such as improved systolic mid-wall performance, normalized autonomic function, enhanced coronary reserve, improved diastolic filling, and decreased ventricular arrhythmia [114]. Thus, it can be speculated that LVH regression may reflect a decreased level of activity, in the long term, of one or more factors potentially active on atherosclerosis. Conversely, lack of regression of LVH may be a marker for a more advanced progression of atherosclerosis.

In conclusion, these observations appear to strengthen the pivotal role of LV mass in the wide spectrum of HHD [41, 66, 84, 102, 115]. LV mass should primarily considered as a biological assay which reflects and integrates the long-term level of activity of several hemodynamic and non-hemodynamic factors potentially active on the heart and atherosclerosis [4, 8, 116–118]. Thus, early diagnosis of increased LV mass should lead to a more aggressive control of CV risk factors in hypertensive patients.

## References

1. Lip GY, Felmeden DC, Li-Saw-Hee FL et al (2000) Hypertensive heart disease. A complex syndrome or a hypertensive 'cardiomyopathy'? Eur Heart J 21(20):1653–1665

2. Crawford MH (2010) Hypertension and hypertensive heart disease. Foreword. Cardiol Clin 28(4):xi
3. Mensah GA (2010) Preface: hypertension and hypertensive heart disease. Cardiol Clin 28(4):xiii–xiv
4. Verdecchia P, Angeli F, Achilli P et al (2007) Echocardiographic left ventricular hypertrophy in hypertension: marker for future events or mediator of events? Curr Opin Cardiol 22(4):329–334
5. Haynes RB, Wilczynski N, McKibbon KA et al (1994) Developing optimal search strategies for detecting clinically sound studies in MEDLINE. J Am Med Inform Assoc 1(6):447–458
6. Verdecchia P, Schillaci G, Borgioni C et al (2002) Prevalent influence of systolic over pulse pressure on left ventricular mass in essential hypertension. Eur Heart J 23(8):658–665
7. Frohlich ED (1989) Left ventricular hypertrophy, cardiac diseases and hypertension: recent experiences. J Am Coll Cardiol 14(7):1587–1594
8. de Simone G, Pasanisi F, Contaldo F (2001) Link of nonhemodynamic factors to hemodynamic determinants of left ventricular hypertrophy. Hypertension 38(1):13–18
9. Komuro I (2000) Molecular mechanism of mechanical stress-induced cardiac hypertrophy. Jpn Heart J 41(2):117–129
10. Sadoshima J, Izumo S (1997) The cellular and molecular response of cardiac myocytes to mechanical stress. Annu Rev Physiol 59:551–571
11. Murdolo G, Angeli F, Reboldi G et al (2015) Left ventricular hypertrophy and obesity: only a matter of fat? High Blood Press Cardiovasc Prev 22(1):29–41
12. Kahan T (2012) The importance of myocardial fibrosis in hypertensive heart disease. J Hypertens 30(4):685–687
13. Shahbaz AU, Sun Y, Bhattacharya SK et al (2010) Fibrosis in hypertensive heart disease: molecular pathways and cardioprotective strategies. J Hypertens 28(Suppl 1):S25–S32
14. Delaughter MC, Taffet GE, Fiorotto ML et al (1999) Local insulin-like growth factor I expression induces physiologic, then pathologic, cardiac hypertrophy in transgenic mice. FASEB J 13(14):1923–1929
15. Verdecchia P, Reboldi G, Schillaci G et al (1999) Circulating insulin and insulin growth factor-1 are independent determinants of left ventricular mass and geometry in essential hypertension. Circulation 100(17):1802–1807
16. Ito H, Hiroe M, Hirata Y et al (1993) Insulin-like growth factor-I induces hypertrophy with enhanced expression of muscle specific genes in cultured rat cardiomyocytes. Circulation 87(5):1715–1721
17. Angeli F, Reboldi G, Verdecchia P (2012) Microcirculation and left-ventricular hypertrophy. J Hypertens 30(3):477–481
18. Angeli F, Reboldi G, Verdecchia P (2014) Hypertension, inflammation and atrial fibrillation. J Hypertens 32(3):480–483
19. Sica DA (2014) Aldosterone and volume management in hypertensive heart disease. Semin Nephrol 34(3):323–332
20. Crowley SD, Gurley SB, Herrera MJ et al (2006) Angiotensin II causes hypertension and cardiac hypertrophy through its receptors in the kidney. Proc Natl Acad Sci U S A 103(47):17985–17990
21. Lerman A, Edwards BS, Hallett JW et al (1991) Circulating and tissue endothelin immunoreactivity in advanced atherosclerosis. N Engl J Med 325(14):997–1001
22. Ichikawa KI, Hidai C, Okuda C et al (1996) Endogenous endothelin-1 mediates cardiac hypertrophy and switching of myosin heavy chain gene expression in rat ventricular myocardium. J Am Coll Cardiol 27(5):1286–1291
23. Schillaci G, Vaudo G, Reboldi G et al (2001) High-density lipoprotein cholesterol and left ventricular hypertrophy in essential hypertension. J Hypertens 19(12):2265–2270
24. Scheler S, Motz W, Strauer BE (1994) Mechanism of angina pectoris in patients with systemic hypertension and normal epicardial coronary arteries by arteriogram. Am J Cardiol 73(7):478–482

25. Diez J, González A, López B, Querejeta R (2005) Mechanisms of disease: pathologic structural remodeling is more than adaptive hypertrophy in hypertensive heart disease. Nat Clin Pract Cardiovasc Med 2(4):209–216
26. Koren MJ, Devereux RB (1993) Mechanism, effects, and reversal of left ventricular hypertrophy in hypertension. Curr Opin Nephrol Hypertens 2(1):87–95
27. Aurigemma GP, Silver KH, Priest MA, Gaasch WH (1995) Geometric changes allow normal ejection fraction despite depressed myocardial shortening in hypertensive left ventricular hypertrophy. J Am Coll Cardiol 26(1):195–202
28. Ciulla M, Paliotti R, Hess DB et al (1997) Echocardiographic patterns of myocardial fibrosis in hypertensive patients: endomyocardial biopsy versus ultrasonic tissue characterization. J Am Soc Echocardiogr 10(6):657–664
29. Rossi MA (1998) Pathologic fibrosis and connective tissue matrix in left ventricular hypertrophy due to chronic arterial hypertension in humans. J Hypertens 16(7):1031–1041
30. Nitenberg A, Antony I (1996) Epicardial coronary arteries are not adequately sized in hypertensive patients. J Am Coll Cardiol 27(1):115–123
31. Mulvany MJ (1992) Vascular growth in hypertension. J Cardiovasc Pharmacol 20(Suppl 1):S7–S11
32. Heron MI, Kuo C, Rakusan K (1999) Arteriolar growth in the postnatal rat heart. Microvasc Res 58(2):183–186
33. Rakusan K, Cicutti N, Sladek T (1996) Ischemic heart: microcirculatory aspects. Adv Exp Med Biol 388:457–461
34. Breisch EA, White FC, Bloor CM (1984) Myocardial characteristics of pressure overload hypertrophy. A structural and functional study. Lab Investig 51(3):333–342
35. Tomanek RJ, Aydelotte MR, Butters CA (1990) Late-onset renal hypertension in old rats alters myocardial microvessels. Am J Phys 259(6 Pt 2):H1681–H1687
36. Angeli F, Verdecchia P, Iacobelli SG et al (2014) Usefulness of QRS voltage correction by body mass index to improve electrocardiographic detection of left ventricular hypertrophy in patients with systemic hypertension. Am J Cardiol 114(3):427–432
37. Casale PN, Devereux RB, Kligfield P et al (1985) Electrocardiographic detection of left ventricular hypertrophy: development and prospective validation of improved criteria. J Am Coll Cardiol 6(3):572–580
38. Sokolow M, Lyon TP (1949) The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am Heart J 37(2):161–186
39. Romhilt DW, Estes EH Jr (1968) A point-score system for the ECG diagnosis of left ventricular hypertrophy. Am Heart J 75(6):752–758
40. Roman MJ, Kligfield P, Devereux RB et al (1987) Geometric and functional correlates of electrocardiographic repolarization and voltage abnormalities in aortic regurgitation. J Am Coll Cardiol 9(3):500–508
41. Verdecchia P, Angeli F, Reboldi G et al (2003) Improved cardiovascular risk stratification by a simple ECG index in hypertension. Am J Hypertens 16(8):646–652
42. Levy D, Salomon M, D'Agostino RB et al (1994) Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. Circulation 90(4):1786–1793
43. Sullivan JM, Vander Zwaag RV, el-Zeky F et al (1993) Left ventricular hypertrophy: effect on survival. J Am Coll Cardiol 22(2): 508-513
44. MacMahon S, Collin G, Rautaharju P et al (1989) Electrocardiographic left ventricular hypertrophy and effects of antihypertensive drug therapy in hypertensive participants in the multiple risk factor Intervention trial. Am J Cardiol 63(3):202–210
45. Verdecchia P, Angeli F, Cavallini C et al (2009) The voltage of R wave in lead aVL improves risk stratification in hypertensive patients without ECG left ventricular hypertrophy. J Hypertens 27(8):1697–1704
46. Verdecchia P, Angeli F, Mazzotta G et al (2011) Simplifying the ECG diagnosis of left ventricular hypertrophy. Curr Cardio Risk Rep 5(1):1–4

47. Verdecchia P, Sleight P, Avanzini F et al (2003) Hypertrophy at ECG and its regression during treatment survey (HEART survey). Rationale, design and baseline characteristics of patients. Ital Heart J 4(7):479–483
48. Kannel WB, Gordon T, Offutt D (1969) Left ventricular hypertrophy by electrocardiogram. Prevalence, incidence, and mortality in the Framingham study. Ann Intern Med 71(1):89–105
49. Levy D, Labib SB, Anderson KM et al (1990) Determinants of sensitivity and specificity of electrocardiographic criteria for left ventricular hypertrophy. Circulation 81(3):815–820
50. Larsen CT, Dahlin J, Blackburn H et al (2002) Prevalence and prognosis of electrocardiographic left ventricular hypertrophy, ST segment depression and negative T-wave; the Copenhagen City heart study. Eur Heart J 23(4):315–324
51. Rautaharju PM, LaCroix AZ, Savage DD et al (1988) Electrocardiographic estimate of left ventricular mass versus radiographic cardiac size and the risk of cardiovascular disease mortality in the epidemiologic follow-up study of the first National Health and nutrition examination survey. Am J Cardiol 62(1):59–66
52. Angeli F, Reboldi G, Verdecchia P (2012) Echocardiographic left ventricular hypertrophy: implications for clinicians. J Hypertens 30(12):2279–2284
53. de Simone G, Muiesan ML, Ganau A et al (1999) Reliability and limitations of echocardiographic measurement of left ventricular mass for risk stratification and follow-up in single patients: the RES trial. Working group on heart and hypertension of the Italian society of hypertension. Reliability of M-mode Echocardiographic Studies. J Hypertens 17(12 Pt 2):1955–1963
54. Muiesan ML, de Simone G, Ganau A et al (2006) Inappropriate left ventricular mass: reliability and limitations of echocardiographic measurement for risk stratification and follow-up in single patients. J Hypertens 24(11):2293–2298
55. Troy BL, Pombo J, Rackley CE (1972) Measurement of left ventricular wall thickness and mass by echocardiography. Circulation 45(3):602–611
56. Devereux RB, Reichek N (1977) Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation 55(4):613–618
57. Devereux RB, Alonso DR, Lutas EM et al (1986) Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 57(6):450–458
58. Verdecchia P, Reboldi G, Schillaci G et al (1999) Value of a simple echocardiographic linear predictor of left ventricular mass in systemic hypertension. Am J Cardiol 84(10):1209–1214
59. Levy D, Savage DD, Garrison RJ et al (1987) Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study. Am J Cardiol 59(9):956–960
60. Devereux RB, Dahlof B, Levy D et al (1996) Comparison of enalapril versus nifedipine to decrease left ventricular hypertrophy in systemic hypertension (the PRESERVE trial). Am J Cardiol 78(1):61–65
61. Hammond IW, Devereux RB, Alderman MH et al (1986) The prevalence and correlates of echocardiographic left ventricular hypertrophy among employed patients with uncomplicated hypertension. J Am Coll Cardiol 7(3):639–650
62. Koren MJ, Devereux RB, Casale PN et al (1991) Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 114(5):345–352
63. de Simone G, Devereux RB, Daniels SR et al (1995) Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. J Am Coll Cardiol 25(5):1056–1062
64. Okin PM, Roman MJ, Devereux RB et al (1998) Time-voltage QRS area of the 12-lead electrocardiogram: detection of left ventricular hypertrophy. Hypertension 31(4):937–942
65. Drazner MH, Rame JE, Marino EK et al (2004) Increased left ventricular mass is a risk factor for the development of a depressed left ventricular ejection fraction within five years: the Cardiovascular Health Study. J Am Coll Cardiol 43(12):2207–2215
66. Levy D, Garrison RJ, Savage DD et al (1990) Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 322(22):1561–1566

67. Schillaci G, Verdecchia P, Porcellati C et al (2000) Continuous relation between left ventricular mass and cardiovascular risk in essential hypertension. Hypertension 35(2):580–586
68. Devereux RB, Wachtell K, Gerdts E et al (2004) Prognostic significance of left ventricular mass change during treatment of hypertension. JAMA 292(19):2350–2356
69. Liao Y, Cooper RS, Durazo-Arvizu R et al (1997) Prediction of mortality risk by different methods of indexation for left ventricular mass. J Am Coll Cardiol 29(3):641–647
70. Gosse P, Cremer A, Vircoulon M et al (2012) Prognostic value of the extent of left ventricular hypertyrophy and its evolution in the hypertensive patients. J Hypertens 30(12):2403–2409
71. Cipriano C, Gosse P, Bemurat L et al (2001) Prognostic value of left ventricular mass and its evolution during treatment in the Bordeaux cohort of hypertensive patients. Am J Hypertens 14(6 Pt 1):524–529
72. Koren MJ, Ulin RJ, Koren AT et al (2002) Left ventricular mass change during treatment and outcome in patients with essential hypertension. Am J Hypertens 15(12):1021–1028
73. Muiesan ML, Salvetti M, Rizzoni D et al (1995) Association of change in left ventricular mass with prognosis during long-term antihypertensive treatment. J Hypertens 13(10):1091–1095
74. Verdecchia P, Schillaci G, Borgioni C et al (1998) Prognostic significance of serial changes in left ventricular mass in essential hypertension. Circulation 97(1):48–54
75. Verdecchia P, Angeli F, Borgioni C et al (2003) Changes in cardiovascular risk by reduction of left ventricular mass in hypertension: a meta-analysis. Am J Hypertens 16(11 Pt 1):895–899
76. Verdecchia P, Schillaci G, Borgioni C et al (1995) Adverse prognostic significance of concentric remodeling of the left ventricle in hypertensive patients with normal left ventricular mass. J Am Coll Cardiol 25(4):871–878
77. Ganau A, Devereux RB, Roman MJ et al (1992) Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. J Am Coll Cardiol 19(7):1550–1558
78. Lavie CJ, Milani RV, Ventura HO, Messerli FH (2006) Left ventricular geometry and mortality in patients >70 years of age with normal ejection fraction. Am J Cardiol 98(10):1396–1399
79. Krumholz HM, Larson M, Levy D (1995) Prognosis of left ventricular geometric patterns in the Framingham heart study. J Am Coll Cardiol 25(4):879–884
80. Verdecchia P, Schillaci G, Borgioni C et al (1996) Prognostic value of left ventricular mass and geometry in systemic hypertension with left ventricular hypertrophy. Am J Cardiol 78(2):197–202
81. Ghali JK, Liao Y, Cooper RS (1998) Influence of left ventricular geometric patterns on prognosis in patients with or without coronary artery disease. J Am Coll Cardiol 31(7):1635–1640
82. Beache GM, Herzka DA, Boxerman JL et al (2001) Attenuated myocardial vasodilator response in patients with hypertensive hypertrophy revealed by oxygenation-dependent magnetic resonance imaging. Circulation 104(11):1214–1217
83. Burke AP, Farb A, Liang YH et al (1996) Effect of hypertension and cardiac hypertrophy on coronary artery morphology in sudden cardiac death. Circulation 94(12):3138–3145
84. Verdecchia P, Carini G, Circo A et al (2001) Left ventricular mass and cardiovascular morbidity in essential hypertension: the MAVI study. J Am Coll Cardiol 38(7):1829–1835
85. Chatterjee S, Bavishi C, Sardar P et al (2014) Meta-analysis of left ventricular hypertrophy and sustained arrhythmias. Am J Cardiol 114(7):1049–1052
86. Messerli FH, Michalewicz L (1997) Hypertensive heart disease, ventricular dysrhythmias, and sudden death. Adv Exp Med Biol 432:263–272
87. Messerli FH, Ventura HO, Elizardi DJ et al (1984) Hypertension and sudden death. Increased ventricular ectopic activity in left ventricular hypertrophy. Am J Med 77(1):18–22
88. Rials SJ, Wu Y, Ford N et al (1995) Effect of left ventricular hypertrophy and its regression on ventricular electrophysiology and vulnerability to inducible arrhythmia in the feline heart. Circulation 91(2):426–430
89. Swynghedauw B, Chevalier B, Charlemagne D et al (1997) Cardiac hypertrophy, arrhythmogenicity and the new myocardial phenotype. II. The cellular adaptational process. Cardiovasc Res 35(1):6–12
90. Gillis AM, Mathison HJ, Kulisz E et al (2000) Dispersion of ventricular repolarization and ventricular fibrillation in left ventricular hypertrophy: influence of selective potassium channel blockers. J Pharmacol Exp Ther 292(1):381–386

91. Hennersdorf MG, Niebch V, Perings C, Strauer BE (2001) T wave alternans and ventricular arrhythmias in arterial hypertension. Hypertension 37(2):199–203
92. Kannel WB, Doyle JT, McNamara PM et al (1975) Precursors of sudden coronary death. Factors related to the incidence of sudden death. Circulation 51(4):606–613
93. Kunisek J, Zaputovic L, Butorac MZ et al (2008) The prevalence of supraventricular arrhythmias with regard to the type and degree of left ventricular hypertrophy in patients with hypertensive heart disease. Wien Klin Wochenschr 120(5-6):171–177
94. Verdecchia P, Reboldi G, Gattobigio R et al (2003) Atrial fibrillation in hypertension: predictors and outcome. Hypertension 41(2):218–223
95. Margey R, Roy A, Tobin S et al (2011) Sudden cardiac death in 14- to 35-year olds in Ireland from 2005 to 2007: a retrospective registry. Europace 13(10):1411–1418
96. Guidera SA, Steinberg JS (1993) The signal-averaged P wave duration: a rapid and noninvasive marker of risk of atrial fibrillation. J Am Coll Cardiol 21(7):1645–1651
97. Su G, Cao H, Xu S et al (2014) Left atrial enlargement in the early stage of hypertensive heart disease: a common but ignored condition. J Clin Hypertens (Greenwich) 16(3):192–197
98. Nattel S (2002) New ideas about atrial fibrillation 50 years on. Nature 415(6868):219–226
99. Boldt A, Wetzel U, Lauschke J et al (2004) Fibrosis in left atrial tissue of patients with atrial fibrillation with and without underlying mitral valve disease. Heart 90(4):400–405
100. Kostin S, Klein G, Szalay Z et al (2002) Structural correlate of atrial fibrillation in human patients. Cardiovasc Res 54(2):361–379
101. Spach MS, Dolber PC (1986) Relating extracellular potentials and their derivatives to anisotropic propagation at a microscopic level in human cardiac muscle. Evidence for electrical uncoupling of side-to-side fiber connections with increasing age. Circ Res 58(3):356–371
102. Verdecchia P, Angeli F, Gattobigio R et al (2005) Asymptomatic left ventricular systolic dysfunction in essential hypertension: prevalence, determinants, and prognostic value. Hypertension 45(3):412–418
103. Gradman AH, Alfayoumi F (2006) From left ventricular hypertrophy to congestive heart failure: management of hypertensive heart disease. Prog Cardiovasc Dis 48(5):326–341
104. Klingbeil AU, Schneide M, Martus P et al (2003) A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. Am J Med 115(1):41–46
105. Verdecchia P, Staessen JA, Angeli F et al (2009) Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (cardio-sis): an open-label randomised trial. Lancet 374(9689):525–533
106. Verdecchia P, Porcellati C, Reboldi G et al (2001) Left ventricular hypertrophy as an independent predictor of acute cerebrovascular events in essential hypertension. Circulation 104(17):2039–2044
107. Verdecchia P, Angeli F, Gattobigio R et al (2006) Regression of left ventricular hypertrophy and prevention of stroke in hypertensive subjects. Am J Hypertens 19(5):493–499
108. Zabalgoitia M, Berning J, Koren MJ et al (2001) Impact of coronary artery disease on left ventricular systolic function and geometry in hypertensive patients with left ventricular hypertrophy (the LIFE study). Am J Cardiol 88(6):646–650
109. Young W, Gofman JW, Tandy R et al (1960) The quantitation of atherosclerosis. II. Quantitative aspects of the relationship of blood pressure and atherosclerosis. Am J Cardiol 6:294–299
110. Khattar RS, Senior R, Swales JD, Lahiri A (1999) Value of ambulatory intra-arterial blood pressure monitoring in the long-term prediction of left ventricular hypertrophy and carotid atherosclerosis in essential hypertension. J Hum Hypertens 13(2):111–116
111. Leoncini G, Ratto E, Viazzi F et al (2006) Increased ambulatory arterial stiffness index is associated with target organ damage in primary hypertension. Hypertension 48(3):397–403
112. Watabe D, Hashimoto J, Hatanaka R et al (2006) Electrocardiographic left ventricular hypertrophy and arterial stiffness: the Ohasama study. Am J Hypertens 19(12):1199–1205
113. Verdecchia P, Angeli F (2004) Reversal of left ventricular hypertrophy: what have recent trials taught us? Am J Cardiovasc Drugs 4(6):369–378
114. Rials SJ, Wu Y, Xu X et al (1997) Regression of left ventricular hypertrophy with captopril restores normal ventricular action potential duration, dispersion of refractoriness, and vulnerability to inducible ventricular fibrillation. Circulation 96(4):1330–1336

115. Verdecchia P, Reboldi G, Angeli F et al (2007) Prognostic value of serial electrocardiographic voltage and repolarization changes in essential hypertension: the HEART survey study. Am J Hypertens 20(9):997–1004
116. Angeli F, Verdecchia P, Pelligrino C et al (2003) Association between periodontal disease and left ventricle mass in essential hypertension. Hypertension 41(3):488–492
117. Verdecchia P, Angeli F, Pittavini L et al (2004) Regression of left ventricular hypertrophy and cardiovascular risk changes in hypertensive patients. Ital Heart J 5(7):505–510
118. Verdecchia P, Angeli F, Gattobigio R et al (2004) Does the reduction in systolic blood pressure alone explain the regression of left ventricular hypertrophy? J Hum Hypertens 18(Suppl 2):S23–SS8

# Perioperative Cardiac Surgery Hypertension

# 14

Solomon Aronson

## 14.1 Introduction

Worldwide, an estimated one in three adults has hypertension with the total number of affected people estimated to be greater than one billion [1–3]. Hypertension (HTN) is a major modifiable risk factor for cardiovascular disease that affects approximately 80 million (32.6%) adults in the United States. The incidence is projected to increase to approximately 38% by 2030 [4]. According to the National Health and Nutrition Examination Survey data from 2009 to 2012, only 54% of hypertensive adults in the United States had their condition under control; 77% were currently treated; 83% were aware of their condition; and 17% were undiagnosed [5]. The economic impact of morbidity and mortality resulting from hypertension is substantial. The additional health-care costs exceeded $70 billion in 2010 and are expected to soar to approximately $200 billion by 2030 [6, 7]. When subjected to the stresses of cardiovascular surgery, patients with preexisting hypertension are subject to wide swings in intraoperative blood pressure and are at increased risk of short- and long-term adverse outcomes [8–16]. Defining appropriate BP guardrails remains elusive, and defining acceptable perioperative target BP thresholds is a complex medical decision which depends on several factors including the patient physiology profile and procedural need.

Intraoperative HTN, independent of preexisting HTN, is common during cardiac surgery, and its management can impact outcomes. Importantly, intraoperative HTN occurs in patients without any prior history of HTN [17–20]. The etiology of intraoperative HTN is multifactorial and mechanistically discrete from that of nonsurgical hypertension. Postoperative hypertension for up to 48 h post-procedure is also common after cardiac surgery and is related to a durable increase in sympathetic tone and ongoing fluid mobilization and shifts [8–10].

S. Aronson, MD, MBA, FACC, FCCP, FAHA, FASE
Department of Anesthesiology, Duke University, 103 Baker House, Durham, NC 27710, USA
e-mail: solomon.aronson@duke.edu



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_14

Defining a "target" blood pressure (BP) during the intraoperative or postoperative period is a routine part of anesthesia and cardiac surgical patient care, yet there is surprisingly little objective evidence on the appropriate clinical goals. Because of comorbidities and the magnitude of acute physiologic stress, intraoperative BP management in the cardiac surgical patient remains an area of active best-practice research. The specific impact of postoperative BP on outcomes in cardiac surgery patients remains poorly understood in part due to a wide variety of underlying contributors to postoperative BP changes and that there is no single established definition nor standard of care for the treatment of postoperative HTN [20–25]. Gaps regarding our understanding of optimal clinical goals for pre-, intra-, and postoperative blood pressure (BP) management in patients undergoing cardiac surgery as well as the consequences of achieving or failing to achieve those goals remain. In this setting, it is understood that preoperative hypertension is predictive of poor postoperative outcomes with a growing appreciation that heretofore clinically acceptable changes in intraoperative BP may also independently be associated with short- and long-term adverse outcomes. The impact of postoperative BP on outcomes following cardiac surgery has remained less clear until a recent retrospective analysis of cardiac surgery patients [26].

## 14.2 BP and Outcomes During Cardiovascular Surgery

### 14.2.1 Preoperative Period

Among patients undergoing cardiac surgery, *preexisting hypertension* exists in over two-thirds of all patients. Preexisting hypertension introduces challenges, as it has been shown that the autoregulatory capacity of the brain [27–29] and kidney is impaired, potentially influencing end-organ tolerance of high or low blood pressures. As a result, the therapeutic window of intra- and postoperative acceptable blood pressure is narrowed and shifted to the right in these patients.

There is evidence that isolated systolic hypertension (ISH) and pulse pressure (PP) are independently associated with adverse cardiovascular outcomes [11–16]. Isolated systolic hypertension (ISH) increases in prevalence with age. Evidence also indicates that adverse ischemic cardiac and cerebral vascular disease increase with age-adjusted increasing SBP. Data on the relationship of preoperative ISH to perioperative outcome have been reported in cardiac surgery. ISH was associated with a 40% increase in perioperative cardiovascular morbidity following coronary artery bypass graft [11]. Interestingly, this risk remained, regardless of preoperative antihypertension medication, anesthetic techniques, or other perioperative cardiovascular risk factors.

In addition, among patients undergoing cardiac surgery, the mean pulse pressure was shown to be associated with adverse outcome. PP was greater in patients who suffered a stroke (81 vs. 65 mmHg) in such a manner that with each additional 10 mmHg there was additive risk (odds ratio [OR], 1.35; confidence interval [CI], 1.13–1.62; $P = 0.001$) [15]. It was also independently observed that a renal

dysfunction outcome as well as death from cardiac and cerebral causes was also directly associated to increasing preoperative PP among these patient population [13, 16] (Figs. 14.1, 14.2, and 14.3).

Patients with preoperative pulse pressure hypertension or isolated systolic hypertension tend to be older (70 ± 8 years) than propensity-matched normotensive patients [16], while patients with isolated diastolic hypertension tend to be younger (60 ± 9 years) than normotensive patients (64 ± 10 years; $P$ <0.001). The incidence of a renal composite event occurred nearly two times as often in patients with PP hypertension (PPH), PP >80 mmHg, compared with patients without PPH (5% vs. 2.9% for renal dysfunction and 5.5% vs. 2.5% for renal failure), with a progressive increase in the risk of renal composite above a PP threshold of 40 mmHg. Moreover,

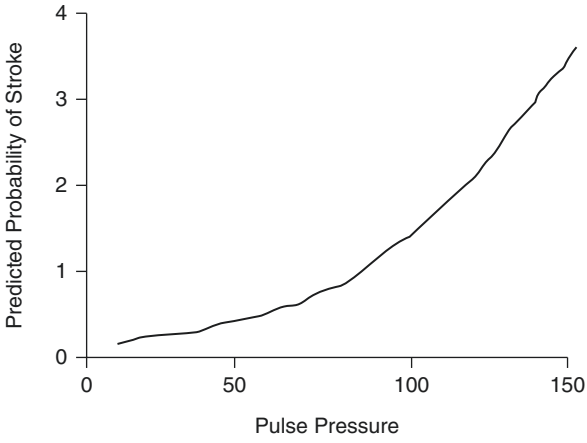



**Fig. 14.1** Stroke after cardiac surgery is proportionate to and predicted by preoperative pulse pressure (derived from [15]; Hypertension 2007;50:630–635)

| Preoperative Risk Factors | Score |
|---|---|
| Age >75 years | 7 |
| PP (mm Hg) | |
| 40 | 0 |
| 41–60 | 4 |
| 61–80 | 8 |
| 81–100 | 12 |
| >100 | 16 |
| History | |
| CHF | 9 |
| MI | 6 |
| Renal disease | 13 |

**Fig. 14.2** Renal dysfunction outcome after cardiac surgery is proportionate to and predicted by preoperative pulse pressure (derived from [16]; Circulation 2007;115:733–742). Relative risk score of renal dysfunction outcomes shown for perioperative risk factors

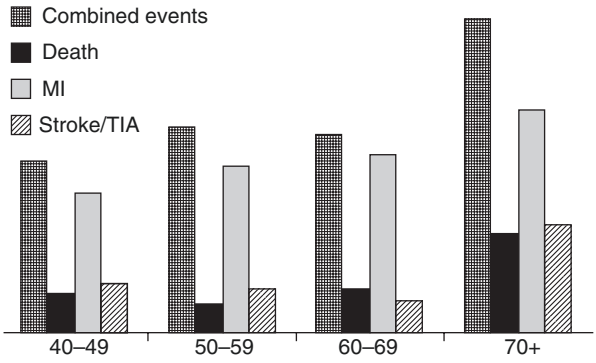



**Fig. 14.3** The composite outcome of stroke, death, and myocardial infarction after cardiac surgery is proportionate to and predicted by preoperative pulse pressure (derived from [14]; Eur J Cardiothorac Surg 2008;33:971–976). *X* axis represents age ranges by 10-year blocks; *Y* axis represents % incidence

patients with PPH were nearly three times more likely to have a renal-related death compared with those without PPH (3.7% vs. 1.1%).

### 14.2.2 Intraoperative Period

The conditions that cause an acute change in systemic hemodynamics *during surgery* are common and include acute changes in systemic vascular resistance due to anesthesia depth, surgical stimulation, aortic occlusive clamping and unclamping, cannulation and decannulation, fluid shifts, hemorrhage, drug effects, as well as the inflammatory response associated with cardiopulmonary bypass (CPB) [16, 17]. These changes commonly occur in the setting of insufficient intravascular volume and likely effect patients differently, depending on their underlying vascular physiology and compliance, fibrinolytic activity, hypercoagulability, vasomotor reactivity, and/or plaque rupture vulnerability [30, 31]. It is possible that the autoregulatory range is distinctly different across individuals with an altered autoregulatory range leading to organ hypoperfusion in some individuals, despite what may be deemed to be a "clinically acceptable" BP.

The active management of BP during cardiovascular surgery has been reported to be extremely common (88% of all cases). Perhaps this behavior reflects that poorly controlled BP during surgery is not tolerated in part because of safety concerns related to ischemia modulation, the need for aortovascular stress-strain modulation (e.g., clamping, unclamping), maintaining adequate perfusion conditions during CPB, and balancing these pressure-perfusion requirements with surgical bleeding concerns throughout surgery. It is well understood that hypertension increases myocardial oxygen consumption and left ventricular end-diastolic pressure and contributes to subendocardial hypoperfusion and myocardial ischemia. It also increases the risk of stroke, neuron-cognitive dysfunction, and renal dysfunction and contributes to surgical bleeding from anastomotic sites [32–34]. In addition, poorly controlled BP during surgery can trigger hyper-inflammatory and procoagulation conditions, including platelet activation, which may compromise microvascular blood flow [35, 36].

Over three million intraoperative blood pressure evaluations were analyzed in over 7500 patients [18]. Systolic blood pressure variability outside a predefined upper and lower blood pressure range was measured and tested to predict 30-day mortality in patients undergoing cardiac surgery (Fig. 14.4). It was observed that mean duration of systolic excursion [outside a range of 105 mmHg (lower)–130 mmHg (upper)] predicted 30-day mortality (OR = 1.03 per minute, 95% CI [1.02–1.39], $P$ <0.0001). The same hypothesis was tested and independently confirmed in the ECLIPSE trials [19] where BP excursion outside a target systolic range was found to be associated with increased postoperative mortality and increased postoperative renal injury. Intraoperative systolic blood pressure variability was again determined in over 7000 patients and characterized by frequency, magnitude (mmHg), duration (min), area under curve (mmHg*min), and % change from baseline [37]. Multivariable linear regression demonstrated an association between % changes in SBP below baseline to % delta creatinine ($p$ <0.0016). The

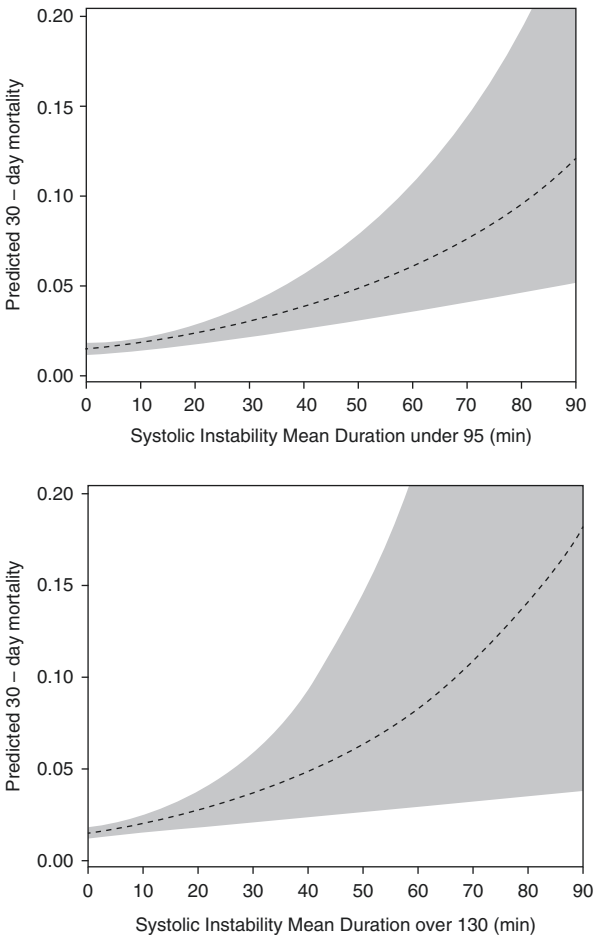



**Fig. 14.4** 30-day mortality outcome after cardiac surgery is proportionate to and predicted by intraoperative systolic blood pressure variation above an upper systolic threshold of 130 mmHg and below a lower systolic threshold of 95 mmHg (derived from [18]; Anesthesiology 2010;113:305–312)

percent change of intraoperative systolic BP below presenting preoperative or baseline BP is associated with the percent increase change from baseline in creatinine observed following cardiac surgery (Fig. 14.5). Intraoperative BP variability was also associated with delayed time to extubation and increased postoperative length of stay (LOS) [38].

### 14.2.3 Postoperative Period

Postoperative hypertension has an arbitrary definition but is understood to have an increased incidence of neurologic deficits and operative mortality. Typically, patients who exhibit postoperative hypertension have some form of hypertension prior to surgery. Postoperative hypertension can be due to a variety of causes, including pain, anxiety, hypercarbia, hypercapnia, hypothermia, volume overload, and bladder distension. Studies have found an elevation in plasma epinephrine and norepinephrine concentrations, suggesting an enhanced sympathetic response to surgery [39–42]. This evidence points to a sympathetic trigger in the development of postoperative hypertension.

We conducted a retrospective outcome analysis [26] of all cardiac surgery patients cared for at a single institution (Charité Hospital, Berlin, Germany) over a 7-year period (2006–2012). Patients were admitted to the cardiac surgical intensive care unit post-surgery, and BP targets were defined and adhered to by strict protocol. Consequences of success or failure at meeting those targets on medical outcomes and health resource utilization were evaluated in 5225 patients. Although 90% of

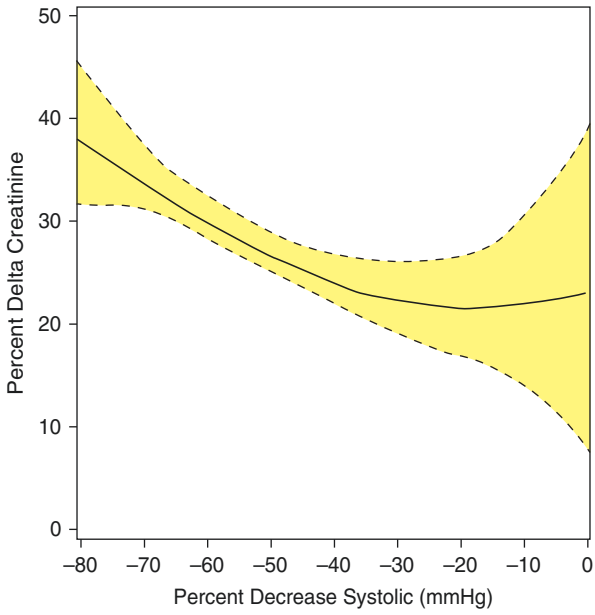



**Fig. 14.5** Renal dysfunction outcome after cardiac surgery is proportionate to and predicted by intraoperative percent change in systolic blood pressure below baseline systolic blood pressure (derived from [37]; Anesthesiol Res Pract 2013;2013:174091. Published online. doi:10.1155/2013/174091)

patients had systolic BP values less than 130 mmHg upon arrival to the ICU, 70% were ultimately treated for high blood pressure within the first 24 h of their postoperative ICU stay. Among the patients who required postoperative antihypertensive treatment, 78% had a history of preoperative HTN. Patients treated for high blood pressure compared to matched case normotensive patients had a higher in-hospital mortality rate (4.97% vs. 1.32%, $p$ <0.001) and a longer hospital stay ($p$ = 0.024). In hypertensive patients, serum creatinine levels from postoperative day (POD) 1 through POD 7 compared to baseline were increased, and postoperative renal dysfunction occurred more often (25.3% vs. 19.7%, $p$ = 0.027).

## 14.3 Discussion

BP monitoring during the perioperative period more than any other single parameter remains a core tenet of provider vigilance, and BP management remains an important focus of perioperative clinical care. Despite this ubiquity, however, BP management considerations are not well supported by a robust evidence base. Existing evidence suggest that heretofore clinically acceptable guidelines for intraoperative and/or postoperative BP management after cardiac surgeries deserve reexamination, as adverse outcomes were observed while adhering to commonly endorsed definitions and management strategies. Due to diverse patient demography, coexisting conditions, and the wide variety of underlying contributors to the perioperative BP alterations, to date, no single established definition nor standard of care for the treatment of perioperative HTN exists.

## References

1. Kearney PM, Whelton M, Reynolds K et al (2005) Global burden of hypertension: analysis of worldwide data. Lancet 365:217–223
2. Ezzati M, Oza S, Danaei G, Murray CJ (2008) Trends and cardiovascular mortality effects of state-level blood pressure and uncontrolled hypertension in the United States. Circulation 117:905–914
3. Wang TJ, Vasan RS (2005) Epidemiology of uncontrolled hypertension in the United States. Circulation 112:1651–1662
4. Mozaffarian D, Benjamin EJ, Go AS et al (2015) Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation 131:e29–e322
5. Huffman MD, Capewell S, Ning H et al (2012) Cardiovascular health behavior and health factor changes (1988-2008) and projections to 2020: results from the National Health and nutrition examination surveys. Circulation 125:2595–2602
6. Go AS, Mozaffarian D, Roger VL et al (2013) Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation 127:e6–e245
7. Heidenreich PA, Trogdon JG, Khavjou OA et al (2011) Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation 123:933–944
8. Hollenberg M, Mangano DT, Browner WS et al (1992) Predictors of postoperative myocardial ischemia in patients undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. JAMA 268:205–209

9. Mangano DT, Layug EL, Wallace A, Tateo I (1996) Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter study of perioperative ischemia research group. N Engl J Med 335:1713–1720
10. Mangano DT (1999) Assessment of the patient with cardiac disease: an anesthesiologist's paradigm. Anesthesiology 91:1521–1526
11. Aronson S, Boisvert D, Lapp W (2002) Isolated systolic hypertension is associated with adverse outcomes from coronary artery bypass grafting surgery. Anesth Analg 94:1079–1084
12. Nikolov NM, Fontes ML, White WD et al (2010) Pulse pressure and long-term survival after coronary artery bypass graft surgery. Anesth Analg 110:335–340
13. Fontes ML, Aronson S, Mathew JP et al (2008) Pulse pressure and risk of adverse outcome in coronary bypass surgery. Anesth Analg 107:1122–1129
14. Aboyans V, Frank M, Nubret K et al (2008) Heart rate and pulse pressure at rest are major prognostic markers of early postoperative complications after coronary bypass surgery. Eur J Cardiothorac Surg 33:971–976
15. Benjo A, Thompson RE, Fine D et al (2007) Pulse pressure is an age-independent predictor of stroke development after cardiac surgery. Hypertension 50:630–635
16. Aronson S, Fontes ML, Miao Y, Mangano DT (2007) Risk index for perioperative renal dysfunction/failure: critical dependence on pulse pressure hypertension. Circulation 115:733–742
17. Reich DL, Bennett-Guerrero E, Bodian CA et al (2002) Intraoperative tachycardia and hypertension are independently associated with adverse outcome in noncardiac surgery of long duration. Anesth Analg 95:273–277
18. Aronson S, Stafford-Smith M, Phillips-Bute B et al (2010) Intraoperative systolic blood pressure variability predicts 30-day mortality in aortocoronary bypass surgery patients. Anesthesiology 113:305–312
19. Aronson S, Dyke CM, Levy JH et al (2011) Does perioperative systolic blood pressure variability predict mortality after cardiac surgery? An exploratory analysis of the ECLIPSE trials. Anesth Analg 113:19–30
20. Aronson S (2014) Perioperative hypertensive emergencies. Curr Hypertens Rep 16:448
21. Cheung AT (2006) Exploring an optimum intra/postoperative management strategy for acute hypertension in the cardiac surgery patient. J Card Surg 21(Suppl 1):S8–S14
22. Chobanian AV, Bakris GL, Black HR et al (2003) The seventh report of the joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 289:2560–2572
23. Oparil S, Aronson S, Deeb GM et al (1999) Fenoldopam: a new parenteral antihypertensive: consensus roundtable on the management of perioperative hypertension and hypertensive crises. Am J Hypertens 12:653–664
24. Vuylsteke A, Feneck RO, Jolin-Mellgard A et al (2000) Perioperative blood pressure control: a prospective survey of patient management in cardiac surgery. J Cardiothorac Vasc Anesth 14:269–273
25. Goldberg ME, Weaver FA (2007) Strategies for managing perioperative hypertension. Crit Care Clin 23(Suppl 1):7–21
26. Balzer F, Aronson S, Treskatsch S et al (2015) Poor post-operative blood pressure control in cardiac surgery patients is associated with acute kidney injury and death. Abstract SCA Annual Meeting, 2015
27. Immink RV, van den Born BJ, van Montfrans GA et al (2004) Impaired cerebral autoregulation in patients with malignant hypertension. Circulation 110(15):2241–2245
28. Toyoda K, Fujii K, Ibayashi S et al (1998) Attenuation and recovery of brain stem autoregulation in spontaneously hypertensive rats. J Cereb Blood Flow Metab 18(3):305–310
29. Ono M, Arnaoutakis GJ, Fine DM et al (2013) Blood pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with acute kidney injury. Crit Care Med 41:464–471
30. Imoto K, Hiro T, Fujii T (2005) Longitudinal structural determinants of atherosclerotic plaque vulnerability: a computational analysis of stress distribution using vessel and three dimensional intravascular ultrasound imaging. J Am Coll Cardiol 46:1507–1515

31. Lee KW, Blann AD, Lip GY (2004) High pulse pressure and nondipping circadian blood pressure in patients with coronary artery disease: relationship to thrombogenesis and endothelial damage/dysfunction. Am J Hypertens 18:104–115
32. Brienza N, Giglio MT, Marucci M, Fiore T (2009) Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. Crit Care Med 37:2079–2090
33. Gurgel ST, do Nascimento P Jr (2011) Maintaining tissue perfusion in high-risk surgical patients: a systematic review of randomized clinical trials. Anesth Analg 112:1384–1391
34. O'Rourke MF, Safar ME (2005) Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension 46:200–204
35. Hennein HA, Ebba H, Rodriguez JL et al (1994) Relationship of the proinflammatory cytokines to myocardial ischemia and dysfunction after uncomplicated coronary revascularization. J Thorac Cardiovasc Surg 108:626–635
36. Kobzar G, Mardla V, Rätsep I, Samel N (2006) Platelet activity before and after coronary artery bypass grafting. Platelets 17:289–291
37. Aronson S, Phillips-Bute B, Stafford Smith M et al (2013) The association of post-cardiac surgery acute kidney injury with intraoperative systolic blood pressure hypotension. Anesthesiol Res Pract 2013:174091. doi:10.1155/2013/174091
38. Aronson S, Levy JH, Lumb PD et al (2014) Impact of perioperative blood pressure variability on health resource utilization after cardiac surgery: an analysis of the ECLIPSE trials. J Cardiothorac Vasc Anesth 28(3):579–585
39. Towne JB, Bernhard VM (1980) The relationship of postoperative hypertension to complications following carotid endarterectomy. Surgery 88:575–580
40. Halpern NA, Goldberg M, Neely C et al (1992) Postoperative hypertension: a multicenter, prospective, randomized comparison between intravenous nicardipine and sodium nitroprusside. Crit Care Med 20:1637–1643
41. Gal TJ, Cooperman LH (1975) Hypertension in the immediate postoperative period. Br J Anaesth 47:70–74
42. Wallach R, Karp RB, Reves JG et al (1980) Pathogenesis of paroxysmal hypertension developing during and after coronary bypass surgery: a study of hemodynamic and humoral factors. Am J Cardiol 46:559–565

# Hypertension: Supravalvular Aortic Stenosis

# 15

Daragh Finn and Colin J. McMahon

## 15.1 Introduction

Supravalvular aortic stenosis (SVAS) is an uncommon form of congenital left ventricular outflow tract obstruction, defined as an obstruction originating at the superior margins of the sinus of Valsalva, just above the level of the coronary arteries [1, 2]. Supravalvular aortic stenosis was first described in 1930 by an Italian pathologist and may present as part of a syndrome, most commonly Williams syndrome, or as a separate non-syndromic genetic entity [3]. Supravalvular aortic stenosis is caused by a defect in the elastin gene (ELN), and Williams syndrome is caused by a microdeletion of the chromosome region 7q11.23 that includes ELN. Although SVAS is a rare congenital cardiac lesion during fetal and early postnatal life, the stenosis may become progressively more severe with age [4]. An hourglass deformity is most commonly described, or more rarely, a diffuse narrowing may be seen [1]. Hypertension has been reported in up to 70% of patients with SVAS, and the risk of hypertension increases over time [5, 6]. A clear etiology is not always evident, but diffuse aortic narrowing and/or renal artery stenosis should be considered. Lifelong follow-up and blood pressure monitoring is paramount in the treatment of such patients.

## 15.2 Incidence

The incidence of Williams syndrome is 1 in 10,000 live births [7]. Reported rates of SVAS in infants with Williams syndrome vary in the literature between 45 and 75% [6, 8–10]. Although no statistical data from population studies exist, overall

D. Finn, M.B., M.R.C.P.I. • C.J. McMahon, MBB.Ch, FRCPI, FAAP, FACC, FAHA (✉)
Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Ireland

University College Dublin Medical Sciences, Dublin, Ireland
e-mail: Cmcmahon992004@yahoo.com



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_15

estimated incidence of SVAS including both syndromic and non-syndromic forms is between 1:20,000 and 50,000 live births [11, 12].

## 15.3 Etiology

Williams syndrome, also known as Williams–Beuren syndrome, is caused by a microdeletion of 1.5–1.8 million base pairs at 7q11.23 and encompasses 26–28 genes [13], including ELN [14]. Williams et al. initially described the syndrome in 1961 as a triad which involved SVAS, learning disability, and dysmorphic facial features [15]. Hemizygosity of ELN coding for the elastin protein is responsible for the vascular abnormalities found in Williams syndrome [16], and the remaining genes account for the other typical phenotypic features. Although familial variants can occur, the majority of cases are caused by de novo microdeletions [17]. Variable expressivity and reduced penetrance are observed in Williams syndrome [18].

Non-syndromic supravalvular aortic stenosis is a separate genetic entity [19, 20] that also features disruption of ELN [21, 22]. It occurs as a consequence of haploinsufficiency of ELN. It is caused most commonly by a microdeletion [21–23]. Point mutations have also been reported [24, 25], and less commonly, it may occur as a result of missense mutations, which account for 10% of cases [11]. ELN is composed of 34 exons, spans 45 Kb of genomic sequence, and produces a transcript of 3.5 Kb comprising 2.2 Kb of coding sequences. Non-syndromic SVAS is an autosomal dominant disease [21], with incomplete penetrance and variable expressivity [11].

## 15.4 Pathophysiology

Reduced elastin synthesis is observed in both syndromic and non-syndromic forms of SVAS. This occurs in conjunction with vascular smooth muscle cell proliferation, although the exact pathways linking elastin deficiency to vascular cell proliferation have yet to be identified [14]. Histologic features in the ascending aorta of affected individuals include diseased media, increased number of diseased hypertrophied smooth muscle cells, increased collagen content, and elastic tissue in the form of broken and disorganized elastin fibers [26, 27].

## 15.5 Classification: Anatomy

Supravalvular aortic stenosis has two morphologic anatomic forms on echocardiographic studies interrogating the ascending aorta, each of which includes evidence of stenosis distal to the valvular cusps [28]:

1. An hourglass deformity of the ascending aorta with a corresponding luminal narrowing at a level just distal to the coronary artery ostia is most commonly described and occurs in 50–75% of patients.

2. A diffuse narrowing of variable length of the ascending aorta may also occur and is reported in <25% of patients and is often associated with stenosis of the brachiocephalic vessels [2, 29].

## 15.6 Clinical Presentation

Following from the reports of Williams and Beuren et al., it was realized that Williams syndrome can present with a constellation of distinctive phenotypic characteristics [15, 30].

Infants with Williams syndrome may have low growth velocities both pre- and postnatally. Microcephaly occurs in almost one third of infants [31]. Feeding difficulties and failure to thrive are common in the first 2 years of life, but in some cases, children may present with short stature later in childhood [32].

Typical facial features include short upturned nose, flat nasal bridge, long philtrum, wide mouth, large lips, micrognathia, a stellate pattern of the irises, widely spaced teeth, and periorbital fullness [5].

Cardiovascular lesions are present in up to 93% of Williams syndrome patients presenting in the first year of life [33]. Supravalvular aortic stenosis may be suspected when an ejection systolic murmur radiating to the carotids +/− a thrill in the suprasternal notch is appreciated on clinical exam. Depending on the severity of the lesions, a large number of patients can be followed up clinically without immediate intervention. Table 15.1 outlines a follow-up strategy devised by Collins et al. and modified from the AHA guidelines [8, 34]. The Coanda effect may also be present when four-limb blood pressures are assessed, with blood pressure disparity between arms and right upper arm pressure often greater than the left by a magnitude of 20 mmHg. This effect is caused by the tendency of a jet stream, in this case the jet caused by supravalvular aortic stenosis to adhere to a wall. Blood flow through the stenotic region has preference for the brachiocephalic vessels and results in increased right upper limb blood pressure compared to the left [35].

Sensorineural hearing loss is common, is often progressive in nature, and can be exacerbated by conductive hearing loss secondary to recurrent middle ear infections [36].

**Table 15.1** Cardiovascular evaluation and follow-up of patients with Williams syndrome [34]

| |
|---|
| Examination every 3 months during the first year of life, then annually until 5 years of age, and biennially or triennially thereafter |
| Four-extremity blood pressures at each visit until adolescence |
| ECG at each visit to assess LVH |
| 24-h ambulatory ECG at 1 year of age, annually until 5 years of age, and then biennially |
| Echocardiography at presentation, at least annually until 5 years of age, and then as needed if heart disease is present |
| CT or MRI of the aorta if severe SVAS is present; imaging of head and neck vessels should also be considered if diffuse SVAS |
| Renal ultrasound if hypertensive or if abdominal bruits are auscultated. Ultrasound of carotids if carotid bruits are present |

Some children have connective tissue abnormalities with lax skin and hypermobile joints on exam. Hernias and diverticula may also be found.

Children may present with developmental delay [37], and most children have mild to moderate learning disabilities, but their verbal strength exceeds a reported mean IQ of 50–60 [38, 39]. Later in childhood, children are often described as overfriendly or hypersocial, with a characteristic ebullient "cocktail personality." However, behavioral problems are common, including inattention and hyperactivity, and almost 50% of children may be diagnosed with autism spectrum disorders [40–42].

Idiopathic hypercalcemia will be present in 50% of infants and resolves during childhood [8, 43]. Other associations are delayed toilet training, nocturnal enuresis [44], and precocious puberty [45, 46].

ECGs in patients with Williams syndrome may display abnormalities of cardiac repolarization, long corrected QT intervals (QTc), and electrical criteria for right ventricular hypertrophy and/or left ventricular hypertrophy [47].

## 15.7 Associated Lesions

*Renal artery stenosis*: In the reported incidence, between 7 and 58% of patients with Williams syndrome [8, 48, 49] and 40% of patients with hypertension and Williams syndrome have renal artery stenosis [8].

*Aortic valve abnormalities*: The localization of the lesion has implications and in 50% of individuals can result in premature degeneration of the aortic valve.

*Pulmonary branch stenosis*: Both Williams syndrome and non-syndromic supravalvular aortic stenosis are associated with pulmonary branch stenosis [1]. Peripheral pulmonary artery stenosis improves with time, and SVAS either progresses or remains stable in Williams syndrome [6, 34, 50]. Supravalvular aortic stenosis associated with peripheral pulmonary stenosis has also been reported in other genetic syndromes such as Alagille syndrome 1, neurofibromatosis type 1, and Noonan syndrome type 1 [3].

*Coronary artery disease*: Pressure of the left ventricle is raised based on severity of the obstruction. Coronary arteries proximal to the obstruction have the same pressure resulting in dilatation, hypertrophy, intimal thickening, and premature atherosclerosis [8]. As a result, there is increased resistance to blood flow and elevated left heart pressure, and concentric left ventricular hypertrophy results from obstruction [35] and exacerbates ischemia. Premature coronary artery disease has been reported in 28–45% of patients with SVAS [1, 51]. Chest pain or dyspnea secondary to SVAS with coronary artery abnormalities and sudden death during exercise have also been reported [52].

## 15.8 Molecular Diagnosis

Ewart was the first to use fluorescent in situ hybridization (FISH) analysis to demonstrate hemizygosity of the ELN locus in patients with Williams syndrome [53], and FISH is now the standard diagnostic tool when Williams syndrome is suspected.

In non-syndromic SVAS, FISH analysis is also the investigation of choice to detect ELN deletions which are the most common mutations in SVAS. Mutation screening will detect point mutations. Family screening and preclinical diagnosis are possible. However, genetic counseling is limited by the large variety of mutations that can cause SVAS [11]. Also the severity of the disease varies widely within families, which further limits the value of genetic counseling [12, 23, 54].

## 15.9 Hypertension

The prevalence of hypertension in Williams syndrome is highly variable in the literature ranging between 5 and 70% [6, 14, 17, 48, 55–60]. Also, screening for hypertension is not universal in this population, which suggests that hypertension is probably underestimated in patients. In a recent cohort study by Bouchireb et al., the mean age when hypertension was diagnosed was 4.7 years [49]. Over 90% of patients diagnosed with hypertension were asymptomatic at the time of diagnosis; however, a number of patients presented with ischemic stroke and myocardial infarctions. Therefore, screening, early diagnosis, and treatment are important in order to reduce the already important vascular risk in patients with Williams syndrome [49].

Hypertension is often related to the lack of vessel distensibility [61]. Daniels et al. first described the causal relationship between vascular abnormalities and hypertension in Williams syndrome [62]. Elastin levels are responsible for the distensibility of the aorta during systole and subsequent recoil during diastole. Hydrodynamic energy is stored during systole and released during diastole known as the Windkessel effect [63], and loss produces a wide pulse pressure with elevated systolic blood pressure and reduced diastolic aortic pressures.

In many patients, hypertension without SVAS is found which suggests that hypertension in Williams syndrome is multifactorial and not solely related to SVAS. The incidence of renal artery narrowing in Williams syndrome is as high as 60% [48, 64] and is an important cause of hypertension in patients with Williams syndrome. Wessel et al. found that mean heart rates are higher over time in both normo- and hypertensive patients with William syndrome [56], suggesting that a high sympathetic activity might play a role in hypertension. Broder et al. found that hypertension is significantly more common in William syndrome patients with a history of infantile hypercalcemia [59], but no direct causal relationship between hypercalcemia and hypertension has been described.

There is little information focusing on medical treatment of hypertension in children with Williams syndrome, and there are no international guidelines, and data-based recommendations for antihypertensive therapies cannot be made [14]. Calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors have been frequently used in many retrospective series [6, 17, 49]. However, therapeutic options for systemic hypertension in patients with Williams syndrome must take into consideration the potential presence of renal artery stenosis. Thus, the use of ACE inhibitors is contraindicated unless renal artery stenosis has been definitively excluded. The link between infantile hypercalcemia and hypertension

suggests a role for calcium channel blockade, and calcium channel blockers of the dihydropyridine type have been reported to be effective for the treatment of hypertension in patients with Williams syndrome [59]. Some authors recommend beta-blockers as first-line agents, as sympathetic overactivity may contribute to the development of hypertension [56]. The use of beta-blocker therapy for hypertension has the attractive additional benefit of potentially decreasing the risk of ventricular arrhythmia or an increased adrenergic response, as well as sudden death, in patients with prolongation of the QTc [34].

Beta-blocker and calcium channel blocker drugs have been utilized frequently in several of the retrospective series [6, 56, 60, 65], and although medical treatment in Williams syndrome can be challenging so that multidrug regimens may be required for adequate control of blood pressure, either agent may be appropriate as a first-line treatment.

Patients with hypertension resistant to drug therapy should be studied for renovascular etiology. Percutaneous transluminal renal angioplasty has been performed for the treatment of renal artery stenosis in patients with Williams syndrome [66]. Angioplasty can be an effective treatment when the stenosis is isolated, but success rates for cure or reducing the need for medical treatment are highly variable in the literature and at present are not encouraging [49, 66].

Approximately 20% of patients with WS will require surgical or transcatheter interventions for cardiovascular abnormalities, the majority of which will be needed by 15 years of age [9]. Surgical intervention is most commonly undertaken for SVAS because transcatheter balloon angioplasty has been found to be ineffective [9, 67, 68]. Surgical approaches to SVAS have evolved over time and include the use of an inverted Y-shaped patch [29] and the modified Brom (three-sinus) technique. The latter has been shown to have excellent outcomes without the need for reintervention and is increasingly being used [69]. The overall survival of patients with SVAS was estimated at 90 ± 7%, 84 ± 9%, and 82 ± 10% at 5, 10, and 20 years, respectively [70]. Freedom from late reoperation in the same cohort was estimated at 97 ± 4%, 93 ± 7%, and 86 ± 10% at 5, 10, and 20 years, respectively. However, in those patients with the diffuse type of SVAS, as many as 35% will require reintervention [71].

**Conclusion**

Hypertension is common in patients with Williams syndrome, and screening is important. Etiology is multifactorial, and causes including SVAS and renal artery stenosis need to be investigated. Medical treatment may be challenging, and calcium channel blockade or beta-blockers should be considered as first-line agents.

## References

1. Stamm C, Kreutzer C, Zurakowski D et al (1999) Forty-one years of surgical experience with congenital supravalvular aortic stenosis. J Thorac Cardiovasc Surg 118(5):874–885
2. Vaideeswar P, Shankar V, Deshpande JR et al (2001) Pathology of the diffuse variant of supravalvar aortic stenosis. Cardiovasc Pathol 10(1):33–37

3. Merla G, Brunetti-Pierri N, Piccolo P et al (2012) Supravalvular aortic stenosis: elastin arteriopathy. Circ Cardiovasc Genet 5(6):692–696. doi:10.1161/CIRCGENETICS.112.962860
4. Smoot LB (1995) Elastin gene deletions in Williams syndrome. Curr Opin Pediatr 7(6):698–701
5. Morris CA, Demsey SA, Leonard CO et al (1988) Natural history of Williams syndrome: physical characteristics. J Pediatr 113(2):318–326
6. Eronen M, Peippo M, Hiippala A et al (2002) Cardiovascular manifestations in 75 patients with Williams syndrome. J Med Genet 39(8):554–558
7. Stromme P, Bjornstad PG, Ramstad K (2002) Prevalence estimation of Williams syndrome. J Child Neurol 17(4):269–271
8. Committee on Genetics (2001) American Academy of Pediatrics: health care supervision for children with Williams syndrome. Pediatrics 107(5):1192–1204
9. Collins RT II, Kaplan P, Somes GW, Rome JJ (2010) Long-term outcomes of patients with cardiovascular abnormalities and Williams syndrome. Am J Cardiol 105(6):874–878. doi:10.1016/j.amjcard.2009.10.069
10. Yau EK, Lo IF, Lam ST (2004) Williams-Beuren syndrome in the Hong Kong Chinese population: retrospective study. Hong Kong Med J 10(1):22–27
11. Metcalfe K, Rucka AK, Smoot L et al (2000) Elastin: mutational spectrum in supravalvular aortic stenosis. Eur J Hum Genet 8(12):955–963. doi:10.1038/sj.ejhg.5200564
12. Duba HC, Doll A, Neyer M et al (2002) The elastin gene is disrupted in a family with a balanced translocation t(7;16)(q11.23;q13) associated with a variable expression of the Williams-Beuren syndrome. Eur J Hum Genet 10(6):351–361. doi:10.1038/sj.ejhg.5200812
13. Merla G, Brunetti-Pierri N, Micale L, Fusco C (2010) Copy number variants at Williams-Beuren syndrome 7q11.23 region. Hum Genet 128(1):3–26. doi:10.1007/s00439-010-0827-2
14. Pober BR, Johnson M, Urban Z (2008) Mechanisms and treatment of cardiovascular disease in Williams-Beuren syndrome. J Clin Invest 118(5):1606–1615. doi:10.1172/JCI35309
15. Williams JC, Barratt-Boyes BG, Lowe JB (1961) Supravalvular aortic stenosis. Circulation 24:1311–1318
16. Keating MT (1995) Genetic approaches to cardiovascular disease. Supravalvular aortic stenosis, Williams syndrome, and long-QT syndrome. Circulation 92(1):142–147
17. Ferrero GB, Biamino E, Sorasio L et al (2007) Presenting phenotype and clinical evaluation in a cohort of 22 Williams-Beuren syndrome patients. Eur J Med Genet 50(5):327–337. doi:10.1016/j.ejmg.2007.05.005
18. Chowdhury T, Reardon W (1999) Elastin mutation and cardiac disease. Pediatr Cardiol 20(2):103–107. doi:10.1007/s002469900415
19. Chiarella F, Bricarelli FD, Lupi G et al (1989) Familial supravalvular aortic stenosis: a genetic study. J Med Genet 26(2):86–92
20. Eisenberg R, Young D, Jacobson B, Boito A (1964) Familial supravalvular aortic stenosis. Am J Dis Child 108:341–347
21. Ewart AK, Jin W, Atkinson D et al (1994) Supravalvular aortic stenosis associated with a deletion disrupting the elastin gene. J Clin Invest 93(3):1071–1077. doi:10.1172/JCI117057
22. Olson TM, Michels VV, Urban Z et al (1995) A 30 kb deletion within the elastin gene results in familial supravalvular aortic stenosis. Hum Mol Genet 4(9):1677–1679
23. Curran ME, Atkinson DL, Ewart AK et al (1993) The elastin gene is disrupted by a translocation associated with supravalvular aortic stenosis. Cell 73(1):159–168
24. Li DY, Toland AE, Boak BB et al (1997) Elastin point mutations cause an obstructive vascular disease, supravalvular aortic stenosis. Hum Mol Genet 6(7):1021–1028
25. Tassabehji M, Metcalfe K, Donnai D et al (1997) Elastin: genomic structure and point mutations in patients with supravalvular aortic stenosis. Hum Mol Genet 6(7):1029–1036
26. Denie JJ, Verheugt AP (1958) Supravalvular aortic stenosis. Circulation 18(5):902–908
27. Perou ML (1961) Congenital supravalvular aortic stenosis. A morphological study with attempt at classification. Arch Pathol 71:453–466
28. Edwards JE (1965) Pathology of left ventricular outflow tract obstruction. Circulation 31:586–599

29. Hickey EJ, Jung G, Williams WG et al (2008) Congenital supravalvular aortic stenosis: defining surgical and nonsurgical outcomes. Ann Thorac Surg 86(6):1919–1927.; discussion 27. doi:10.1016/j.athoracsur.2008.08.031
30. Beuren AJ, Apitz J, Harmjanz D (1962) Supravalvular aortic stenosis in association with mental retardation and a certain facial appearance. Circulation 26:1235–1240
31. Pankau R, Partsch CJ, Neblung A et al (1994) Head circumference of children with Williams-Beuren syndrome. Am J Med Genet 52(3):285–290. doi:10.1002/ajmg.1320520307
32. Huang L, Sadler L, O'Riordan MA, Robin NH (2002) Delay in diagnosis of Williams syndrome. Clin Pediatr (Phila) 41(4):257–261
33. Collins RT II, Kaplan P, Somes GW, Rome JJ (2010) Cardiovascular abnormalities, interventions, and long-term outcomes in infantile Williams syndrome. J Pediatr 156(2):253–258. e1. doi:10.1016/j.jpeds.2009.08.042
34. Collins RT II (2013) Cardiovascular disease in Williams syndrome. Circulation 127(21):2125–2134. doi:10.1161/CIRCULATIONAHA.112.000064
35. French JW, Guntheroth WG (1970) An explanation of asymmetric upper extremity blood pressures in supravalvular aortic stenosis: the Coanda effect. Circulation 42(1):31–36
36. Marler JA, Elfenbein JL, Ryals BM et al (2005) Sensorineural hearing loss in children and adults with Williams syndrome. Am J Med Genet A 138(4):318–327. doi:10.1002/ajmg.a.30970
37. Tsai SW, Wu SK, Liou YM, Shu SG (2008) Early development in Williams syndrome. Pediatr Int 50(2):221–224. doi:10.1111/j.1442-200X.2008.02563.x
38. Carrasco X, Castillo S, Aravena T et al (2005) Williams syndrome: pediatric, neurologic, and cognitive development. Pediatr Neurol 32(3):166–172. doi:10.1016/j.pediatrneurol.2004.09.013
39. Martens MA, Wilson SJ, Reutens DC (2008) Research review: Williams syndrome: a critical review of the cognitive, behavioral, and neuroanatomical phenotype. J Child Psychol Psychiatry 49(6):576–608. doi:10.1111/j.1469-7610.2008.01887.x
40. Davies M, Udwin O, Howlin P (1998) Adults with Williams syndrome. Preliminary study of social, emotional and behavioural difficulties. Br J Psychiatry 172:273–276
41. Einfeld SL, Tonge BJ, Rees VW (2001) Longitudinal course of behavioral and emotional problems in Williams syndrome. Am J Ment Retard 106(1):73–81. doi:10.1352/0895-8017(2001)106<0073:LCOBAE>2.0.CO;2
42. Pober BR (2010) Williams-Beuren syndrome. N Engl J Med 362(3):239–252. doi:10.1056/NEJMra0903074
43. Sforzini C, Milani D, Fossali E et al (2002) Renal tract ultrasonography and calcium homeostasis in Williams-Beuren syndrome. Pediatr Nephrol 17(11):899–902. doi:10.1007/s00467-002-0889-z
44. Schulman SL, Zderic S, Kaplan P (1996) Increased prevalence of urinary symptoms and voiding dysfunction in Williams syndrome. J Pediatr 129(3):466–469
45. Partsch CJ, Japing I, Siebert R et al (2002) Central precocious puberty in girls with Williams syndrome. J Pediatr 141(3):441–444. doi:10.1067/mpd.2002.127280
46. Partsch CJ, Pankau R, Blum WF et al (1994) Hormonal regulation in children and adults with Williams-Beuren syndrome. Am J Med Genet 51(3):251–257. doi:10.1002/ajmg.1320510316
47. Collins RT II, Aziz PF, Swearingen CJ, Kaplan PB (2012) Relation of ventricular ectopic complexes to QTc interval on ambulatory electrocardiograms in Williams syndrome. Am J Cardiol 109(11):1671–1676. doi:10.1016/j.amjcard.2012.01.395
48. Rose C, Wessel A, Pankau R et al (2001) Anomalies of the abdominal aorta in Williams-Beuren syndrome—another cause of arterial hypertension. Eur J Pediatr 160(11):655–658
49. Bouchireb K, Boyer O, Bonnet D et al (2010) Clinical features and management of arterial hypertension in children with Williams-Beuren syndrome. Nephrol Dial Transplant 25(2):434–438. doi:10.1093/ndt/gfp522
50. Kim YM, Yoo SJ, Choi JY et al (1999) Natural course of supravalvar aortic stenosis and peripheral pulmonary arterial stenosis in Williams' syndrome. Cardiol Young 9(1):37–41
51. Stamm C, Li J, Ho SY et al (1997) The aortic root in supravalvular aortic stenosis: the potential surgical relevance of morphologic findings. J Thorac Cardiovasc Surg 114(1):16–24. doi:10.1016/S0022-5223(97)70112-0

52. Kitchiner D, Jackson M, Walsh K et al (1996) Prognosis of supravalve aortic stenosis in 81 patients in Liverpool (1960-1993). Heart 75(4):396–402
53. Ewart AK, Morris CA, Atkinson D et al (1993) Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. Nat Genet 5(1):11–16. doi:10.1038/ng0993-11
54. Morris CA, Loker J, Ensing G, Stock AD (1993) Supravalvular aortic stenosis cosegregates with a familial 6; 7 translocation which disrupts the elastin gene. Am J Med Genet 46(6):737–744. doi:10.1002/ajmg.1320460634
55. Aggoun Y, Sidi D, Levy BI et al (2000) Mechanical properties of the common carotid artery in Williams syndrome. Heart 84(3):290–293
56. Wessel A, Motz R, Pankau R, Bursch JH (1997) Arterial hypertension and blood pressure profile in patients with Williams-Beuren syndrome. Z Kardiol 86(4):251–257
57. Committee on Obstetric Practice, American College of Obstetricians and Gynecologists (2012) Committee opinion no.543: timing of umbilical cord clamping after birth. Obstet Gynecol 120(6):1522–1526. doi:10.1097/01.aog.0000423817.47165.48
58. Lopez-Rangel E, Maurice M, McGillivray B, Friedman JM (1992) Williams syndrome in adults. Am J Med Genet 44(6):720–729. doi:10.1002/ajmg.1320440605
59. Broder K, Reinhardt E, Ahern J et al (1999) Elevated ambulatory blood pressure in 20 subjects with Williams syndrome. Am J Med Genet 83(5):356–360
60. Cherniske EM, Carpenter TO, Klaiman C et al (2004) Multisystem study of 20 older adults with Williams syndrome. Am J Med Genet A 131(3):255–264. doi:10.1002/ajmg.a.30400
61. McElhinney DB, Petrossian E, Tworetzky W et al (2000) Issues and outcomes in the management of supravalvar aortic stenosis. Ann Thorac Surg 69(2):562–567
62. Daniels SR, Loggie JM, Schwartz DC et al (1985) Systemic hypertension secondary to peripheral vascular anomalies in patients with Williams syndrome. J Pediatr 106(2):249–251
63. Izzo JL Jr (2004) Arterial stiffness and the systolic hypertension syndrome. Curr Opin Cardiol 19(4):341–352
64. Ingelfinger JR, Newburger JW (1991) Spectrum of renal anomalies in patients with Williams syndrome. J Pediatr 119(5):771–773
65. Giordano U, Turchetta A, Giannotti A et al (2001) Exercise testing and 24-hour ambulatory blood pressure monitoring in children with Williams syndrome. Pediatr Cardiol 22(6):509–511. doi:10.1007/s002460010285
66. Courtel JV, Soto B, Niaudet P et al (1998) Percutaneous transluminal angioplasty of renal artery stenosis in children. Pediatr Radiol 28(1):59–63. doi:10.1007/s002470050294
67. Bruno E, Rossi N, Thuer O et al (2003) Cardiovascular findings, and clinical course, in patients with Williams syndrome. Cardiol Young 13(6):532–536
68. Del Pasqua A, Rinelli G, Toscano A et al (2009) New findings concerning cardiovascular manifestations emerging from long-term follow-up of 150 patients with the Williams-Beuren-Beuren syndrome. Cardiol Young 19(6):563–567. doi:10.1017/S1047951109990837
69. Kaushal S, Backer CL, Patel S et al (2010) Midterm outcomes in supravalvular aortic stenosis demonstrate the superiority of multisinus aortoplasty. Ann Thorac Surg 89(5):1371–1377. doi:10.1016/j.athoracsur.2010.02.019
70. Deo SV, Burkhart HM, Schaff HV et al (2012) Late outcomes for surgical repair of supravalvar aortic stenosis. Ann Thorac Surg 94(3):854–859. doi:10.1016/j.athoracsur.2012.04.022
71. Brown JW, Ruzmetov M, Vijay P, Turrentine MW (2002) Surgical repair of congenital supravalvular aortic stenosis in children. Eur J Cardiothorac Surg 21(1):50–56

# Coarctation of the Aorta

# 16

Harsimran S. Singh, Omar Kalim, Mark Osten,
Lee N. Benson, and Eric M. Horlick

## 16.1 Introduction

Aortic coarctation is an uncommon but partially reversible cause of secondary hypertension. In this chapter, we will discuss the pathophysiology, epidemiology, and clinical presentation. We will review the known mechanisms for hypertension development in coarctation. Finally, we will consider medical, surgical, and interventional treatment strategies for coarctation and their effects on hypertension and overall prognosis.

H.S. Singh, M.D., M.Sc. • O. Kalim, M.D.
Division of Cardiology, Departments of Medicine and Pediatrics, Weill Cornell Medicine, New York Presbyterian Hospital, Cornell Center for Adult Congenital Heart Disease, New York, NY, USA

M. Osten, M.D.
Division of Cardiology, Department of Medicine, Toronto General Division, University Health Network, Toronto, ON, Canada

L.N. Benson, M.D.
Division of Cardiology, Department of Medicine, Toronto General Division, University Health Network, Toronto, ON, Canada

Division of Cardiology, Department of Pediatrics, The Labatt Family Heart Center, The Hospital for Sick Children, University of Toronto School of Medicine, Toronto, ON, Canada

E.M. Horlick, M.D., F.R.C.P.C. (✉)
Division of Cardiology, Department of Medicine, Toronto General Division, University Health Network, Toronto, ON, Canada

Toronto General Hospital, University of Toronto,
200 Elizabeth Street, 6ES-249, Toronto, ON, Canada, M5G 2G4
e-mail: eric.horlick@uhn.ca



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_16

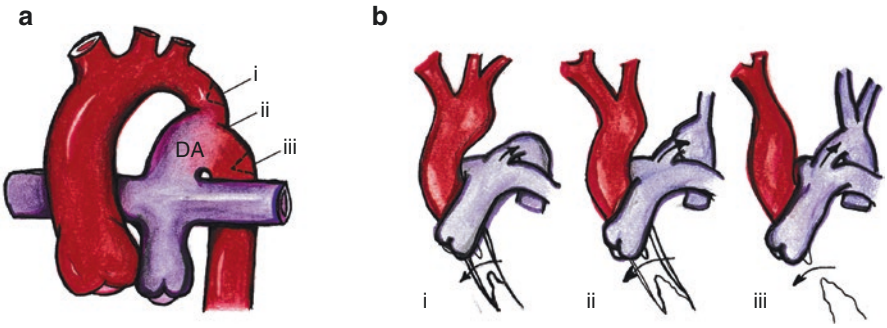



**Fig. 16.1** Classification of coarctation of the aorta. (**a**) Coarctation can be (i) preductal, occurring proximal to the ductus arteriosus (DA); (ii) juxtaductal, occurring at the level of the DA; and (iii) postductal, occurring distal to the DA. (**b**) Aortic arch interruption is essentially a complete form of coarctation, in which there is a gap between the ascending and descending thoracic aorta. The interruption can be (i) distal to the left subclavian artery, (ii) between the left carotid and left subclavian arteries, and (iii) between the innominate and left carotid arteries. Printed with permission from artist Mr. Talmur Ahmed

## 16.2 Epidemiology and Associations

Aortic coarctation is defined as a narrowing or stenosis in an aortic segment. Most commonly, discrete coarctation is focal and juxtaductal, near the insertion of the ligamentum arteriosum in the upper segment of the descending thoracic aorta (i.e., aortic isthmus). Other anatomic presentations of coarctation include diffuse aortic arch hypoplasia, abdominal aortic stenosis, and even aortic atresia when the obstruction is absolute (Fig. 16.1).

Coarctation represents 6–8% of congenital heart defects (CHD) with an incidence of 1 in 2500 live births and a male-to-female predominance of about 1.5–1 [1]. It can occur either as an isolated lesion or in association with bicuspid aortic valve (BAV), Turner's syndrome, patent ductus arteriosus (PDA), mitral valve abnormalities, ventricular septal defect (VSD), and additional left heart obstructive lesions (e.g., Shone's complex or hypoplastic left heart syndrome) [2–6]. Abdominal aortic coarctation also referred to as midaortic syndrome typically includes aortic hypoplasia, and it is associated with renal artery stenosis [7]. The term simple coarctation implies an absence of additional intracardiac pathology (other than BAV or PDA), whereas complex coarctation is associated with additional forms of CHD.

## 16.3 Histology and Genetics

Morphologically, the tissue ridge (often circumferential) that comprises focal coarctation intrudes into the aortic lumen leading to obstruction. While there remains controversy as to its development, there are several hypotheses including (1) hemodynamic effects in development from low flow state and (2) abnormal migration of ductal tissue [2].

The hemodynamic hypothesis considers abnormal ductal flow and/or unfavorable angulation of ductal insertion to the isthmus during fetal development that leads to coarctation upon ductal closure at birth [2]. A mechanism of medial infolding and migration of ductal tissue with surrounding secondary cystic medial necrosis has been supported by pathology specimens finding a sling of ductal tissue at the isthmus and even in hypoplastic arch tissue [6].

Several studies have focused on the maldevelopment of neural crest cells that could broadly tie in coarctation with the company that it keeps (e.g., outflow tract and noncardiac vascular anomalies) [8, 9]. The Notch signaling pathway appears to have an important role in cardiovascular development. Defects in the Notch pathway have been linked with neural crest abnormalities and cardiovascular defects in both mice and humans, including aortic arch malformations [10].

## 16.4 Mechanism of Hypertension Development

When the degree of aortic obstruction is significant, areas below the level of coarctation see decreased blood pressure and perfusion relative to proximal arterial beds. In discrete juxtaductal coarctation, this leads to reduced blood pressure to abdominal organs including the kidneys and lower extremities in comparison to the upper extremities, coronary arteries, and cerebral vasculature. The lack of renal blood flow leads to activation of the renin-angiotensin system (RAS) thereby increasing peripheral afterload and intrarenal sodium uptake (Fig. 16.2).

To some extent the body can mitigate hypoperfusion by development of collaterals later in life that arise from above the coarctation segment and provide perfusion past the obstruction. There are two anatomic sources of collateral circulation that can develop (1) anterior circulation, bilateral internal mammary arteries connecting to external iliacs via epigastric arteries, and (2) posterior circulation, thyrocervical arteries to descending aorta via intracostal arteries [11]. There is considerable variation in collateral development that is not well understood.

There are two proposed mechanisms of hypertension development in coarctation: (1) direct consequence of mechanical obstruction and (2) maladaptation of the RAS [2]. The mechanical obstruction of coarctation may mandate a higher blood pressure to allow for systemic flow through the increased systemic vascular resistance (SVR) inherent in aortic obstruction or from small-caliber collateral vessels. Based on this mechanism, the treatment of secondary hypertension would be resection of the coarctation to allow unhindered aortic flow. However, this mechanism alone does not adequately explain the variability in hypertension reduction after coarctation repair or the late hypertension that can develop in patients years later [12]. In addition, the severity of obstruction does not always correlate with hypertension severity [2].

This humoral theory of RAS activation secondary to renal underperfusion is conjectured to be the primary mechanism of late hypertension and vascular abnormalities in coarctation patients [2]. Animal studies transplanting one kidney proximal to the coarctation segment demonstrate significant reduction in SVR and blood pressure [12, 13]. This explains why measured SVR is often increased even distal to the

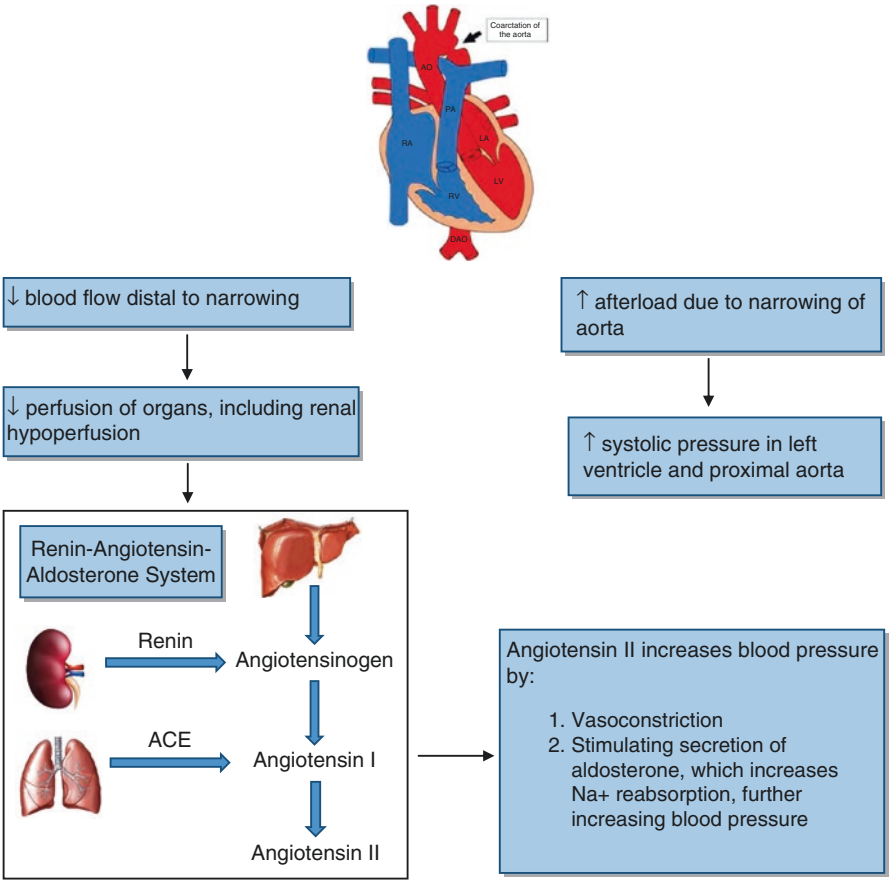



**Fig. 16.2** Mechanism of hypertension in patients with coarctation of the aorta. (*1*) The narrowed aorta results in decreased blood flow distal to the obstruction, which leads to hypoperfusion of the organs, including the kidneys. The kidneys respond by activating the renin-angiotensin-aldosterone axis to normalize blood pressure. This results in normalization of blood pressure in the lower extremities with adequate perfusion of the organs but at the expense of increased blood pressure in the upper body. (*2*) The narrowed aorta also forces the left ventricle to contract more forcefully to maintain cardiac output, thus increasing systolic pressure in the left ventricle and proximal aorta

obstruction. Nonetheless, human and animal studies of coarctation have not consistently documented increased renin levels [14].

## 16.5 Clinical Presentation and Diagnosis

It is the specifics of (1) coarctation location (e.g., arch, juxtaductal, or abdominal); (2) severity of stenosis, ranging from mild obstruction to total occlusion with thoracic collaterals; and (3) concomitant cardiac and vascular abnormalities that dictate

the age of clinical presentation and severity of illness. Symptoms can range from patients being asymptomatic with a murmur to a constellation of hypertension, claudication, hypertensive headaches, and congestive heart failure. In cases where the coarctation segment involves the left subclavian artery ostium, reversal of left vertebral flow at high outputs can lead to subclavian steal syndrome.

Most coarctation patients will be diagnosed in childhood based on physical exam, clinical symptoms, or as part of a secondary hypertension work-up. There are some patients with a combination of minimal symptoms, adequate collateral development, and/or inadequate access to informed health care who are not diagnosed until much later in life. Patients with inadequate collateral development across the coarctation will be more symptomatic with greater propensity for distal hypoperfusion. Abdominal aortic coarctation nearly always is diagnosed in neonatal period and can present with life-threatening neonatal hypertension.

One notable extracardiac vascular association of coarctation is the increased incidence of saccular berry aneurysms (3–5%) in the circle of Willis. This coupled with upper extremity and cerebrovascular hypertension creates the potential for aneurysmal rupture, which can be fatal or result in a debilitating stroke. Any suggestive neurologic symptoms (e.g., acute severe headache or sudden neurologic loss) should trigger evaluation for this condition by CT, MRI, or angiography. Given the clinical association, many advocate routine lifetime screening for cerebral aneurysms, even in the absence of symptoms.

A thorough cardiovascular exam should assess for evidence of LV pressure overload/hypertrophy through a prominent LV point of maximal impulse, decreased ventricular compliance via the presence of an S4, severe obstructive coarctation with or without collateral flow by the presence of systolic and/or continuous murmurs on the front chest, back, or abdomen. As BAV is found in 80% of coarctation patients, there may be signs of the bicuspid valve including a systolic click and a murmur of regurgitation or stenosis. Pulses should be palpated in all extremities and may be absent or diminished in the femoral artery, dorsalis pedis, and posterior tibialis. Simultaneous pulse measurement of brachial and femoral artery can reveal a brachiofemoral delay implying obstruction to lower extremity blood flow.

All patients presenting with hypertension or prehypertension, especially at an early age, should have four-extremity blood pressure measurements upon initial evaluation. In patients without significant aortic obstruction or vascular disease, the principle of pressure amplification ensures that the lower extremities have higher blood pressure readings than upper extremities. In patients with coarctation or obstructive peripheral vascular disease, noninvasive assessment of lower extremity blood pressure can be reduced to absent. In general, four-extremity blood pressure should also help rule out aortic arch involvement of the coarctation if both upper extremity blood pressures are equal. However, there is a higher incidence in coarctation of anomalous right subclavian artery from descending aorta (~5%) compared to standard population. In the absence of aortic imaging, this can make it challenging for the unaware clinician to distinguish juxtaductal coarctation from arch hypoplasia.

Aortic imaging is crucial for coarctation diagnosis and evaluation including echocardiography, CT, and MRI, though classic rib notching and thoracic collaterals

and aortic patterns from pre- and post-stenotic dilation can be appreciated on chest X-ray. Echocardiography will reveal associated congenital heart defects in addition to visualizing bicuspid aortic valves with corresponding aortopathy of the root and ascending aorta. In adults, suprasternal notch views of the aortic arch and descending aorta can help visualize the juxtaductal region on 2D echo and quantify coarctation gradients using continuous-wave Doppler. In general, peak gradients from echo overestimate the gradients achieved by extremity blood pressures or in the catheterization laboratory. When coarctation is severe, pulse-wave Doppler of the abdominal aorta can display a dulled systolic peak and increased diastolic flow.

## 16.6 Medical Therapy in Repaired Coarctation

There are a few studies with conflicting findings to guide treatment of early or late hypertension in repaired coarctation patients [15–17]. Prior to coarctation repair, blood pressure control can be challenging and require polypharmacy. Blood pressure treatment may be limited by underperfusion below the coarctation level, leading to symptoms such as claudication or signs of underperfusion of abdominal organs.

Given the presumed mechanisms of hypertension development in coarctation, it is not surprising that ACE inhibitors, ARBs, and beta blockers are often first-line therapies. In two open-label prospective trials, enalapril and candesartan were slightly more effective in lowering blood pressure and reducing LV mass index compared to atenolol [16, 17]. In another study, metoprolol was more effective than candesartan to effectively lower blood pressure [15]. As such there is no definitive evidence as to the choice of antihypertensive. Similar to the state of affairs in hypertension as a whole, the goal to treat high blood pressure may supersede choice of therapeutics.

## 16.7 Surgical and Interventional Treatment of Coarctation

In adults, the majority of patients followed with aortic coarctation have either unrepaired disease with a new diagnosis or recurrent coarctation with prior repair. Indications for treatment include a gradient or blood pressure differential $\geq$20 mmHg or a peak gradient <20 mmHg in the presence of significant collaterals. Additional considerations include symptoms related to coarctation, upper extremity hypertension, hypertensive response to exercise, and pathologic left ventricular hypertrophy [18, 19]. The European Society of Cardiology guidelines provide a Class IIb recommendation for treatment when the aortic narrowing is $\geq$50% of the aortic diameter at the diaphragm, regardless of pressure gradient or the presence of hypertension [19, 20].

Both surgical and interventional approaches are viable therapies for coarctation; the choice of modality depends on patient age and size, technical suitability, concomitant cardiovascular abnormalities, and institutional experience [20]. In neonates, surgery remains the standard of care with operative survival ~99%. In children, stenting is possible when the aorta can accommodate a stent that maybe

expanded to larger adult diameters in the future. In adults, stenting and surgery are considered depending on the anatomic details and comorbid conditions though coarctation surgery in adults does have higher perioperative risk. Surgical repair has been shown to have 91% survival at 20 years when surgery is performed <14 yo and 79% survival when >14 yo [21].

There are multiple surgical approaches that have been used to repair coarctation (Fig. 16.3)—each technique has pros and cons (Fig. 16.4a) [22]. Crafoord first performed aortic resection with end-to-end anastomosis in 1944 though recurrence rates were over 50% [20, 23]. This technique was later modified by Amato in 1977 to include a broader longitudinal resection and extended anastomosis. In many modern-day institutions, extended end-to-end repair remains the preferred surgical technique with low mortality and low restenosis rates of 4–11% [22, 24].

Additional surgical methods include aortic patch augmentation described by Vosschulte in 1961 which allows for the resection of longer coarctation segments with low recoarctation rates of 5–12% [25]. However, there is an increased risk of aneurysm formation along the patch in 18–50% of patients [22]. Subclavian flap repair was developed by Waldhausen and Nahrwold in 1966 that uses left subclavian tissue to augment the lumen. This negates the need for patch material, however does leave the scepter of subclavian steal or arm claudication in the future [26]. Interposition grafts (either homografts or Dacron based) were used as early as 1951 by Gross. There are inherent limitations to growth with this technique in children, and there is a risk of aneurysm formation at the suture lines of the graft [22]. Still this technique is used successfully in adults [27]. Ascending-to-descending aorta bypass grafts can intuitively avoid the complication of recoarctation; however this technique does entail its own concerns of long-term graft patency [28].

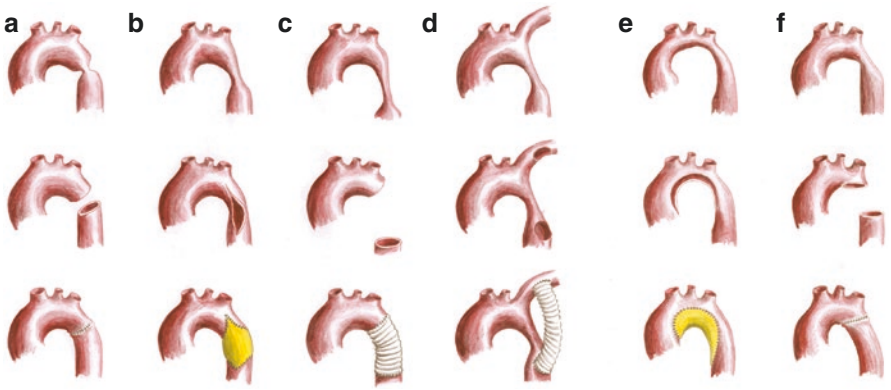



**Fig. 16.3** Different types of surgical repair for aortic coarctation. (**a**) End-to-end anastomosis. The coarctation segment is resected and the aorta is reapproximated. (**b**) Patch augmentation. The aorta is incised longitudinally and covered with a patch of polytetrafluoroethylene. (**c**) Interposition graft. (**d**) Ascending-to-descending aorta bypass graft. (**e**) Subclavian flap. After performing an extended aortotomy, the left subclavian artery is sewn over the isthmus of the aorta. (**f**) Extended aortic arch repair. This is done when there is severe transverse arch hypoplasia. Permission to use illustrations obtained from Dr. J. P. M. Hamer at the University of Groningen, The Netherlands

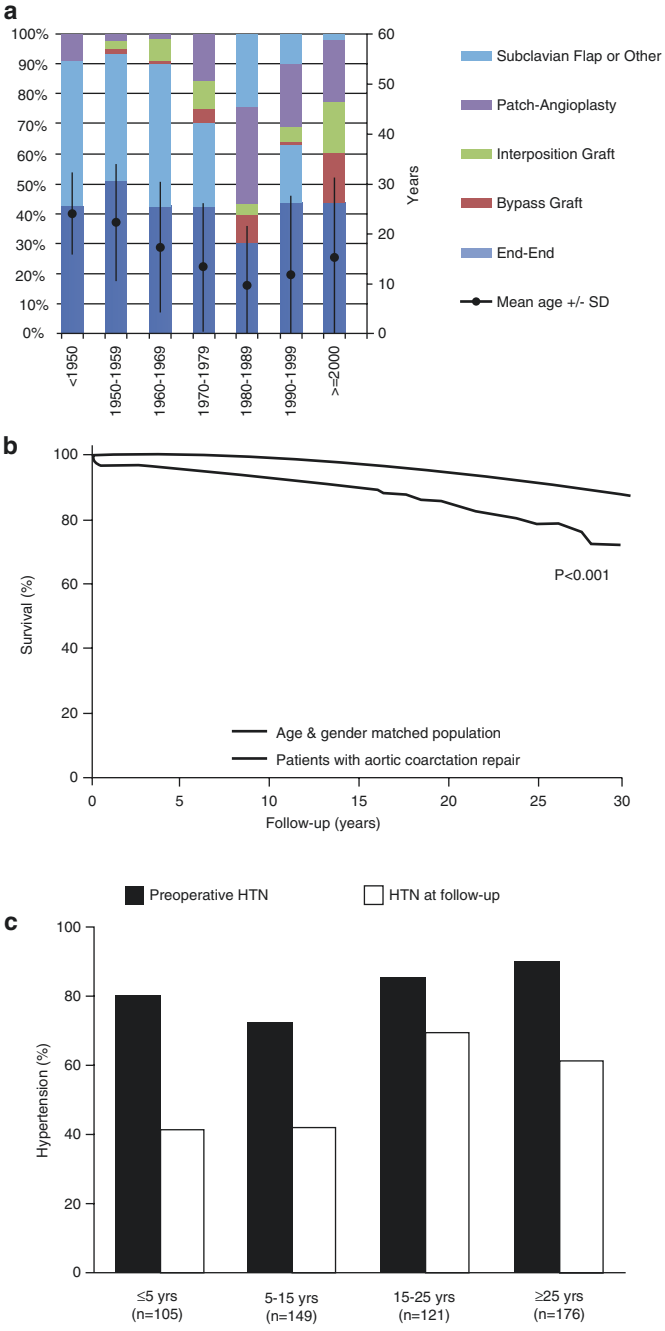



**Fig. 16.4** Prognosis of patients with coarctation of the aorta. (**a**) Type of aortic coarctation repair stratified by decade. (**b**) Long-term survival rates of patients with aortic coarctation repair (~70%) vs. age- and sex-matched population (~90%). (**c**) Comparison of hypertension pre- and postoperatively at various time intervals of follow-up. Permission to use figures obtained from Brown ML et al (2013) J Am Coll Cardiol 62(11):1020–1025

While balloon angioplasty remains a feasible option for focal coarctation, there are higher rates of recurrence (50% vs. 21%) compared to surgery [29]. Other publications have found balloon angioplasty of discrete coarctation to be a durable therapy with reported follow-up from 8 to 15 years in small prospective cohorts [30, 31]. Compared to angioplasty alone, stenting helps prevent elastic recoil of the aorta, requires less aortic overexpansion in treatment (thus decreasing risk of aneurysm formation), and still allows the possibility of future re-dilation [32–35]. In many institutions, covered stents have become a preferred strategy over bare metal stents [36]. The aortic covering can help mitigate many aortic wall complications (e.g., intimal tear or intramural hematoma). In the USA, the Cheatham Platinum (CP) stent (NuMED, Hopkinton, NY) has been approved by the FDA in 2016 for treatment of aortic coarctation (Fig. 16.5).

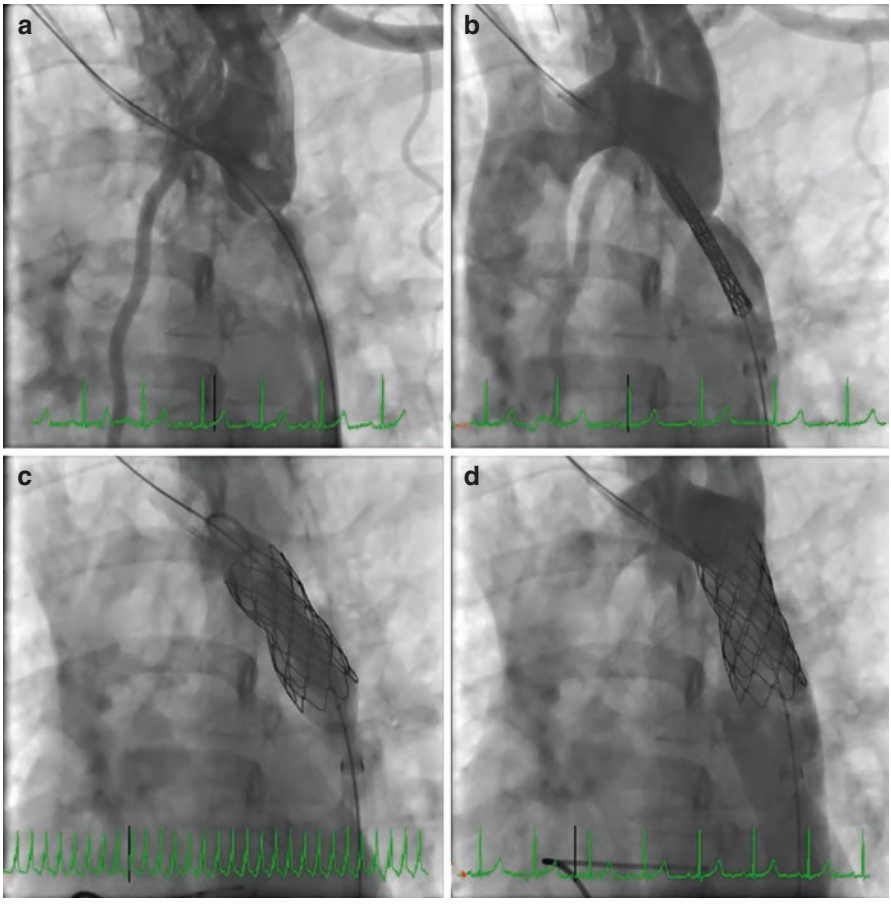



**Fig. 16.5** (**a–d**) Interventional repair of coarctation with covered CP stent. Once the stent is put in position and fully dilated, normal blood flow is restored. An alternative to stent placement is balloon dilation, which is preferred in children and neonates due to concerns about stent size—smaller stents cannot undergo serial dilation to keep pace with somatic growth, and larger stents may not fit into the femoral artery of smaller patients

There is limited prospective data comparing surgery with stenting [32, 37, 38]. Several cohorts and one meta-analysis have suggested comparable rates of procedural success with overall reduction in periprocedural morbidity and length of hospital stay tempered by slight increase in rates of restenosis or reintervention [39–41]. The Congenital Cardiovascular Interventional Study Consortium has published the largest prospective comparisons of stent, balloon, and surgery [20, 42]. Stenting had a lower short-term complication rate (12.5%) compared to surgery (25%) and balloon angioplasty (44%). Complications include moderate or severe re-obstruction, aortic wall injury, and stent fracture. Total re-interventions were higher with stenting compared to other modalities though the majority of these were staged interventions for further stent expansion in native coarctation [20].

## 16.8 Hypertension After Coarctation Treatment

Surgical or interventional repair remains the mainstay treatment for native or recurrent coarctation. These interventions change the natural history of disease with improved survival and decreased vascular complications of MI and stroke though life expectancy curves of even repaired coarctation remain below in those of age- and gender-matched population (Fig. 16.4b) [2, 43, 44]. Its effects on hypertension, however, are more complex.

Both surgical and interventional repair of coarctation have been shown to decrease hypertension in the short-to-medium term or make it more manageable with pharmacotherapy (Fig. 16.4c) [45–47]. While preprocedural hypertension will regress or improve, especially if coarctation repair is performed earlier in life, many patients remain at risk for developing systemic arteriopathy including late hypertension [21, 48, 49].

After surgical or interventional repair, one national cohort study suggested a 20-year freedom from hypertension of only 51% and 79%, respectively [50]. Coarctation had a statistically significant odds ratio of 15.7 for late development of hypertension and 6.6 for stroke (Fig. 16.6) [48]. In Hager et al. cohort study of nearly 500 operated patients, prevalence of hypertension was over 50%, most related to duration of follow-up, as nearly all patients >55 yo were hypertensive [51, 52].

Even in adult patients who had successful coarctation repair with “normal range” resting blood pressures, accentuated systolic blood pressure and pulse pressure response was observed during daytime activities with higher LV mass measurements [53]. This was determined to be partly secondary to upper limb conduit artery dysfunction, finding a reduced brachial artery vascular response to both endothelium-dependent flow-mediated dilation and glyceryl trinitrate administration compared to age- and gender-matched controls. Even in normotensive patients after coarctation repair, vascular studies have suggested a shift in the relationship between vascular resistance and central venous pressure, suggesting a reset of the integrated cardiopulmonary-arterial baroreflex [54].

Another potential contributor to development of late hypertension in treated coarctation may be residual juxtaductal coarctation gradient or mild transverse aortic arch hypoplasia (TAA). Cases of de novo coarctation or repaired coarctation with residual gradients have found stenting to eliminate even mild coarctation

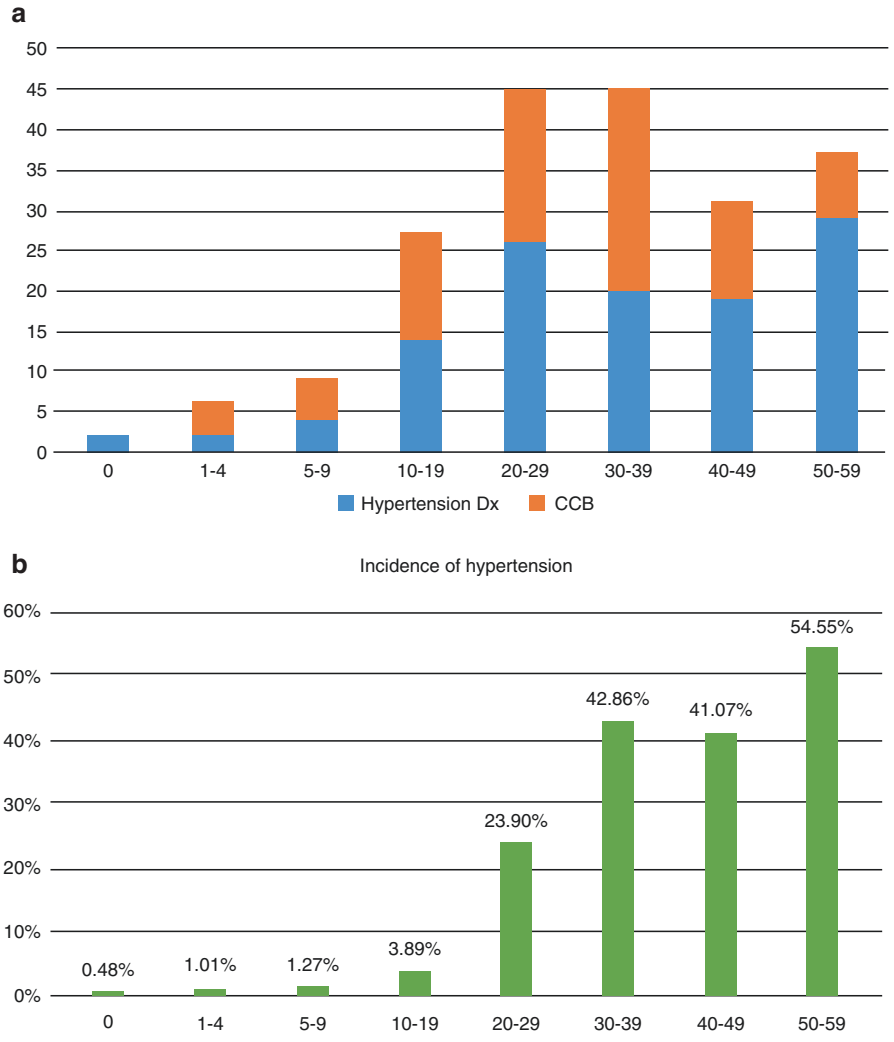



**Fig. 16.6** The age group distribution of the number (**a**) and the incidence (**b**) of patients with coarctation of the aorta and systemic hypertension. (**c**) The age group distribution of cerebrovascular accident (CVA). Permission to use figures obtained from Wu MH et al (2015) Am J Cardiol 116(5):779–784

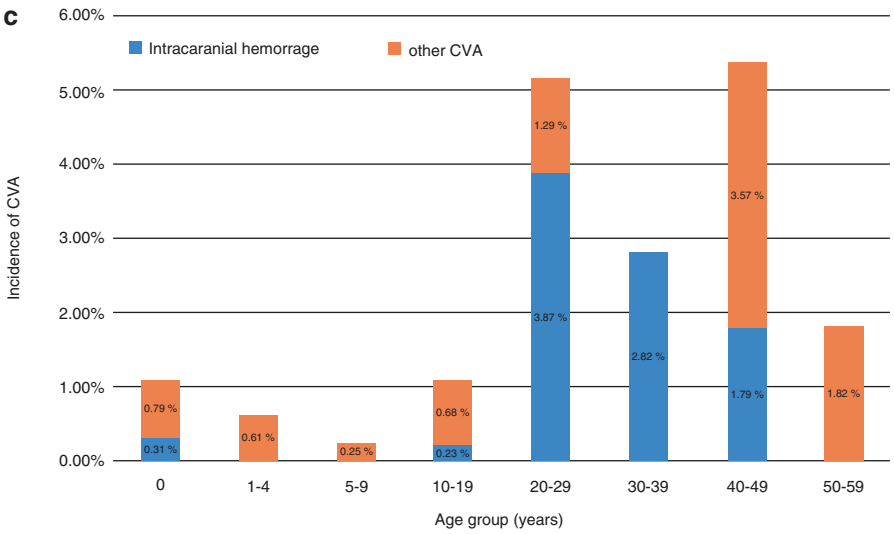



**Fig. 16.6** (continued)

(clinical gradient of ~20 mmHg) to help reduce systolic blood pressure in the medium term [47, 51].

After repair, a number of patients will appear to have TAA on imaging in the absence of any resting arm-leg gradient. While traditionally this is considered benign, there is one study linking it to late hypertension with an odds ratio 6.4 [55]. It is not known whether the operative risks of a more aggressive surgical arch reconstruction would ameliorate this increased risk of late hypertension.

This potential for late hypertension and late vascular complications demands careful monitoring and follow-up of all coarctation patients. Early emphasis of lifestyle modifications including optimal weight, diet, and aggressive pharmacologic treatment of coarctation should be the mainstay. Management of other reversible risk factors such as smoking cessation and hyperlipidemia should be emphasized from an early age.

## Conclusion

Aortic coarctation remains a rare but important secondary cause of hypertension. The diagnosis should be considered and can be excluded through simple physical examination and confirmed through vascular and cardiac imaging techniques. Surgical and interventional repair of aortic coarctation is corrective with good medium- and long-term outcomes. While coarctation repair will ameliorate hypertension, these patients remain at risk for the development of late hypertension and future vascular abnormalities. All coarctation patients should receive lifelong care and risk factor modification.

## References


1. Brown ML, Burkhart HM, Connolly HM et al (2013) Coarctation of the aorta: lifelong surveillance is mandatory following surgical repair. J Am Coll Cardiol 62:1020–1025
2. Rao PS (2005) Coarctation of the aorta. Curr Cardiol Rep 7:425–434
3. Vulliamy DG (1953) Turner's syndrome with coarctation of the aorta. Proc R Soc Med 46:279–280
4. Shone JD, Sellers RD, Anderson RC et al (1963) The developmental complex of "parachute mitral valve," supravalvular ring of left atrium, subaortic stenosis, and coarctation of aorta. Am J Cardiol 11:714–725
5. Anderson RH, Lenox CC, Zuberbuhler JR (1983) Morphology of ventricular septal defect associated with coarctation of aorta. Br Heart J 50:176–181
6. Ho SY, Anderson RH (1979) Coarctation, tubular hypoplasia, and the ductus arteriosus. Histological study of 35 specimens. Br Heart J 41:268–274
7. Porras D, Stein DR, Ferguson MA et al (2013) Midaortic syndrome: 30 years of experience with medical, endovascular and surgical management. Pediatr Nephrol 28:2023–2033
8. Kappetein AP, Gittenberger-de Groot AC, Zwinderman AH et al (1991) The neural crest as a possible pathogenetic factor in coarctation of the aorta and bicuspid aortic valve. J Thorac Cardiovasc Surg 102:830–836
9. Jain R, Engleka KA, Rentschler SC et al (2011) Cardiac neural crest orchestrates remodeling and functional maturation of mouse semilunar valves. J Clin Invest 121:422–430
10. High FA, Zhang M, Proweller A et al (2007) An essential role for notch in neural crest during cardiovascular development and smooth muscle differentiation. J Clin Invest 117: 353–363
11. Beekman RH (2013) Coarctation of the aorta. In: Allen HD, Driscoll DJ, Shaddy RE, Feltes TF (eds) Moss and Adams heart disease in infants, children, and adolescents: including the fetus and young adult, vol 2. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia, pp 1044–1060
12. Ferguson JC, Barrie WW, Schenk WG Jr (1977) Hypertension of aortic coarctation: the role of renal and other factors. Ann Surg 185:423–428
13. Scott HW Jr, Bahnson HT (1951) Evidence for a renal factor in the hypertension of experimental coarctation of the aorta. Surgery 30:206–217
14. Werning C, Schönbeck M, Weidmann P et al (1969) Plasma renin activity in patients with coarctation of the aorta. A comment of the pathogenesis prestenotic hypertension. Circulation 40:731–737
15. Moltzer E, Mattace Raso FU, Karamermer Y et al (2010) Comparison of candesartan versus metoprolol for treatment of systemic hypertension after repaired aortic coarctation. Am J Cardiol 105:217–222
16. Giordano U, Cifra B, Giannico S et al (2009) Mid-term results, and therapeutic management, for patients suffering hypertension after surgical repair of aortic coarctation. Cardiol Young 19:451–455
17. Di Salvo G, Castaldi B, Gala S et al (2016) Atenolol vs enalapril in young hypertensive patients after successful repair of aortic coarctation. J Hum Hypertens 30:363–367
18. Warnes CA, Williams RG, Bashore TM et al (2008) ACC/AHA 2008 guidelines for the Management of Adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). Circulation 118:e714–e833
19. Baumgartner H, Bonhoeffer P, De Groot NM et al (2010) ESC guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J 31:2915–2957
20. Singh HS, Horlick E, Osten M, Benson LN (2013) Interventional cardiology in adults with congenital heart disease. Nat Rev Cardiol 10:662–678

21. Cohen M, Fuster V, Steele PM et al (1989) Coarctation of the aorta. Long-term follow-up and prediction of outcome after surgical correction. Circulation 80:840–845
22. Torok RD, Campbell MJ, Fleming GA, Hill KD (2015) Coarctation of the aorta: management from infancy to adulthood. World J Cardiol 7:765–775
23. Williams WG, Shindo G, Trusler GA et al (1980) Results of repair of coarctation of the aorta during infancy. J Thorac Cardiovasc Surg 79:603–608
24. Burch PT, Cowley CG, Holubkov R et al (2009) Coarctation repair in neonates and young infants: is small size or low weight still a risk factor? J Thorac Cardiovasc Surg 138:547–552
25. Backer CL, Paape K, Zales VR et al (1995) Coarctation of the aorta. Repair with polytetrafluoroethylene patch aortoplasty. Circulation 92:II132–II136
26. Pandey R, Jackson M, Ajab S et al (2006) Subclavian flap repair: review of 399 patients at median follow-up of fourteen years. Ann Thorac Surg 81:1420–1428
27. Yousif A, Kloppenburg G, Morshuis WJ, Heijmen R (2016) Repair of adult aortic coarctation by resection and interposition grafting. Interact Cardiovasc Thorac Surg 23:526–530
28. Arakelyan V, Spiridonov A, Bockeria L (2005) Ascending-to-descending aortic bypass via right thoracotomy for complex (re-) coarctation and hypoplastic aortic arch. Eur J Cardiothorac Surg 27:815–820
29. Hernandez-Gonzalez M, Solorio S, Conde-Carmona I et al (2003) Intraluminal aortoplasty vs. surgical aortic resection in congenital aortic coarctation. A clinical random study in pediatric patients. Arch Med Res 34:305–310
30. Walhout RJ, Suttorp MJ, Mackaij GJ et al (2009) Long-term outcome after balloon angioplasty of coarctation of the aorta in adolescents and adults: is aneurysm formation an issue? Catheter Cardiovasc Interv 73:549–556
31. Fawzy ME, Awad M, Hassan W et al (2004) Long-term outcome (up to 15 years) of balloon angioplasty of discrete native coarctation of the aorta in adolescents and adults. J Am Coll Cardiol 43:1062–1067
32. Krasemann T, Bano M, Rosenthal E, Qureshi SA (2011) Results of stent implantation for native and recurrent coarctation of the aorta-follow-up of up to 13 years. Catheter Cardiovasc Interv 78:405–412
33. Rosenthal EC (2005) Oarctation of the aorta from fetus to adult: curable condition or life long disease process? Heart 91:1495–1502
34. O'Laughlin MP, Perry SB, Lock JE, Mullins CE (1991) Use of endovascular stents in congenital heart disease. Circulation 83:1923–1939
35. Duke C, Rosenthal E, Qureshi SA (2003) The efficacy and safety of stent redilatation in congenital heart disease. Heart 89:905–912
36. Tanous D, Collins N, Dehghani P et al (2010) Covered stents in the management of coarctation of the aorta in the adult: initial results and 1-year angiographic and hemodynamic follow-up. Int J Cardiol 140:287–295
37. Cowley CG, Orsmond GS, Feola P et al (2005) Long-term, randomized comparison of balloon angioplasty and surgery for native coarctation of the aorta in childhood. Circulation 111:3453–3456
38. San Norberto Garcia EM, Gonzalez-Fajardo JA, Gutiérrez V et al (2010) Open surgical repair and endovascular treatment in adult coarctation of the aorta. Ann Vasc Surg 24:1068–1074
39. Rodes-Cabau J, Miró J, Dancea A et al (2007) Comparison of surgical and transcatheter treatment for native coarctation of the aorta in patients > or = 1 year old. The Quebec Native Coarctation of the Aorta Study. Am Heart J 154:186–192
40. Carr JA (2006) The results of catheter-based therapy compared with surgical repair of adult aortic coarctation. J Am Coll Cardiol 47:1101–1107
41. Holzer R, Qureshi S, Ghasemi A et al (2010) Stenting of aortic coarctation: acute, intermediate, and long-term results of a prospective multi-institutional registry—Congenital Cardiovascular Interventional Study Consortium (CCISC). Catheter Cardiovasc Interv 76:553–563
42. Forbes TJ, Kim DW, Du W et al (2011) Comparison of surgical, stent, and balloon angioplasty treatment of native coarctation of the aorta: an observational study by the CCISC (Congenital Cardiovascular Interventional Study Consortium). J Am Coll Cardiol 58:2664–2674

43. Bobby JJ, Emami JM, Farmer RD, Newman CG (1991) Operative survival and 40 year follow up of surgical repair of aortic coarctation. Br Heart J 65:271–276
44. Campbell M (1970) Natural history of coarctation of the aorta. Br Heart J 32:633–640
45. Hamid T, Motwani M, Schneider H et al (2015) Benefit of endovascular stenting for aortic coarctation on systemic hypertension in adults. Arch Cardiovasc Dis 108:626–633
46. Harrison DA, McLaughlin PR, Lazzam C et al (2001) Endovascular stents in the management of coarctation of the aorta in the adolescent and adult: one year follow up. Heart 85:561–566
47. Bentham JR, English K, Ballard G, Thomson JD (2013) Effect of interventional stent treatment of native and recurrent coarctation of aorta on blood pressure. Am J Cardiol 111:731–736
48. Wu MH, Chen HC, Kao FY, Huang SK (2015) Risk of systemic hypertension and cerebrovascular accident in patients with aortic coarctation aged <60 years (from a National Database Study). Am J Cardiol 116:779–784
49. O'Sullivan JJ, Derrick G, Darnell R (2002) Prevalence of hypertension in children after early repair of coarctation of the aorta: a cohort study using casual and 24 hour blood pressure measurement. Heart 88:163–166
50. Chiu HH, Chiu SN, Hu FC et al (2009) Late cardiovascular complications after surgical or balloon angioplasty of coarctation of aorta in an Asian cohort. Am J Cardiol 104:1139–1144
51. O'Sullivan J (2014) Late hypertension in patients with repaired aortic coarctation. Curr Hypertens Rep 16:421
52. Hager A, Kanz S, Kaemmerer H et al (2007) Coarctation long-term assessment (COALA): significance of arterial hypertension in a cohort of 404 patients up to 27 years after surgical repair of isolated coarctation of the aorta, even in the absence of restenosis and prosthetic material. J Thorac Cardiovasc Surg 134:738–745
53. de Divitiis M, Pilla C, Kattenhorn M et al (2003) Ambulatory blood pressure, left ventricular mass, and conduit artery function late after successful repair of coarctation of the aorta. J Am Coll Cardiol 41:2259–2265
54. Johnson D, Perrault H, Vobecky SJ et al (2001) Resetting of the cardiopulmonary baroreflex 10 years after surgical repair of coarctation of the aorta. Heart 85:318–325
55. Quennelle S, Powell AJ, Geva T, Prakash A (2015) Persistent aortic arch hypoplasia after coarctation treatment is associated with late systemic hypertension. J Am Heart Assoc 4(7). pii: e001978

# Atrial Fibrillation and Hypertension: Two Entities That Usually Coexist

# 17

S. Giannitsi, M.S. Kallistratos, L.E. Poulimenos, and A.J. Manolis

## 17.1 Epidemiology of Atrial Fibrillation

Atrial fibrillation is the most common sustained arrhythmia in humans, and its prevalence is 1–2% of the general population worldwide [1]. It affects six million people in Europe, while it is expected that its incidence will increase up to 2.5-fold over the next 50 years. It is estimated that atrial fibrillation poses a high economic burden for the healthcare system, since it is responsible for up to one third of the hospitalizations for cardiac arrhythmias. Subjects, who have reached the age of 40, present a lifetime risk of 25% for developing atrial fibrillation, and its incidence increases as the population ages [2]. Atrial fibrillation affects significantly morbidity and mortality (two- to sevenfold increased risk for stroke, two- to threefold increased risk for dementia, and threefold increased risk for heart failure), while it is responsible for approximately 20% of all strokes. Finally, undiagnosed or silent episodes of atrial fibrillation may be the main cause of cryptogenic strokes [3–5].

## 17.2 Etiology of Atrial Fibrillation

Different risk factors are responsible for the development of atrial fibrillation. Among the most established and well identified are age, hypertension (which forms a physiopathologic substrate favoring atrial fibrillation), coronary artery disease (>20% of the patients with AF), heart failure (30% of the patients with AF), valvular disease, congenital heart disease, hyperthyroidism, chemotherapeutic agents, obesity, diabetes mellitus, chronic obstructive pulmonary disease, sleep apnea, and chronic kidney disease [6]. Hypertension (HTN) is the most common cause of atrial

S. Giannitsi • M.S. Kallistratos • L.E. Poulimenos • A.J. Manolis (✉)
Department of Cardiology, Asklepeion General Hospital, Athens, Greece
e-mail: ajmanol@otenet.gr



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_17

fibrillation encountered in clinical practice. Epidemiologic studies have shown that HTN is associated with 1.8-fold increased risk of developing new-onset atrial fibrillation and 1.5-fold risk of progression to permanent atrial fibrillation. In an analysis of the Framingham Heart Study, men and women with hypertension had 50 and 40% higher risk of developing atrial fibrillation, respectively. In many different atrial fibrillation clinical trials, 49–90% of the participants suffered from HTN, indicating that these two entities usually coexist. Hypertension is the most prevalent concomitant medical condition in patients with atrial fibrillation, in both Europe and the USA [7].

## 17.3 Hypertension and Atrial Fibrillation: Pathophysiological Mechanism and Linkage

Hypertension per se increases the risk of atrial fibrillation by about twofold, and it is likely to be a reversible causative factor of atrial fibrillation. Untreated or suboptimal treated hypertension leads to left ventricular hypertrophy, one of the most important subclinical organ damages responsible for major cardiovascular events including atrial fibrillation. In the Framingham Heart Study, the levels of the systolic blood pressure and the duration of hypertension predicted the adverse atrial remodeling [8]. Moreover, pulse pressure was associated with the incidence of atrial fibrillation [9]. Many studies gave proof that hypertension is an independent risk factor for atrial fibrillation. In an analysis of 5000 individuals in the Cardiovascular Health Study, it was found that patients with 10 mmHg higher baseline systolic blood pressure had an 11% increased risk of atrial fibrillation over the 3-year follow-up. Once left ventricular hypertrophy is established, left ventricular compliance decreases; stiffness, filling pressures, as well as left ventricular wall stress increase; and as a consequence the sympathetic nervous system and the renin-angiotensin-aldosterone system are activated.

Moreover, in the atria, alterations characterized by proliferation and differentiation of fibroblasts into myofibroblasts, enhanced connective tissue deposition, fibrosis, intracellular substrate accumulation, and inflammatory changes, lead to structural remodeling. These structural alterations result in electrical dissociation between atrial muscle bundles and local conduction heterogeneities that facilitate the initiation and perpetuation of atrial fibrillation. Over the time, tissue remodeling promotes and maintains atrial arrhythmia. Atrial remodeling consists of three components: electrical remodeling mainly due to intracellular changes in calcium handling, contractile remodeling, and structural tissue remodeling which needs weeks or months to occur and affects the function of the heart muscle [10, 11].

## 17.4 Consequences of Atrial Fibrillation

Loss of atrial contraction and atrioventricular synchrony affects the hemodynamics during atrial fibrillation. It may reduce the cardiac output up to 15%, may induce tachycardiomyopathy, or may cause functional mitral regurgitation (due to atrial

dilatation and hence mitral annular dilatation or due to the tachycardia-induced ventricular dilatation). Decreased blood flow and stasis are mainly responsible for the thrombotic material that usually exists in the left atrial appendage. This is a major risk factor for stroke. Atrial fibrillation is responsible for 15–20% of all ischemic strokes [12], increases the risk of stroke four- to fivefold, and is an independent risk factor for stroke severity and recurrence. Atrial fibrillation also affects the cognitive function and the quality of life of patients [13]. It is known that the coexistence of atrial fibrillation and hypertension triples the annual risk for stroke.

## 17.5 Diagnosis

Atrial fibrillation may present with palpitations, dizziness, anxiety, weakness, and shortness of breath or may be silent and identified in an incidental ECG or by cardiac rhythm management devices (pacemakers-ICDs). More serious symptoms like chest pain, severe dyspnea, or hemodynamic instability may be attributed to the serious comorbidities such as ischemic heart disease or heart failure. When there is suspicion for atrial fibrillation, a 12-lead ECG should be performed, and it is a fact that a considerable number of clinicians still need to improve their ability to recognize this type of arrhythmia [14]. Complete history, physical examination, blood pressure measurement, echocardiography, and basic laboratory workup should be performed in every patient with newly diagnosed atrial fibrillation. Atrial fibrillation is classified as first diagnosed (irrespective of the duration or the presence and severity of the related symptoms), paroxysmal (self-terminating usually within 48 hours or in fewer than 7 days), persistent (that lasts more than 7 days or requires termination by cardioversion either with drugs or by direct current cardioversion), long-standing persistent (that lasted more than 1 year when patient decided to adopt a rhythm control strategy), and permanent (the presence of arrhythmia is accepted by the patient and the physician) [15].

## 17.6 Risk Stratification and Prevention of Thromboembolism from Atrial Fibrillation in Hypertensive Patients: Therapeutic Management

The main complications of atrial fibrillation are thromboembolism and impairment of the left ventricular function. History of stroke or transient ischemic attack, increasing age, hypertension, and structural heart disease are identifiable predictors of stroke in patients with atrial fibrillation. The simplest risk stratification scheme was $CHADS_2$ score which has been lately revised as $CHA_2DS_2VASc$ score (each letter stands for congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age 65–74, and sex category (i.e., female sex), respectively) that is used by the current guidelines and identifies more precisely patients at low risk for developing thromboembolic episodes. Patients with $CHA_2DS_2VASc$ >1 should take antithrombotic therapy either with vitamin K antagonist or new oral anticoagulants (oral direct

thrombin inhibitor or oral factor $X_a$ inhibitors). In any case a discussion with the patient on the advantages and disadvantages of each approach and safety issues should be obligatory. Moreover, the risk of bleeding should be calculated before starting anticoagulation therapy. A helpful tool for this purpose is the HAS-BLED score (the HAS-BLED mnemonic stands for hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs, elderly, drugs or alcohol). A result ≥3 indicates a patient with high risk for bleeding, and some caution and regular review of the patient are needed. Nevertheless, the most intriguing fact is that conditions as hypertension or age confer to both an increased thrombotic risk as by the $CHA_2DS_2VASc$ score and an increased hemorrhagic risk as assessed by the HAS-BLED score. In patients receiving anticoagulant therapy, optimal control of their blood pressure has the further advantage of reducing bleeding events.

A lot of trials have been conducted investigating patients with atrial fibrillation but none to estimate on purpose the direct effect of antihypertensive agents on the risk of atrial fibrillation. The results available are derived only from meta-analyses and post hoc analyses of randomized trials [16].

## 17.7 Major Antihypertensive Drug Classes and Atrial Fibrillation

Secondary analyses of trials showed a benefit in primary prevention of atrial fibrillation when using renin-angiotensin-aldosterone system (RAAS) blocking agents as antihypertensives, but one should keep in mind that these trials were not designed to investigate atrial fibrillation. Blockade of the RAAS may prevent left atrial dilation, atrial fibrosis, atrial dysfunction, and slowing of conduction velocity or may have antiarrhythmic properties. Their effect on atrial remodeling and their antifibrillatory, antifibrotic, and anti-inflammatory properties may explain the reduction in new-onset atrial fibrillation [17]. Some studies have found that ARBs (angiotensin receptor blockers) (losartan, valsartan) are better in primary prevention of atrial fibrillation than β blockers (atenolol) (LIFE study: the Losartan Intervention For End Point Reduction in Hypertension) [18]. In addition, one meta-analysis has shown a statistically significant 25% reduction in RR of incident atrial fibrillation [19]. Likewise, several studies with calcium channel blocker (amlodipine) had shown similar results in patients with heart failure. On the contrary, these findings were not confirmed by other studies that included high-risk patients, such as the PRofeSS [20] (Telmisartan to prevent recurrent stroke and cardiovascular events) and TRANSCEND (Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease) [21], where the authors didn't find a protective effect of ARBs vs. placebo on new-onset atrial fibrillation (although the absolute numbers of participants were low and the detection power of the analysis may have been insufficient). Moreover, in the ACTIVE I (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events) [22] trial, irbesartan did not improve survival in patients with established atrial fibrillation. In ONTARGET study [23] (Ongoing Telmisartan Alone and in Combination with Ramipril Global

End Point Trial), ARBs showed no difference from ACEs in the prevention of new-onset atrial fibrillation.

As for the secondary prevention, meta-analyses of some small randomized controlled trials showed a significant 45–50% reduction in the relative risk (RR) of recurrent atrial fibrillation, but these recurrences could not be avoided when ARBs were coadministered with antiarrhythmic therapy in CAPRAF, GISSI-AF, and ANTIPAF trials [24].

A meta-analysis has shown that beta-blockers in heart failure demonstrate a 27% reduction in atrial fibrillation onset [25]. As it was mentioned above, in hypertension trials like the LIFE study, the use of ARB was superior to beta-blocker in reducing the risk of recurrent atrial fibrillation. Beta-blockers are recommended as antihypertensive therapy in patients with atrial fibrillation and high ventricular rates. There is a possibility that beta-blockers maintain sinus rhythm, especially in heart failure and in cardiac postoperative settings. Beta-blockers may act by preventing adverse remodeling and ischemia and by reducing the sympathetic system activation. However, recurrence rate of atrial fibrillation is high even under beta-blocker prophylaxis, and they are no longer considered as effective rhythm control agents (except sotalol which should be considered as a class III antiarrhythmic rather than as a beta-blocker).

Calcium channel blockers have antihypertensive properties and could theoretically attenuate the calcium overload in tachycardia-induced electrical remodeling of the atria. Different trials, for example, as the VALUE study [26], have compared CCBs with other antihypertensive agents for their effectiveness in preventing new-onset atrial fibrillation, nevertheless with disappointing results. On the other hand, several studies with calcium channel blocker (amlodipine) had shown a statistically significant reduction in RR of incident atrial fibrillation in patients with heart failure.

Diuretics have not been adequately investigated for their ability to prevent new-onset atrial fibrillation. They have significant antihypertensive effects, but their potential proarrhythmic risk due to hypokalemia or hypomagnesemia should not be overlooked.

Patients with primary hyperaldosteronism have a 12-fold higher risk of developing atrial fibrillation than their matched counterparts with essential hypertension. The role aldosterone antagonists have not been studied in humans, but preliminary results of ongoing trials indicate that the use of spironolactone reduces the incidence of recurrent atrial fibrillation in hypertensives with mild left ventricular dysfunction. In patients with systolic heart failure and mild symptoms, eplerenone reduced the incidence of new-onset atrial fibrillation [27].

While antihypertensive therapy is associated with a significant 10% relative reduction in the risk of atrial fibrillation, this effect is confined to patients with heart failure, with no clear benefit in population without heart failure according to a large recent meta-analysis [28].

Current ESH/ESC guidelines for the management of arterial hypertension [18] suggest that the use of ACE inhibitors and angiotensin receptor blockers in patients who suffer from hypertension and are at high risk of new or recurrent atrial

fibrillation may be beneficial (class IIa Level of evidence C). The same indication is given for the initiation of beta-blockers or mineralocorticoid receptor antagonists in hypertensive patients in whom heart failure coexist. In any case this indication is based on consensus of opinion of the experts or small studies, retrospective studies, and registries, and the results and benefits (in terms of AF prevention) are conflicting and controversial.

**Conclusion**

Hypertensive patients are at high risk of developing atrial fibrillation, and patients with atrial fibrillation often suffer from high levels of blood pressure. Both of these entities may confer on serious cardiovascular outcomes. Awareness of this increased risk warrants a closer follow up of these patients, treatment of atrial fibrillation with appropriate regimens and control of the levels of blood pressure as mentioned above.

## References

1. Davis RC, Hobbs FD, Kenkre JE et al (2012) Prevalence of atrial fibrillation management: a prospective survey in the general population and in high-risk groups: the ECHOES study. Europace 14:1553–1559
2. Wilke T, Groth A, Mueller S et al (2013) Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. Europace 15:486–493
3. Knecht S, Oelschläger C, Duning T et al (2008) Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. Eur Heart J 29:2125–2132
4. Santageli P, Di Biase L, Bai R et al (2012) Atrial fibrillation and the risk of incident dementia: a meta-analysis. Heart Rhythm 9:1761–1768
5. Wolf PA, Abbott RD, Kannel WB (1991) Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 22:983–988
6. Wong ND, Lopez VA, L'Italien G et al (2007) Inadequate control of hypertension in US adults with cardiovascular disease comorbidities in 2003–2004. Arch Intern Med 167:2431–2436
7. Manolis AJ, Rosei EA, Coca A et al (2012) Hypertension and atrial fibrillation: diagnostic approach, prevention and treatment. Position paper of the Working Group 'Hypertension Arrhythmias and Thrombosis' of the European Society of Hypertension. J Hypertens 30: 239–252
8. Vaziri SM, Larson MG, Lauer MS et al (1995) Influence of blood pressure on left atrial size. The Framingham Heart Study. Hypertension 25:1155–1160
9. Mitchell GF, Vasan RS, Keyes MJ et al (2007) Pulse pressure and risk of new-onset atrial fibrillation. JAMA 297:709–715
10. Van Gelder IC, Hemels ME (2006) The progressive nature of atrial fibrillation: a rationale for early restoration and maintenance of sinus rhythm. Europace 8:943–949
11. Allessie M, Ausma J, Schotten U et al (2005) Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res 54:230–246
12. Penado S, Cano M, Acha O et al (2003) Atrial fibrillation as a risk factor for stroke recurrence. Am J Med 114:206–210
13. Bunch TJ, Weiss JP, Crandall BG et al (2010) Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. Heart Rhythm 7:433–437
14. Mant J, Fitzmaurice DA, Hobbs FD et al (2007) Accuracy of diagnosing atrial fibrillation on electrocardiogram by primary care practitioners and interpretative diagnostic software: analysis of data from screening for atrial fibrillation in the elderly (SAFE) trial. BMJ 335:380

15. EHRA, EACTS, Camm AJ, Kirchhof P, Lip GY et al (2010) Guidelines for the Management of Atrial Fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Eur Heart J 31:2369–2429
16. Manolis AJ, Kallistratos MS, Poulimenos LE (2012) Recent clinical trials in atrial fibrillation in hypertensive patients. Curr Hypertens Rep 4:350–359
17. Ogunsua AA, Shaikh AY, Ahmed M, McManus DD (2015) Atrial fibrillation and hypertension: mechanistic, epidemiologic, and treatment parallels. Methodist Debakey Cardiovasc J 11(4):228–234
18. Wachtell K, Lehto M, Gerdts E et al (2005) Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the losartan intervention for end point reduction in hypertension (LIFE) study. J Am Coll Cardiol 45:712–719
19. Jibrini MB, Molnar J, Arora RR (2008) Prevention of atrial fibrillation by way of abrogation of the renin-angiotensin system: a systematic review and meta-analysis. Am J Ther 15(1): 36–43
20. Yusuf S, Diener HC, Sacco RL et al (2008) PRoFESS study Group. Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med 359:1225–1237
21. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant Subjects with Cardiovascular Disease (TRANSCEND) Investigators, Yusuf S, Teo K, Anderson C et al (2008) Effects of the angiotensin-receptor blocker Telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomized controlled trial. Lancet 372:1174–1183
22. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R et al (2006) Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the atrial fibrillation Clopidogrel trial with Irbesartan for prevention of vascular events (ACTIVE W): a randomized controlled trial. Lancet 367:1903–1912
23. Liebson PR, Amsterdam EA (2009) Ongoing Telmisartan alone and in combination with Ramipril global endpoint trial (ONTARGET): implications for reduced cardiovascular risk. Prev Cardiol 12(1):43–50
24. Schneider MP, Hua TA, Böhm M et al (2010) Prevention of atrial fibrillation by renin-angiotensin system inhibition a meta-analysis. J Am Coll Cardiol 55(21):2299–2307. doi:10.1016/j.jacc.2010.01.043
25. Nasr IA, Bouzamondo A, Hulot JS et al (2007) Prevention of atrial fibrillation onset by beta-blocker treatment in heart failure: a meta-analysis. Eur Heart J 28(4):457–462
26. Schmieder RE, Kjeldsen SE, Julius S et al (2008) Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. J Hypertens 26:403–411
27. Swedberg K, Zannad F, McMurray JJ et al (2012) Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in mild patients hospitalization and SurvIval study in heart failure) study. J Am Coll Cardiol 59:1598–1603
28. Emdin CA, Callender T, Cao J, Rahimi K (2015) Effect of antihypertensive agents on risk of atrial fibrillation: a meta-analysis of large-scale randomized trials. Europace 17:701–710

# Part V

# Hypertension Phenotypes: The Central Nervous System and the Brain

# Sleep Disturbances/Sleep Apnea

# 18

Gianfranco Parati, Carolina Lombardi, Krzysztof Narkiewicz, Jacek Wolf, and Juan Eugenio Ochoa

## 18.1 Effects of OSAS on Mechanisms of Integrated Cardiovascular Regulation

### 18.1.1 Effects of OSAS on Neural Reflex Mechanisms of Cardiovascular Modulation

Recurrent episodes of airway obstruction during sleep lead to significant respiratory and ventilatory changes (hypoxemia, reoxygenation, hypercapnia, changes in pulmonary volume, reduced intrathoracic pressures) with important effects on mechanisms of integrated autonomic cardiovascular modulation, in particular, activation of central and peripheral chemoreflexes and dysfunction of arterial, cardiopulmonary, and cardiac baroreflexes. The overall effect is a marked sympathetic activation, a major determinant of the autonomic and hemodynamic alterations observed in OSAS patients (Fig. 18.1).

G. Parati (✉)
Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

Department of Cardiovascular, Neural and Metabolic Sciences, S.Luca Hospital, IRCCS Istituto Auxologico Italiano & University of Milan-Bicocca, Piazza Brescia 20, Milan 20149, Italy
e-mail: gianfranco.parati@unimib.it

C. Lombardi • J.E. Ochoa
Department of Cardiovascular, Neural and Metabolic Sciences, S.Luca Hospital, IRCCS Istituto Auxologico Italiano & University of Milan-Bicocca, Piazza Brescia 20, Milan 20149, Italy

K. Narkiewicz • J. Wolf
Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk, Poland



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_18

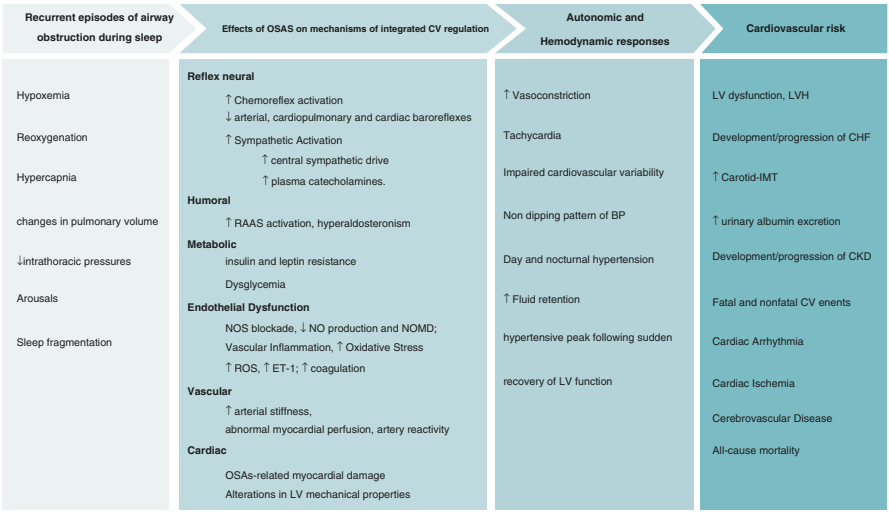



**Fig. 18.1** Effects of OSAS on mechanisms of cardiovascular regulation; the resultant neural, humoral, metabolic, and hemodynamic alterations; and their consequences for cardiovascular risk. *CV* cardiovascular, *LV* left ventricular, *RAAS* renin-angiotensin-aldosterone system, *ROS* reactive oxygen species, *ET-1* endothelin-1, *NOS* nitric oxide synthase, *NO* nitric oxide, *LVH* left ventricular hypertrophy, *BP* blood pressure, *NOMD* nitric oxide-mediated dilatation, *CKD* chronic kidney disease, *CHF* congestive heart failure, *IMT* intima-media thickness

In normal physiological conditions, control of BP levels is achieved through a complex combination between central and reflex neural influences, leading to a continuous modulation of efferent sympathetic and parasympathetic nerve activity and the associated activity of neurohormonal systems primarily regulated by the hypothalamus. The sympathetic activation in OSAS is largely explained by stimulation of the peripheral and central chemoreflexes, triggered by the reductions in arterial oxygen content and by hypercapnia, respectively. The importance of arterial chemoreceptors has been highlighted by studies showing their relevant influence on neural circulatory control even during conditions of normoxia [1]. Indeed, elimination of the influences of arterial chemoreceptors using 100% oxygen in a double-blind study showed that in patients with OSA, suppression of the chemoreflexes slowed heart rate and decreased MSNA (Fig. 18.2).

Furthermore, the autonomic, hemodynamic, and ventilator responses to peripheral chemoreceptor activation by hypoxia are selectively potentiated in patients with OSA [3].

Moreover, in OSAS, the sustained chemoreflex activation, the related adrenergic overactivity, and the resulting hypertension may blunt and/or reset arterial and cardiopulmonary reflexes which in turn may lead to chemoreflex potentiation [3, 4].

In addition, repetitive sympathetic activation and blood pressure (BP) surges during sleep may also cause cardiac baroreflex impairment leading to a reduced sympathoinhibition and to impaired cardiac parasympathetic modulation [5, 6] further contributing to adrenergic overdrive and rise in BP levels (Fig. 18.3). In

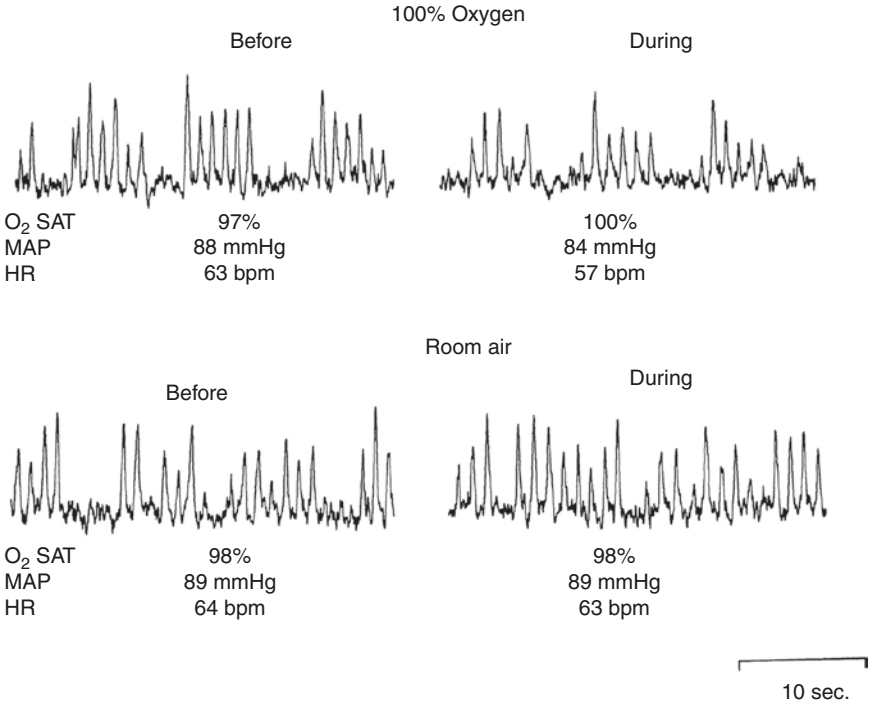



**Fig. 18.2** Recordings of muscle sympathetic nerve activity (MSNA) in a single patient with obstructive sleep apnea (OSA) during administration of 100% oxygen (*top*) and room air (*bottom*). MSNA, mean arterial pressure (MAP), and heart rate (HR) decreased during administration of 100% oxygen but did not change during administration of room air. Taken from Narkiewicz et al. [2] by permission

particular, the observation of a reduced spontaneous cardiac baroreflex sensitivity (as assessed by the sequence method) and the absence of 24-h baroreflex modulation (i.e., blunted increase in baroreflex sensitivity during sleep compared with its values during wakefulness) in OSAS patients [5] have provided indirect support to the concept that baroreflex dysfunction and not only chemoreceptor stimulation by hypoxia may contribute to the acute and long-term sympathetic activation in OSAS patients (Fig. 18.3). The depressed cardiac baroreflex sensitivity during sleep may thus in turn contribute to the pathophysiology of BP elevation in OSAS patients.

This concept has been further supported by the results of interventional studies in OSAS patients showing a significant improvement in baroreflex sensitivity after long-term implementation of CPAP treatment [7–9].

Further evidence that sleep-related breathing disorders may induce alterations in autonomic cardiovascular modulation has been provided by a study in untreated subjects with OSAS of different severity indicating that excessive daytime sleepiness is accompanied by lower baroreflex sensitivity and significantly higher low-to-high frequency power ratio of heart rate variability (which is believed to be a marker of sympatho-vagal balance in cardiac regulation) during the different stages

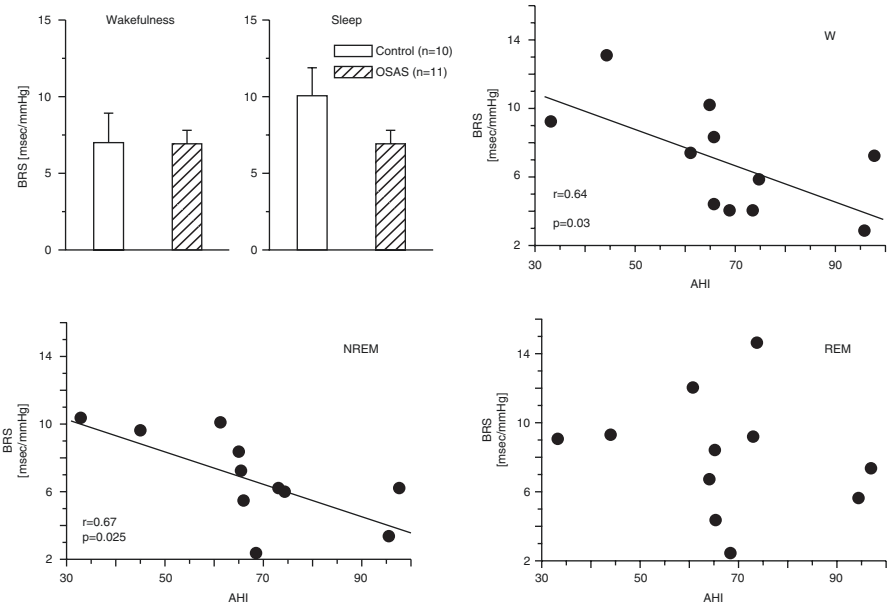



**Fig. 18.3** Relationship between spontaneous baroreflex sensitivity (BRS) and the severity of obstructive sleep apnea syndrome, as quantified by the apnea-hypopnea index (AHI). Data are shown as individual values in 11 patients separately for a period of wakefulness (W), a period of non-rapid-eye-movement (REM) sleep (NREM) and a period of REM sleep (REM). Taken from Parati et al. [5] by permission

of nocturnal sleep as compared not only to control subjects but also to OSAS patients without daytime somnolence [10] (Fig. 18.4).

The consequence of chemoreflex activation and impairment of arterial, cardiac, and cardiopulmonary reflexes is sympathetic nervous system activation, which is considered a major pathophysiological mechanism underlying the alterations in BP regulation reported in OSAS (Fig. 18.1). Normal sleep is associated with important changes in BP and heart rate (HR) which are dependent upon sleep stage and appear to be mediated primarily by changes in autonomic circulatory control [11]. During non-REM sleep, there is a reduction in HR, BP, and sympathetic nerve traffic. This overall inhibition of the cardiovascular system increases progressively from Stage I to Stage IV. During Stage IV sleep, HR, BP, and sympathetic activities are lowest. During REM sleep, there is a marked increase in sympathetic activity about twofold the levels seen during wakefulness. In patients with OSA, sympathetic activity and BP during sleep are determined primarily by the responses to apneas. The duration of apnea and the level of oxygen desaturation are key factors in causing sympathetic activation during the episodes of obstructive sleep apnea. During the apnea, sympathetic activity rises gradually. At the end of the apnea, when oxygen desaturation and carbon dioxide retention are most marked, sympathetic activity is greatest [12]. On release of the airway obstruction and resumption of breathing, increased cardiac

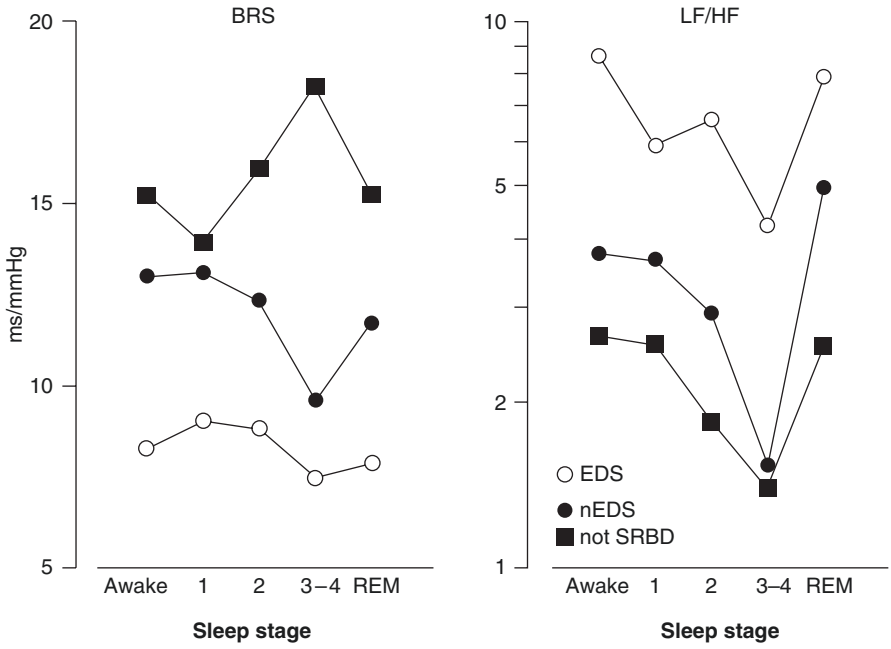



**Fig. 18.4** Trends of baroreflex sensitivity (BRS), and of the ratio between low- and high-frequency powers of RRI (LF/HF), in healthy controls without sleep-related breathing disorders (SRBD, *square symbols*); in patients with OSA and excessive daytime sleepiness (EDS, *open circles*) and in patients with OSA not affected by EDS (nEDS, *solid circles*). Taken from Lombardi et al. [10] by permission

output together with the vasoconstricted peripheral vasculature results in marked increases in BP levels.

Since most patients have repetitive apneas throughout the night, the sympathetic-hemodynamic profile of these subjects is determined by the apneas and consists of repetitive increases in sympathetic activity and surges of BP with an important interindividual variability [5, 13, 14].

These disturbances in HR and BP oscillatory profiles may be secondary to several factors including autonomic responses to sleep and apnea, as well as altered patterns of respiration.

The activation of the sympathetic nervous system in OSAS has been consistently demonstrated by studies implementing direct techniques for assessment of sympathetic nervous system activity (i.e., recording of efferent postganglionic muscle sympathetic nerve activity via microneurography (MSNA) and assessment of norepinephrine plasma levels. In these reports an increase in central sympathetic drive was positively correlated with important increases in BP levels during resumption of ventilation after each apneic episode [12] (Fig. 18.5a). Moreover, sleep fragmentation, related to repeated arousals after each apnea-hypopnea event, might play an additional role in this context.

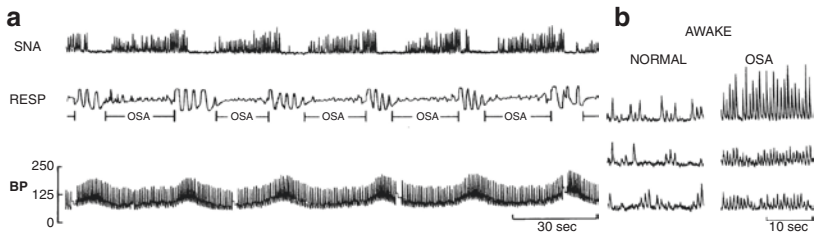



**Fig. 18.5** (**a**) Recordings of sympathetic nerve activity (SNA), respiration (RESP), and blood pressure (BP) during 3 min of Stage II sleep, showing incessant oscillations in BP and SNA in response to the repetitive OSAs. These oscillations occurred continuously during sleep, throughout all sleep stages. (**b**) Recordings of SNA during wakefulness in patients with OSAS and matched controls showing high levels of SNA in patients with OSA. Taken from Somers et al. [12], by permission

Of remark, the sympathetic activation in OSAS subjects is not only limited to nighttime but may persist even after resuming normal breathing pattern during daytime wakefulness, despite normal arterial oxygen saturation and carbon dioxide levels [12, 15] (Fig. 18.5b). Reinforcing this concept, several long-term implementation of continuous positive airway pressure (CPAP) resulted in marked reductions in sympathetic nerve traffic [12] and BP levels [16] both during nighttime and daytime wakefulness [17], further supporting the pathogenetic role of the sympathetic activation in explaining BP elevation in OSAS.

### 18.1.2 Effects of OSAS on Humoral Regulatory Mechanisms

The frequent association of OSAS with hyperaldosteronism reported in patients with resistant hypertension has led to suggest that activation of renin-angiotensin-aldosterone system and OSAS may interact on a pathophysiological basis contributing to BP elevation [18–20]. Although evidence is still needed to determine the causality of this association, it has been hypothesized that OSAS may contribute to the pathogenesis of resistant hypertension by stimulating aldosterone secretion [21] (Fig. 18.1). This concept has been supported by several studies showing positive and significant correlations between plasma aldosterone concentrations and OSAS severity in patients with resistant hypertension but not in normotensive subjects nor in treated hypertensives with BP controlled [22]. It is likely that aldosterone excess by promoting fluid accumulation in the neck, and thus increasing upper airway resistance, may increase the severity of OSAS and the related increase in BP levels [23, 24]. Indirect evidence favoring this concept has been provided by interventional studies in subjects with OSAS and resistant hypertension where addition of spironolactone to current antihypertensive treatment resulted in significant reductions in the severity of OSA (i.e., reductions in apnea-hypopnea index and the number of central and obstructive events) on top of its BP-lowering effects [25]. Additional evidence is still needed, however, to consistently determine a causal association between aldosterone excess in OSAS and resistant hypertension.

### 18.1.3 Effects of OSAS on Endothelial Function

The intermittent hypoxia, the associated neural and humoral alterations and repeated BP surges during OSA episodes may contribute to impairment in endothelial function. In turn, the inhibition of nitric oxide (NO) production, decreased vasodilatation, and increased vasoconstriction associated with endothelial dysfunction may substantially contribute to BP elevation (Fig. 18.1). Several studies assessing brachial artery endothelium-dependent flow-mediated dilation (FMD, an indirect marker of endothelial NO-mediated reactivity) and forearm blood flow responses to different stimuli (i.e., infusion of acetylcholine, sodium nitroprusside, nitroglycerin) have shown that compared to healthy controls, patients with OSAS often exhibit an impairment of resistance-vessel endothelium-dependent vasodilation [26, 27]. Even when accounting for important confounding factors such as body weight, brachial artery FMD has been shown to be significantly lower in normal-weight OSAS patients than in OSAS-free controls [28]. Remarkably, interventional studies have shown substantial improvements in different indices of endothelial function following implementation of regular CPAP use in subjects with hypertension and OSAS [27–29] which indirectly supports a role for endothelial dysfunction in the pathogenesis of OSAS-related arterial hypertension.

On the other hand, repetitive episodes of hypoxia/reoxygenation during transient cessation of breathing in OSA may also reduce nitric oxide (NO) availability, promoting vascular endothelial inflammation and elevated oxidative stress [26, 27, 30–32] (Fig. 18.1). When compared to OSAS-free controls and regardless of the presence of obesity, OSAS patients have been shown to present a reduced expression of endothelial NO synthase (eNOS) and phosphorylated eNOS (proteins which regulate basal nitric oxide production and activity) as well as an increased expression of nitrotyrosine (a marker of oxidative stress) and of NFk-B (a marker of inflammation) [28]. Most importantly, after 1 month of regular treatment with CPAP, flow-mediated dilation, expression of eNOS, and phosphorylated eNOS were significantly increased, whereas expression of nitrotyrosine and nuclear factor-K B were decreased [28]. It has also been proposed that intermittent hypoxia/hypercapnia by increasing production/release of endothelin-1 (ET-1), i.e., a potent vasoconstrictor with mitogenic effects [33], may contribute to the pathogenesis of hypertension. Altered vascular responsiveness to neural mechanisms, as a result of vasoconstriction and/or structural vascular changes, may interfere with BP regulation. This has been supported by experimental studies in rats showing significant increases in plasma levels of endothelin-1 and higher BP levels in rats exposed to intermittent hypoxia (i.e., cycles of hypoxia/hypercapnia of 8 h a day during 11 days) compared to those breathing normoxic air [34]. Data from several studies have indicated that selective activation of inflammatory pathways may be an additional important molecular mechanism for the pathogenesis of arterial hypertension in OSAS. This has been supported by translational studies showing a selective activation of the pro-inflammatory transcription factor NFk-B in HeLa cells of OSAS patients exposed to intermittent hypoxia/reoxygenation cycles [35]. In addition, compared to healthy controls, subjects with OSAS showed significantly higher levels of circulating pro-inflammatory cytokines (i.e., tumor necrosis factor-alpha and

the adaptive factor erythropoietin) as well as higher levels of circulating neutrophils. Interestingly, levels of tumor necrosis factor-alpha (TNF-alpha) were normalized after 6 weeks of continuous treatment with CPAP [35]. Other studies have shown that compared to healthy controls, serum levels of inflammatory markers (i.e., C-reactive protein, CRP) are significantly higher in OSAS patients and independently associated with OSAS severity [36]. Besides, interventional studies have shown significant reductions in serum levels of C-reactive protein and interleukin-6 following implementation of regular CPAP treatment [37]. Finally, evidence has also been provided that OSAS may induce activation of adhesion molecules participating in inflammation. This has been supported by case-control studies showing significantly higher levels of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and L-selectin in OSAS patients compared to healthy controls [38].

### 18.1.4 Effects of OSAS on Vascular Function

OSAS may induce not only endothelial dysfunction and inflammation but also important changes in vascular structure and function. This has been supported by studies showing abnormal myocardial perfusion, attenuated brachial artery reactivity, and reduced cutaneous perfusion response in OSAS patients as compared to healthy controls [29]. A systematic review of relevant studies has also indicated an independent effect of OSAS on arterial stiffness, which in turn may contribute to elevation in BP levels and to resistant hypertension [39] (Fig. 18.1). A number of studies have consistently reported significantly higher values of carotid-femoral pulse wave velocity (cfPWV) (which is considered the "gold-standard" measure of aortic stiffness), in patients with OSAS compared to healthy controls [39, 40]. Of note, the increase in cfPWV has been shown to be directly related to the severity of OSAS and to be even higher in subjects with OSAS and associated hypertension or in the presence of other cardiovascular risk factors [41]. In Asian populations, several studies implementing brachial-ankle PWV (baPWV) have also reported significant associations between OSAS and increased arterial stiffness [42]. Even when comparisons have been performed between individuals with or without OSAS entirely free from other CV risk factors, an independent effect of OSAS on arterial stiffening has been reported [43]. Remarkably, in randomized interventional studies, effective treatment of OSAS with CPAP has been associated with significant decreases in arterial stiffness [44, 45]. In one of such reports, CPAP was also associated with significant reductions in sympathetic nerve activity and in ambulatory BP (ABP) levels and with significant improvements in arterial baroreflex sensitivity [44].

### 18.1.5 Metabolic Effects of OSAS

A number of studies have confirmed the association between OSAS and metabolic alterations (i.e., insulin and leptin resistance) which in turn may contribute to alterations in glucose metabolism and to the pathogenesis of arterial hypertension

(Fig. 18.1). Although alterations in glucose metabolism are thought to be the consequence of other conditions associated with OSAS (i.e., an increased BMI, metabolic syndrome, and/or type 2 diabetes) rather than being OSAS outcomes, evidence has been provided that OSAS, independently of the presence of other confounding factors, is associated with alterations in glucose metabolism which may indeed favor development of type 2 diabetes [46]. In addition, interventional studies have shown the efficacy of regular CPAP treatment in improving the abnormalities in glucose metabolism in OSAS patients [46]. Compared to healthy controls, OSAS patients have also been shown to have a higher degree of insulin and leptin resistance [47–49] even after accounting for body fat content [50]. Although the above-mentioned metabolic alterations should theoretically contribute to the pathogenesis of hypertension in OSAS, their relative contribution to BP elevation independently of other concomitant factors still needs to be further explored.

## 18.2 Autonomic and Hemodynamic Responses to Impaired Integrated Cardiovascular Control in OSAS

The marked sympathetic activation resulting from chemoreceptor activation and impaired baroreflex control of circulation in OSAS causes significant increases in central sympathetic drive to the heart and peripheral circulation and in plasma catecholamines, leading to important autonomic and hemodynamic changes (vasoconstriction, elevated blood pressure and blood pressure variability, elevated heart rate, and reduced heart rate variability). Activation of the RAAS and the associated hyperaldosteronism also contribute to the hemodynamic imbalance in OSAS by causing fluid retention. Of note, the magnitude of these alterations has been directly associated to the severity of OSAS. This not only promotes future development of hypertension but also makes hypertension occurring in OSAS more severe and resistant to antihypertensive treatment [51–54] and associated with profound alterations in day-to-night BP changes (i.e., marked increases in BP levels and in BP variability during nighttime) [55, 56]. Of remark, alterations in cardiovascular variability in OSAS are not limited to the nighttime hours, during which OSA episodes occur, but are often sustained also during the daytime. Evidence of this has been provided by studies implementing direct assessment of MSNA indicating that the sympathetic overdrive in OSAS is persistent also during daytime, and by case-control studies using 24-h ABPM confirming that ABP levels in subjects with OSAS are elevated not only during the nighttime sleep but also during daytime wakefulness [57–59].

Reinforcing this concept, other studies have also found increase in central sympathetic drive to be associated with alterations in circadian BP variation (i.e., absence of nocturnal BP fall or increase in BP at night) and with nocturnal hypertension in OSAS patients [60]. Additional studies implementing noninvasive assessment of cardiovascular variability either in the time or in the frequency domain (spectral analysis) along with direct estimation of central sympathetic drive through MSNA, have provided evidence that autonomic cardiovascular modulation and cardiovascular variability in OSAS are impaired even during wakefulness. Overall,

these studies have shown that compared to controls, OSAS patients are characterized by elevated HR and average BP levels, increased blood pressure variability (BPV), and reduced heart rate variability (HRV) when applying spectral analysis to BP and HR recordings. In OSAS subjects a relative predominance of the LF component over the HF component of RR interval has been shown, the LF/HF ratio of RR variability being significantly increased in patients with moderate-to-severe OSAS versus controls and versus patients with mild OSAS. Notably, the degree of these alterations has been shown to be directly related to the severity of OSAS [61] (Fig. 18.6).

It was also shown that compared to healthy controls, patients with OSAS exhibit faster HR, increased BP variability, and markedly elevated muscle sympathetic nerve activity not only during nighttime sleep but also during wakefulness when breathing patterns are normal and no evidence of hypoxia or hypercapnia is apparent (Fig. 18.7).

Of note, apnea-hypopnea index was inversely correlated with RR interval and directly related with both MSNA and systolic BP variability. In turn, MSNA was inversely correlated with RR interval and RR variability and directly related to systolic BP variability [61].

Evidence from recent studies has indicated that OSAS increases nighttime BP variability in patients with hypertension, the increase being proportional to the severity of OSAS [56]. This may be another pathway linking sleep abnormalities to cardiovascular disease. Finally, the abnormalities in indices of autonomic cardiovascular modulation observed in normotensive OSAS patients, in whom absolute BP levels were similar to those of non-OSAS subjects, have led to suggest that an

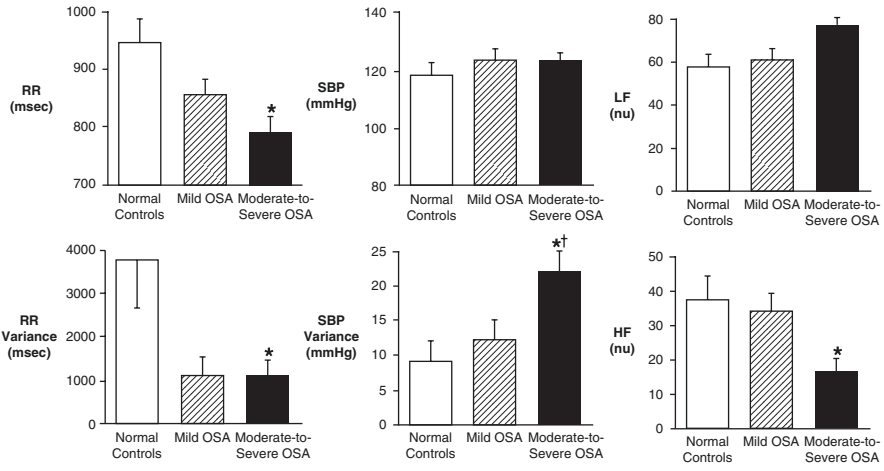



**Fig. 18.6** RR interval and systolic blood pressure (SBP) mean values and their variances and normalized low-frequency (LF) and high-frequency (HF) spectral components of RR interval in control subjects, patients with mild OSA, and patients with moderate-to-severe OSA $^{*}P < 0.05$ versus control subjects. $^{\dagger}P < 0.05$ versus mild OSA. Data are mean ± SEM. Modified from Narkiewicz et al. [61] by permission

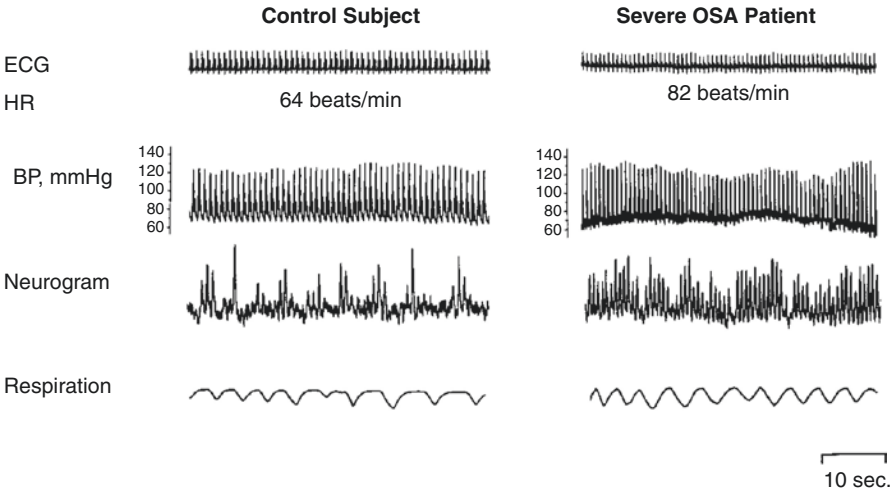



**Fig. 18.7** Electrocardiogram (ECG), blood pressure, sympathetic neurograms, and respiration in a control subject (*left panel*) and in a patient with severe obstructive sleep apnea (OSA; *right*). Taken from Narkiewicz et al. [61] by permission

abnormal cardiovascular variability may precede, and possibly even predispose to, the development of hypertension in patients with OSAS [61].

## 18.3 Epidemiological Evidence Supporting the Association of Elevated BP with OSAS

OSAS is not only a recognized cause of secondary hypertension [51–54] but is also associated with a high prevalence of alterations in BP regulation, which make hypertension more severe and resistant to antihypertensive treatment. A number of studies either in the general population or in cohorts of OSAS patients [52, 54, 62–65] have indicated a variable frequency of hypertension in subjects with OSAS which may range from 35 to 80% [66, 67]. Conversely, when properly investigated, OSAS has been shown to be present in up to 40% of hypertensive subjects [23]. Although the association between OSAS and hypertension frequently overlaps with the presence of other cardiovascular risk factors such as increased BMI and obesity [68–70], longitudinal studies have supported the association between OSAS and hypertension independently of other potential contributing factors indicating that OSAS is not only associated with an increased risk of prevalent hypertension but may predict future development of hypertension, in particular if not properly treated [53, 65, 70, 71] (Fig. 18.8).

Furthermore, in the Wisconsin Sleep Cohort Study, a dose-response relationship between sleep-disordered breathing at baseline and the development of hypertension

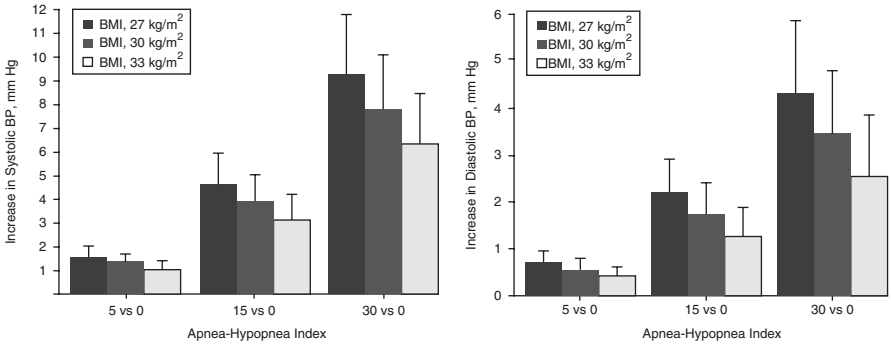



**Fig. 18.8** Predicted increase in systolic blood pressure (SBP) and in diastolic blood pressure (DBP) associated with sleep-disordered breathing at three body mass index (BMI) categories in the Wisconsin Sleep Cohort Study. Modified from Young et al. [65] by permission

after 4 years of follow-up was reported independently of baseline BP levels, BMI, neck and waist circumference, age, sex, and other potential confounders [53].

Because OSAS interferes with several mechanisms involved in BP regulation, hypertension in OSAS tends to be more severe and resistant to antihypertensive treatment, the degree of BP elevation being proportional to the severity of the disease [52, 72, 73]. Conversely, in adult patients with drug-resistant hypertension, in whom an extremely high prevalence of OSA of about 80% has been reported [74], the rates of BP control decrease as the severity of sleep-related breathing disorder increases [52].

Compared to normal subjects, hypertension in subjects with OSAS is more frequently associated with alterations in day-to-night BP changes (i.e., nocturnal hypertension and non-dipping profile of BP on 24-h ABPM) [52, 72, 73].

Indeed, hypertension related to OSAS is predominantly nocturnal in its early stages and frequently accompanied by a non-dipper profile of BP (i.e., nocturnal BP fall <10% compared to daytime BP levels) [67, 75]. Remarkably, the degree of impairment in nocturnal BP fall has been found to be related to the severity of OSAS [76]. On the other hand, an increased prevalence of alterations in day-to-night BP profiles and nocturnal hypertension has been reported in subjects with resistant hypertension regardless of the presence of OSAS [77–79]. It is thus expected that alterations in day-to-night BP changes might be even more pronounced in subjects with OSAS and resistant hypertension [80, 81].

## 18.4 Prognostic Significance of OSAS-Related Hypertension

Evidence from several studies has supported an independent association between OSAS and cardiovascular disease [82]. When it comes to subclinical organ damage, evidence has been provided that OSAS is independently associated with cardiac (i.e., LV hypertrophy and dysfunction) [45, 83, 84], vascular (i.e., increased carotid

intima-media thickness, increased arterial stiffness) [39], renal organ damage (i.e., increased urinary albumin excretion) [85, 86], and endothelial dysfunction (i.e., blunted endothelium-dependent dilatation) [39]. OSAS, particularly if severe, has been linked to fatal and nonfatal cardiovascular events including cardiac arrhythmia (bradycardia, A-V block, atrial fibrillation), cardiac ischemia (coronary artery disease, myocardial infarction, nocturnal ST-segment depression, nocturnal angina), and cerebrovascular disease [87–91], with systolic and diastolic dysfunction and development and progression of congestive heart failure [89] and with all-cause mortality [92, 93] (Fig. 18.9). However, because the link between OSAS and cardiovascular disease may be related to age, obesity, and visceral adiposity, in some of these studies, the associations have lost strength when adjusting for these factors. Evidence has also been provided that resistant hypertension which is more frequent among OSAS patients considerably increases the risk for cardiovascular complications including myocardial infarction, stroke, congestive heart failure, and chronic kidney disease [77, 94, 95]. In consideration of the increased CV risk associated with OSAS and resistant hypertension, current guidelines for the management of arterial hypertension include OSAS among the modifiable causes to be considered in the diagnostic approach to resistant hypertension, in order to properly manage both of these conditions [96, 97]. It should be mentioned however, that no studies have specifically addressed how and to which extent the addition of hypertension to OSAS may increase the risk of cardiovascular disease independently of other cardiovascular risk factors that are often clustered in the context of OSAS. Although OSAS and resistant hypertension have been shown to be independent predictors of cardiovascular prognosis, evidence is still needed to determine the actual prognostic relevance of their interaction independently of other concomitant cardiovascular risk factors.

Not only the presence of resistant hypertension but also the higher frequency of alterations in day-to-night BP profiles and nocturnal hypertension contribute to the elevated cardiovascular risk of OSAS patients. As mentioned above, nocturnal sympathetic activation during OSAS episodes importantly contributes to increases in

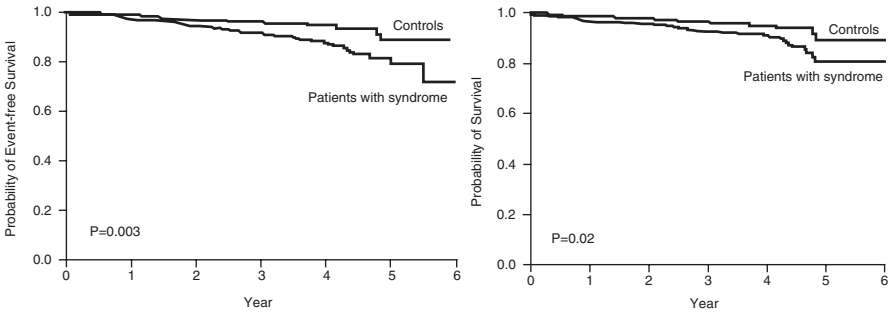



**Fig. 18.9** Kaplan-Meier estimates of the probability of event-free survival (*left panel*) and overall survival (*right panel*) among patients with the obstructive sleep apnea syndrome and controls. Modified by permission from Yaggi et al. [87]

BP during sleep, thus attenuating the physiologic nocturnal dipping of BP (i.e., on average by 10–20% of daytime BP values) or even increasing nocturnal BP levels (rising pattern of nighttime BP). It is thus not surprising the high frequency of non-dipping profile of BP reported in OSAS patients independently of the presence of hypertension [98]. From a prognostic point of view, identification of nocturnal hypertension and alterations in day-to-night BP changes in subjects with OSAS-related hypertension is of upmost relevance on the background of the evidence showing the superior prognostic value of nocturnal BP levels compared to awake or 24-h BP means in predicting cardiovascular morbidity and mortality [99–104], development of cardiovascular events [99, 100, 105–107], as well as overall mortality [99–101, 106, 108, 109]. Identification of "non-dipping" pattern of BP in OSAS patients is also important if we consider that subjects in whom nocturnal decrease in BP is blunted have been reported to have a higher prevalence of subclinical organ damage [110, 111] and an increased risk of cardiovascular events [112] and mortality [104], which is even higher in patients in whom BP increases rather than decreases at night (so called risers or "inverted dippers"). Despite the very high prevalence of nocturnal hypertension and alterations in day-to-night BP changes in OSAS patients, these are often undiagnosed (thus representing a form of so called masked resistant hypertension), mainly because BP measurements are prevalently measured during daytime at the moment of the clinical visit. Given their relevant prognostic value, alterations in circadian BP should be properly investigated in patients with OSAS-resistant hypertension through the use of 24-h ABPM in order to guide antihypertensive treatment toward their normalization and optimization of cardiovascular protection.

## 18.5 Diagnostic Approach to OSAS-Related Hypertension

Confirming the diagnosis of OSAS in subjects with hypertension and in particular in those with resistant hypertension is relevant in order to implement specific treatment strategies (i.e., CPAP, weight reduction). This might allow achievement of BP control reducing the elevated cardiovascular risk of these subjects. Polysomnography is currently considered the standard technique for diagnosis of OSAS and requires simultaneous monitoring of several cardiovascular and respiratory variables during night sleep (i.e., sleep, air flow, respiratory effort, oxygen saturation, and brain activity through electroencephalogram). Based on the number of apneas and hypopneas lasting >10 s during each hour of recording, the severity of the disease is graded using the apnea-hypopnea index (AHI) [113]. Whether polysomnography should be employed systematically in individuals with resistant hypertension is still a matter of debate in the absence of cost-effectiveness studies supporting this suggestion. According to a recent position paper of the European Respiratory Society (ERS)/European Society of Hypertension (ESH) [114], polysomnography should be performed in all subjects with a high pretest probability of OSA based on structured questionnaires (e.g., Epworth and Berlin questionnaires).

Considering the extremely high frequency of alterations in ambulatory BP profiles during nighttime in subjects with resistant hypertension and OSAS, the task force of the ERS/ESH also recommends performing ABPM in order to identify alterations in day-to-night BP changes in subjects with resistant hypertension in order to guide the decision to perform polysomnography in subjects with otherwise a low probability of OSA based on questionnaires. Indeed, in subjects with a low pretest probability of OSAS, polysomnography is only recommended in those who present alterations in day-to-night BP changes (i.e., non-dipping pattern of BP) (Fig. 18.10).

It is worth mentioning that before starting the instrumental tests to discard OSAS, a first step in the diagnostic approach of the patient with suspected OSAS-related hypertension consists in confirming whether resistance to antihypertensive treatment is true or corresponds to false resistance. Current guidelines for the management of arterial hypertension define resistant hypertension as the persistence of BP values above the BP goal (i.e., ≥140/90 mmHg for office systolic/diastolic BP) despite the concomitant use of three optimally dosed antihypertensive medications from different classes at near-maximal doses, one of which should ideally be

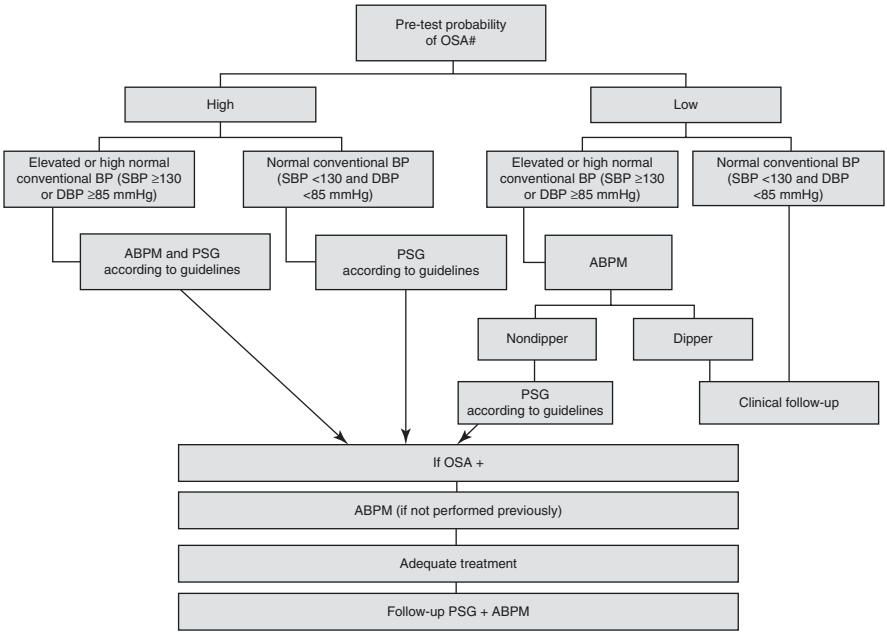



**Fig. 18.10** Proposed algorithm for the diagnostic management of patients with hypertension associated with obstructive sleep apnea (OSA). *BP* blood pressure, *SBP* systolic BP, *DBP* diastolic BP, *ABPM* ambulatory blood pressure monitoring, *PSG* polysomnography. According to clinical evaluation and questionnaires, e.g., Epworth and Berlin, ¶ hypertension guidelines recommend use of home BP monitoring in most hypertensive patients. Reproduced by permission from Parati et al. [114]

a diuretic [96, 97]. However, this definition is based on office BP measurements which have acknowledged limitations in assessing BP control including the inherent inaccuracy of the technique, the observer's bias and digit preference, a variable interference by the "white-coat effect," and the inability of this approach to collect information on BP during subjects' usual activities and over a long period of time [115]. Thus, for confirmation of true resistant hypertension, out-of-office BP measuring techniques such as ambulatory and/or home BP monitoring (which are not affected by the limitations of office BP) should be performed in addition to office BP measurements. Based on the measures obtained with these methods, a substantial and sometimes larger than expected number of subjects initially diagnosed with resistant hypertension or with BP control based on OBP may actually correspond to false-resistant hypertension or white-coat resistant hypertension (i.e., elevated OBP but normal out-of-office BP values) or to masked hypertension (i.e., normal OBP but elevated out-of-office BP values) [77, 116, 117].

From a prognostic point of view, identification of OSAS patients with true resistant hypertension as well as of those with masked resistant hypertension (treated patients with normal OBP and elevated ABP or HBP) [118, 119] is of the highest relevance on the background of the evidence showing these conditions to be associated with a higher prevalence of target organ damage [120, 121], as well as with a higher risk of future cardiovascular and renal events when compared to those with true BP control [107, 122, 123] which ultimately translates in greater healthcare costs [124, 125], [73]. The most recent European arterial hypertension guidelines have included OSAS among the causes responsible for true resistant hypertension [97].

## 18.6 Effects of Different Therapeutic Strategies on OSAS-Related Hypertension

### 18.6.1 Effects of Lifestyle Changes and Weight Loss on OSAS-Related Hypertension

Obesity is the single most important cause of OSAS and elevation in BP levels. It is thus expected that weight loss might reduce the severity of OSAS and BP levels. Indeed, in subjects who achieve significant reductions in body weight either through dietary [126], pharmacological [127], or surgical [128] measures, considerable reductions of various indices of OSA severity (i.e., AHI) and in BP levels have been reported. In particular, bariatric surgery has been shown to be a highly effective measure to achieve OSAS improvement and BP control as supported by a large meta-analysis of 136 randomized controlled trials [129]. It has to be emphasized that BP was normalized in 61.7% of patients and normalized or better controlled in 78.5%. Obstructive sleep apnea was cured in 85.7% of patients and was cured or improved in 83.6% of patients [129]. However, despite its efficacy, bariatric surgery is reserved for selected patients groups, i.e., type 2 diabetes mellitus, patients with severe obesity (BMI >35 kg/m$^2$), and moderately obese patients (BMI 30–35 kg/m$^2$) who are inadequately controlled by conventional medical and behavioral therapies to reduce body weight.

### 18.6.2 Effects of CPAP Treatment on OSAS-Related Hypertension

Nasal continuous positive airway pressure (CPAP) is currently considered the optimal treatment for OSA [130]. When properly implemented, CPAP not only provides relative instant relief of clinical symptoms [131] and reduction in the severity of OSA (i.e., AHI) but also improves many of the acute and chronic pathophysiological alterations induced by OSAS, such as arterial baroreflex impairment and sympathetic activation [44], systemic inflammation [28, 35, 37], endothelial dysfunction [27–29], RAAS activation [132], arterial stiffness [44, 45], and metabolic alterations (insulin resistance) [46].

Notably, CPAP use has been shown to induce marked and acute reductions in MSNA not only during nighttime sleep but also during daytime wakefulness if maintained in the long term [12] (Fig. 18.11).

Although improvements in these pathophysiological alterations should theoretically translate into substantial BP reductions, most interventional trials in OSAS

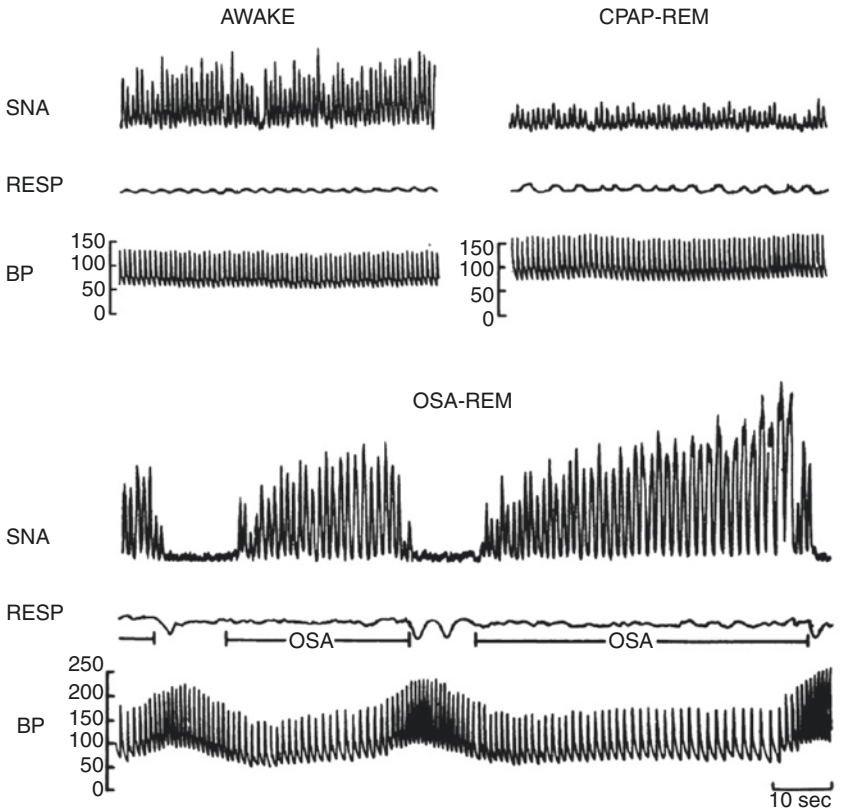



**Fig. 18.11** Elimination of apneas by continuous positive airway pressure (CPAP) reduces muscle sympathetic nerve activity (SNA) and prevents blood pressure (BP) surge during rapid eye movement (REM) sleep. Taken from Somers et al. [12] by permission

and subsequent meta-analyses have indicated that although CPAP has a significant effect on BP levels, the overall effect on 24-h, daytime, and nighttime systolic and diastolic ambulatory BP levels is rather small (in the order of 1–3 mmHg only) [133–135]. In spite of this, the effects of CPAP on BP levels have been shown to be variable as a function of patients' compliance with nocturnal CPAP, of the number of CPAP hours during nighttime, and of the implementation of ambulatory BP monitoring to assess its effects. In some subgroups of patients, in particular those with more severe OSAS [136] or with resistant hypertension [137], substantial effects of CPAP on BP levels have been reported. Indeed, effective CPAP treatment in patients with moderate-to-severe OSAS has been shown to induce important reductions both in day- and nighttime BP levels [136]. This has also been the case of subjects with resistant hypertension in whom regular CPAP implementation has resulted in marked reductions in ambulatory BP levels not only during nighttime but also during daytime wakefulness [137]. In a study addressing the effects of 1-year treatment with CPAP, whereas no effects on BP levels were observed in patients with BP controlled at baseline, marked and significant reductions in BP levels were observed in subjects with resistant hypertension [138].

A critical aspect when assessing the clinical effects of CPAP is to guarantee patients' adherence to therapy. Given the mechanical nature of CPAP (i.e., facial interface mask and the pressure required to prevent airway collapse), this therapeutic intervention is not always well accepted by patients specially those free of OSA-related symptoms. Indeed, compliance with CPAP has been shown to be directly related to the severity of OSAS [80]. On the other hand, several studies have indicated that in order to observe an effect of CPAP on BP, CPAP treatment should be implemented for enough time and for a sufficient number of hours per night and its effects on BP levels ideally assessed by means of ABPM. Proof of this has been provided by several studies in OSAS in which the benefits of CPAP have been evident only in subjects with confirmed resistant hypertension (i.e., persistent elevation both in office and out-of-office BP levels), in whom CPAP has been implemented for at least 3 months and for more than 5.8 h per night [139]. A positive effect of CPAP has also been reported in non-sleepy hypertensive patients with OSA, among whom the most significant reductions in BP have been observed in those patients using CPAP for more than 5.6 h per night [80]. Further studies are still needed, however, focusing on early start of CPAP treatment before hypertensive organ damage develops and makes hypertension control more difficult, in order to better determine whether CPAP implementation in OSAS patients with hypertension is indeed associated with better BP control rates and/or with reduction in the number of antihypertensive medications needed in order to achieve BP control.

A recent meta-analysis of RCTs [140] addressing the effect of CPAP on BP in patients with OSAS and hypertension evaluated seven RCTs reporting 24-h ABP data. Overall, CPAP was associated with significant reductions in 24-h ambulatory systolic (S) BP (−2.32 mm Hg; 95% confidence interval [CI], −3.65 to −1.00) and diastolic (D) BP (−1.98 mm Hg; 95% CI, −2.82 to −1.14). CPAP led to more significant improvement in nocturnal SBP than that in daytime SBP. Subgroup analysis showed that patients with resistant hypertension or receiving antihypertensive drugs benefited most from CPAP. Meta-regression indicated that CPAP compliance, age,

and baseline SBP were positively correlated with decrease in 24-h DBP, but not with reduction in 24-h SBP.

A recent study addressing the effect of CPAP treatment on BP in patients with OSA and resistant hypertension reported that CPAP treatment for 12 weeks compared with untreated OSA patients as controls resulted in a significant decrease in 24-h mean BP (3.1 mm Hg [95% CI, 0.6 to 5.6]; P = 0.02) and 24-h DBP (3.2 mm Hg [95% CI, 1.0 to 5.4]; P = 0.005) but not in 24-h SBP (3.1 mm Hg [95% CI, −0.6 to 6.7]; P = 0.10). Moreover, the percentage of patients displaying a nocturnal BP dipping pattern at the 12-week follow-up was greater in the CPAP group than in the control group (35.9% vs 21.6%; adjusted odds ratio [OR], 2.4 [95% CI, 1.2 to 5.1]; P = 0.02) [141].

Another study evaluated the effect of CPAP on BP in patients with resistant hypertension and OSAS in the frame of a RCT with blinded assessment of outcomes in 117 patients with moderate/severe OSAS, defined by an AHI ≥15. Subjects were randomized to 6-month CPAP treatment (57 patients) or no therapy (60 patients), while maintaining antihypertensive treatment. Clinic and 24-h ABPs were obtained before and after 6-month treatment. Primary outcomes were changes in clinic and ambulatory BPs and in nocturnal BP fall patterns. On intention-to-treat analysis, there was no significant difference in any BP change, neither in nocturnal BP fall, between CPAP and control groups. The best effect of CPAP was on nighttime SBP in per-protocol analysis, with a tendentially, although non significant, greater reduction of 4.7 mm Hg (95% Cl, −11.3 to +3.1 mm Hg; P = 0.24) and an increase in nocturnal BP fall of 2.2% (95% Cl, −1.6% to +5.8%; P = 0.25), in comparison with control group. The conclusion of this study is that CPAP treatment had no significant effect on clinic and ambulatory BPs in patients with resistant hypertension and moderate/severe OSAS, although a beneficial effect on nighttime SBP and on nocturnal BP fall might exist in patients with uncontrolled ambulatory BP levels [142].

Overall, also in the light of these recent trials, the reported poor efficacy of CPAP in reducing BP levels in OSAS patients with hypertension may depend on a combination of different factors, including poor patients' compliance with nocturnal CPAP use, too short treatment duration, inaccurate CPAP calibration, failure to use 24-h ABPM to evaluate CPAP effects on BP, and, most importantly, delayed use of CPAP in the clinical history of OSA patients, when hypertension may have become more resistant to treatment due to appearance of organ damage [80, 81].

## 18.7 Effects of Instrumental, Alternative Therapeutic Approaches to CPAP on OSAS-Related Hypertension

Recent studies have provided evidence that effective oral appliance (OA), i.e., an important alternative therapy to CPAP for patients with mild to moderate OSA, not only is effective in improving the severity of the disease but also in reducing BP levels in hypertensive OSAS patients [143, 144]. Although systematic reviews and a meta-analyses of available literature showed a favorable effect of OAs on SBP, MAP, and DBP, however, since most of the studies included were observational, this question remains still to be defined, ideally on the frame of well-designed interventional

RCT's [145]. Evidence has also been provided that treatment during 3 months with a specific oral jaw-positioning appliance improves cardiac autonomic modulation in otherwise healthy patients with OSA of mild degree [146] and that use of an adjustable mandibular advancement device is not inferior to CPAP in its impact on 24-h mean ambulatory BP [147].

## 18.8 Effects of Renal Sympathetic Denervation in OSAS-Related Resistant Hypertension

Sympathetic activation in OSAS determines an increase in sympathetic drive to the heart, the peripheral vasculature, and the kidneys. In relation to the latter, the sympathetic nerves arriving to the renal district have been identified as a major contributing factor to the pathophysiology of hypertension both in experimental models and in human studies [148]. This has been the basis for the development of interventional strategies aimed at modulating renal sympathetic nerve activity through radiofrequency catheter-based renal sympathetic denervation (RND) [149]. In subjects with uncontrolled hypertension, RND has been shown to induce significant reductions in renal sympathetic efferent nerve activity, in whole-body sympathetic nerve activity and norepinephrine spillover, as well as substantial and sustained reductions in BP levels [150]. A small, interventional study in OSAS patients who were refractory to lifestyle modifications, weight loss, pharmacological treatment, and CPAP have also suggested that RND may represent an effective strategy for the management of resistant hypertension associated with OSAS, inducing significant and sustained changes in BP levels at 3 and 6 months of follow-up [151]. Remarkably, the changes in BP levels reported in this study have also been accompanied by improvements in OSAS severity as indicated by the significant reductions in AHI at 3 and 6 months after denervation [151]. Renal sympathetic denervation might thus represent a potentially useful option for the management of resistant hypertension in OSAS patients, who are refractory to lifestyle modifications, weight loss, pharmacological treatment, and CPAP. Nonetheless, given the very small sample size of this paper, adequately powered longitudinal studies are needed to confirm these anecdotal findings and to assess the long-term impact of RND on hypertension control, as well as its benefits in terms of organ damage and incidence of cardiovascular morbid-mortality in subjects with OSAS.

## 18.9 Do Different Antihypertensive Drug Classes Have Different Effects on OSAS-Related Hypertension?

Different antihypertensive drug classes might have a differential effect on the pathophysiological mechanisms involved in the pathogenesis of OSAS-related hypertension. However, the few studies that have comparatively assessed the BP-lowering effects of different drug classes in OSAS have been of small size, and their statistical power was limited to derive consistent conclusions. In a randomized study assessing the effects of different classes of antihypertensive drugs (i.e., beta-blockers, calcium

antagonists, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and thiazide diuretics) on office and ambulatory BP levels in patients with hypertension and OSAS, no significant differences between drug classes were observed in their ability to reduce office and daytime ambulatory BP levels. However, treatment with β-blockers was more effective in reducing nighttime ambulatory BP than administration of other compounds, probably through their effects on sympathetic activation. In general, however, no consistent evidence has been provided supporting a superior antihypertensive efficacy of any antihypertensive drug in OSAS patients [152]. Long-term effects of treatment with different antihypertensive agents on hypertension severity in OSAS have not been systematically addressed in clinical trials, however. Evidence is therefore still needed in order to identify preferred compounds for an adequate BP control in this group of high-risk patients.

Recent studies in resistant hypertension have suggested that spironolactone should be considered in all patients with uncontrolled hypertension on three or more antihypertensive agents [153]. In some studies, addition of spironolactone in doses of 25–50 mg a day to the current antihypertensive treatment in resistant hypertensive patients was shown to reduce the severity of OSAS on top of its BP-lowering effects [25]. This is in line with the concept that aldosterone-mediated chronic fluid retention may influence severity of OSA.

Finally, several studies have explored the role of chronotherapy for improving BP control and profiles of BP variation in OSAS. Evidence from a crossover study indicated that evening dosing of antihypertensive drugs improves nighttime BP and dipping status in non-sleepy patients with OSA, irrespective of CPAP application [154]. Another study by Kario et al. showed that nighttime dosing of both vasodilating and sympatholytic antihypertensive drugs is effective to reduce sleep BP but with different BP-lowering profiles [155].

**Conclusions**

The pathogenesis of OSAS-related hypertension is likely to be multifactorial, involving alterations in several regulatory systems. OSAS is associated with impairment in important mechanisms of cardiovascular regulation, in particular with neural central and reflex mechanisms involved in BP control.

However, the mechanisms by which OSAS promotes arterial hypertension still need to be better understood. Evidence has also been provided that independently of the presence of arterial hypertension, heart failure, or other comorbidities, OSAS is associated with important autonomic and hemodynamic changes which not only promote future development of hypertension but make hypertension occurring in OSAS more severe and resistant to antihypertensive treatment [51–54] and associated with profound alterations in day-to-night BP changes [52, 72, 73]. Remarkably, a dose-response relationship between OSAS severity and the degree of BP elevation [52, 72, 73] has been shown.

Although OSAS and drug-resistant hypertension are independent predictors of cardiovascular morbi-mortality, evidence from longitudinal studies is still needed to determine the actual prognostic relevance of OSAS-related hypertension. In a subject with resistant hypertension and suspected OSAS, ABPM should be performed whenever possible for confirmation of resistant

hypertension, for identification of alterations in day-night BP changes and in order to define the need of performing additional diagnostic procedures (i.e., polysomnography) and/or implementing more aggressive pharmacological or interventional strategies for the management of resistant hypertension. In turn, identification of OSAS and proper implementation of specific treatment strategies (i.e., CPAP) in subjects with resistant hypertension might favor achievement of BP control optimizing cardiovascular protection. Evidence from additional longitudinal interventional studies in OSAS controlling for potential confounders (i.e., visceral obesity, increased BMI) is still needed, however, not only to determine the prognostic relevance of the interaction between OSAS and hypertension but also for determining whether treating OSAS in resistant HT confers significant benefits in terms of cardiovascular protection.

## References

1. Trzebski A (1992) Arterial chemoreceptor reflex and hypertension. Hypertension 19(6 Pt 1):562–566
2. Narkiewicz K, van de Borne PJ, Montano N et al (1998) Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea. Circulation 97(10):943–945
3. Narkiewicz K, van de Borne PJ, Pesek CA et al (1999) Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea. Circulation 99(9):1183–1189
4. Hedner JA, Wilcox I, Laks L et al (1992) A specific and potent pressor effect of hypoxia in patients with sleep apnea. Am Rev Respir Dis 146(5 Pt 1):1240–1245
5. Parati G, Di Rienzo M, Bonsignore MR et al (1997) Autonomic cardiac regulation in obstructive sleep apnea syndrome: evidence from spontaneous baroreflex analysis during sleep. J Hypertens 15(12 Pt 2):1621–1626
6. Narkiewicz K, Pesek CA, Kato M et al (1998) Baroreflex control of sympathetic nerve activity and heart rate in obstructive sleep apnea. Hypertension 32(6):1039–1043
7. Noda A, Nakata S, Koike Y et al (2007) Continuous positive airway pressure improves daytime baroreflex sensitivity and nitric oxide production in patients with moderate to severe obstructive sleep apnea syndrome. Hypertens Res 30(8):669–676
8. Ryan S, Ward S, Heneghan C, McNicholas WT (2007) Predictors of decreased spontaneous baroreflex sensitivity in obstructive sleep apnea syndrome. Chest 131(4):1100–1107
9. Bonsignore MR, Parati G, Insalaco G et al (2002) Continuous positive airway pressure treatment improves baroreflex control of heart rate during sleep in severe obstructive sleep apnea syndrome. Am J Respir Crit Care Med 166(3):279–286
10. Lombardi C, Parati G, Cortelli P et al (2008) Daytime sleepiness and neural cardiac modulation in sleep-related breathing disorders. J Sleep Res 17(3):263–270
11. Somers VK, Dyken ME, Mark AL, Abboud FM (1993) Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med 328(5):303–307
12. Somers VK, Dyken ME, Clary MP, Abboud FM (1995) Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 96(4):1897–1904
13. Leroy M, Van Surell C, Pilliere R et al (1996) Short-term variability of blood pressure during sleep in snorers with or without apnea. Hypertension 28(6):937–943
14. Shiomi T, Guilleminault C, Sasanabe R et al (1996) Augmented very low frequency component of heart rate variability during obstructive sleep apnea. Sleep 19(5):370–377

15. Narkiewicz K, van de Borne PJ, Cooley RL et al (1998) Sympathetic activity in obese subjects with and without obstructive sleep apnea. Circulation 98(8):772–776
16. Ali NJ, Davies RJ, Fleetham JA, Stradling JR (1992) The acute effects of continuous positive airway pressure and oxygen administration on blood pressure during obstructive sleep apnea. Chest 101(6):1526–1532
17. Narkiewicz K, Kato M, Phillips BG et al (1999) Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea. Circulation 100(23):2332–2335
18. Gonzaga CC, Gaddam KK, Ahmed MI et al (2010) Severity of obstructive sleep apnea is related to aldosterone status in subjects with resistant hypertension. J Clin Sleep Med 6(4):363–368
19. Pimenta E, Calhoun DA, Oparil S (2009) Sleep apnea, aldosterone, and resistant hypertension. Prog Cardiovasc Dis 51(5):371–380
20. Goodfriend TL, Calhoun DA (2004) Resistant hypertension, obesity, sleep apnea, and aldosterone: theory and therapy. Hypertension 43(3):518–524
21. Calhoun DA, Nishizaka MK, Zaman MA, Harding SM (2004) Aldosterone excretion among subjects with resistant hypertension and symptoms of sleep apnea. Chest 125(1):112–117
22. Pratt-Ubunama MN, Nishizaka MK, Boedefeld RL et al (2007) Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. Chest 131(2):453–459
23. Calhoun DA (2010) Obstructive sleep apnea and hypertension. Curr Hypertens Rep 12(3):189–195
24. Dudenbostel T, Calhoun DA (2012) Resistant hypertension, obstructive sleep apnoea and aldosterone. J Hum Hypertens 26(5):281–287
25. Gaddam K, Pimenta E, Thomas SJ et al (2010) Spironolactone reduces severity of obstructive sleep apnoea in patients with resistant hypertension: a preliminary report. J Hum Hypertens 24(8):532–537
26. Kato M, Roberts-Thomson P, Phillips BG et al (2000) Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. Circulation 102(21):2607–2610
27. Ip MS, Tse HF, Lam B et al (2004) Endothelial function in obstructive sleep apnea and response to treatment. Am J Respir Crit Care Med 169(3):348–353
28. Jelic S, Lederer DJ, Adams T et al (2010) Vascular inflammation in obesity and sleep apnea. Circulation 121(8):1014–1021
29. Butt M, Khair OA, Dwivedi G et al (2011) Myocardial perfusion by myocardial contrast echocardiography and endothelial dysfunction in obstructive sleep apnea. Hypertension 58(3):417–424
30. Jelic S, Padeletti M, Kawut SM et al (2008) Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. Circulation 117(17):2270–2278
31. Dyugovskaya L, Lavie P, Lavie L (2002) Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. Am J Respir Crit Care Med 165(7):934–939
32. Minoguchi K, Yokoe T, Tazaki T et al (2005) Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnea. Am J Respir Crit Care Med 172(5):625–630
33. Phillips BG, Narkiewicz K, Pesek CA et al (1999) Effects of obstructive sleep apnea on endothelin-1 and blood pressure. J Hypertens 17(1):61–66
34. Kanagy NL, Walker BR, Nelin LD (2001) Role of endothelin in intermittent hypoxia-induced hypertension. Hypertension 37(2 Part 2):511–515
35. Ryan S, Taylor CT, McNicholas WT (2005) Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. Circulation 112(17):2660–2667
36. Shamsuzzaman AS, Winnicki M, Lanfranchi P et al (2002) Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation 105(21):2462–2464

37. Yokoe T, Minoguchi K, Matsuo H et al (2003) Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. Circulation 107(8):1129–1134
38. Ohga E, Nagase T, Tomita T et al (1999) Increased levels of circulating ICAM-1, VCAM-1, and L-selectin in obstructive sleep apnea syndrome. J Appl Physiol 87(1):10–14
39. Doonan RJ, Scheffler P, Lalli M et al (2011) Increased arterial stiffness in obstructive sleep apnea: a systematic review. Hypertens Res 34(1):23–32
40. Tsioufis C, Thomopoulos K, Dimitriadis K et al (2007) The incremental effect of obstructive sleep apnoea syndrome on arterial stiffness in newly diagnosed essential hypertensive subjects. J Hypertens 25(1):141–146
41. Drager LF, Bortolotto LA, Figueiredo AC et al (2007) Obstructive sleep apnea, hypertension, and their interaction on arterial stiffness and heart remodeling. Chest 131(5):1379–1386
42. Shiina K, Tomiyama H, Takata Y et al (2006) Concurrent presence of metabolic syndrome in obstructive sleep apnea syndrome exacerbates the cardiovascular risk: a sleep clinic cohort study. Hypertens Res 29(6):433–441
43. Nagahama H, Soejima M, Uenomachi H et al (2004) Pulse wave velocity as an indicator of atherosclerosis in obstructive sleep apnea syndrome patients. Intern Med 43(3):184–188
44. Kohler M, Pepperell JC, Casadei B et al (2008) CPAP and measures of cardiovascular risk in males with OSAS. Eur Respir J 32(6):1488–1496
45. Drager LF, Bortolotto LA, Figueiredo AC et al (2007) Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med 176(7):706–712
46. Rasche K, Keller T, Tautz B et al (2010) Obstructive sleep apnea and type 2 diabetes. Eur J Med Res 15(Suppl 2):152–156
47. Basoglu OK, Sarac F, Sarac S et al (2011) Metabolic syndrome, insulin resistance, fibrinogen, homocysteine, leptin, and C-reactive protein in obese patients with obstructive sleep apnea syndrome. Ann Thoracic Med 6(3):120–125
48. Zirlik S, Hauck T, Fuchs FS et al (2011) Leptin, obestatin and apelin levels in patients with obstructive sleep apnoea syndrome. Med Sci Monit 17(3):CR159–CR164
49. Bonsignore MR, Esquinas C, Barcelo A et al (2012) Metabolic syndrome, insulin resistance and sleepiness in real-life obstructive sleep apnoea. Eur Respir J 39(5):1136–1143
50. Phillips BG, Kato M, Narkiewicz K et al (2000) Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. Am J Physiol Heart Circ Physiol 279(1):H234–H237
51. Mancia G, De Backer G, Dominiczak A et al (2007) 2007 Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 25(6):1105–1187
52. Grote L, Hedner J, Peter JH (2000) Sleep-related breathing disorder is an independent risk factor for uncontrolled hypertension. J Hypertens 18(6):679–685
53. Peppard PE, Young T, Palta M, Skatrud J (2000) Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 342(19):1378–1384
54. Nieto FJ, Young TB, Lind BK et al (2000) Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 283(14):1829–1836
55. Coccagna G, Mantovani M, Brignani F et al (1972) Continuous recording of the pulmonary and systemic arterial pressure during sleep in syndromes of hypersomnia with periodic breathing. Bull Physiopathol Respir (Nancy) 8(5):1159–1172
56. Steinhorst AP, Goncalves SC, Oliveira AT et al (2014) Influence of sleep apnea severity on blood pressure variability of patients with hypertension. Sleep Breath 18(2):397–401
57. Lavie P, Herer P, Hoffstein V (2000) Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. BMJ 320(7233):479–482
58. Davies CW, Crosby JH, Mullins RL et al (2000) Case-control study of 24 hour ambulatory blood pressure in patients with obstructive sleep apnoea and normal matched control subjects. Thorax 55(9):736–740

59. Pankow W, Nabe B, Lies A et al (1997) Influence of sleep apnea on 24-hour blood pressure. Chest 112(5):1253–1258
60. Portaluppi F, Provini F, Cortelli P et al (1997) Undiagnosed sleep-disordered breathing among male nondippers with essential hypertension. J Hypertens 15(11):1227–1233
61. Narkiewicz K, Montano N, Cogliati C et al (1998) Altered cardiovascular variability in obstructive sleep apnea. Circulation 98(11):1071–1077
62. Bixler EO, Vgontzas AN, Lin HM et al (2000) Association of hypertension and sleep-disordered breathing. Arch Intern Med 160(15):2289–2295
63. Duran J, Esnaola S, Rubio R, Iztueta A (2001) Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med 163(3 Pt 1):685–689
64. Tanigawa T, Tachibana N, Yamagishi K et al (2004) Relationship between sleep-disordered breathing and blood pressure levels in community-based samples of Japanese men. Hypertens Res 27(7):479–484
65. Young T, Peppard P, Palta M et al (1997) Population-based study of sleep-disordered breathing as a risk factor for hypertension. Arch Intern Med 157(15):1746–1752
66. Kiely JL, McNicholas WT (2000) Cardiovascular risk factors in patients with obstructive sleep apnoea syndrome. Eur Respir J 16(1):128–313
67. Baguet JP, Hammer L, Levy P, Pierre H, Rossini E, Mouret S et al (2005) Night-time and diastolic hypertension are common and underestimated conditions in newly diagnosed apnoeic patients. J Hypertens 23(3):521–527
68. Garrison RJ, Kannel WB, Stokes J 3rd, Castelli WP (1987) Incidence and precursors of hypertension in young adults: the Framingham Offspring Study. Prev Med 16(2):235–251
69. Bramlage P, Pittrow D, Wittchen HU et al (2004) Hypertension in overweight and obese primary care patients is highly prevalent and poorly controlled. Am J Hypertens 17(10): 904–910
70. O'Connor GT, Caffo B, Newman AB et al (2009) Prospective study of sleep-disordered breathing and hypertension: the Sleep Heart Health Study. Am J Respir Crit Care Med 179(12):1159–1164
71. Cano-Pumarega I, Duran-Cantolla J, Aizpuru F et al (2011) Obstructive sleep apnea and systemic hypertension: longitudinal study in the general population: the Vitoria Sleep Cohort. Am J Respir Crit Care Med 184(11):1299–1304
72. Somers VK, White DP, Amin R et al (2008) Sleep apnea and cardiovascular disease: an American Heart Association/American College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation 118(10):1080–1111
73. Calhoun DA, Jones D, Textor S et al (2008) Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension 51(6):1403–1419
74. Logan AG, Perlikowski SM, Mente A et al (2001) High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertens 19(12):2271–2277
75. Hla KM, Young T, Finn L et al (2008) Longitudinal association of sleep-disordered breathing and nondipping of nocturnal blood pressure in the Wisconsin Sleep Cohort Study. Sleep 31(6):795–800
76. Lavie-Nevo K, Pillar G (2006) Evening-morning differences in blood pressure in sleep apnea syndrome: effect of gender. Am J Hypertens 19(10):1064–1069
77. de la Sierra A, Segura J, Banegas JR et al (2011) Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension 57(5):898–902
78. Muxfeldt ES, Cardoso CR, Salles GF (2009) Prognostic value of nocturnal blood pressure reduction in resistant hypertension. Arch Intern Med 169(9):874–880

79. Muxfeldt ES, Bloch KV, Nogueira AR, Salles GF (2003) Twenty-four hour ambulatory blood pressure monitoring pattern of resistant hypertension. Blood Press Monit 8(5):181–185
80. Barbe F, Duran-Cantolla J, Capote F et al (2010) Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. Am J Respir Crit Care Med 181(7):718–726
81. Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M et al (2012) Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA 307(20): 2161–2168
82. McNicholas WT, Bonsigore MR (2007) Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. Eur Respir J 29(1):156–178
83. Otto ME, Belohlavek M, Romero-Corral A et al (2007) Comparison of cardiac structural and functional changes in obese otherwise healthy adults with versus without obstructive sleep apnea. Am J Cardiol 99(9):1298–1302
84. Tavil Y, Kanbay A, Sen N et al (2007) Comparison of right ventricular functions by tissue Doppler imaging in patients with obstructive sleep apnea syndrome with or without hypertension. Int J Card Imaging 23(4):469–477
85. Agrawal V, Vanhecke TE, Rai B et al (2009) Albuminuria and renal function in obese adults evaluated for obstructive sleep apnea. Nephron Clin Pract 113(3):c140–c147
86. Sim JJ, Rasgon SA, Derose SF (2010) Review article: managing sleep apnoea in kidney diseases. Nephrology (Carlton) 15(2):146–152
87. Yaggi HK, Concato J, Kernan WN et al (2005) Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 353(19):2034–2041
88. Selim B, Won C, Yaggi HK (2010) Cardiovascular consequences of sleep apnea. Clin Chest Med 31(2):203–220
89. Gottlieb DJ, Yenokyan G, Newman AB et al (2010) Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation 122(4):352–360
90. Redline S, Yenokyan G, Gottlieb DJ et al (2010) Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. Am J Respir Crit Care Med 182(2):269–277
91. Capampangan DJ, Wellik KE, Parish JM et al (2010) Is obstructive sleep apnea an independent risk factor for stroke? A critically appraised topic. Neurologist 16(4):269–273
92. Marshall NS, Wong KK, Liu PY et al (2008) Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. Sleep 31(8):1079–1085
93. Young T, Finn L, Peppard PE et al (2008) Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep 31(8):1071–1078
94. Persell SD (2011) Prevalence of resistant hypertension in the United States, 2003-2008. Hypertension 57(6):1076–1080
95. Egan BM, Zhao Y, Axon RN et al (2011) Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. Circulation 124(9):1046–1058
96. James PA, Oparil S, Carter BL et al (2014) 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 311(5):507–520
97. Mancia G, Fagard R, Narkiewicz K et al (2013) 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 31(7):1281–1357
98. Wolf J, Hering D, Narkiewicz K (2010) Non-dipping pattern of hypertension and obstructive sleep apnea syndrome. Hypertens Res 33(9):867–871
99. Staessen JA, Thijs L, Fagard R et al (1999) Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. JAMA 282(6):539–546

100. Sega R, Facchetti R, Bombelli M et al (2005) Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. Circulation 111(14):1777–1783
101. Kikuya M, Ohkubo T, Asayama K et al (2005) Ambulatory blood pressure and 10-year risk of cardiovascular and noncardiovascular mortality: the Ohasama study. Hypertension 45(2):240–245
102. Fagard RH, Celis H, Thijs L et al (2008) Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. Hypertension 51(1):55–61
103. Boggia J, Li Y, Thijs L et al (2007) Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. Lancet 370(9594):1219–1229
104. Hansen TW, Li Y, Boggia J, Thijs L et al (2011) Predictive role of the nighttime blood pressure. Hypertension 57(1):3–10
105. Clement DL, De Buyzere ML, De Bacquer DA et al (2003) Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. N Engl J Med 348(24):2407–2415
106. Fagard RH, Van Den Broeke C, De Cort P (2005) Prognostic significance of blood pressure measured in the office, at home and during ambulatory monitoring in older patients in general practice. J Hum Hypertens 19(10):801–807
107. Redon J, Campos C, Narciso ML et al (1998) Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: a prospective study. Hypertension 31(2):712–718
108. Dolan E, Stanton A, Thijs L et al (2005) Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. Hypertension 46(1):156–161
109. Hansen TW, Jeppesen J, Rasmussen S et al (2005) Ambulatory blood pressure and mortality: a population-based study. Hypertension 45(4):499–504
110. Sander D, Kukla C, Klingelhofer J et al (2000) Relationship between circadian blood pressure patterns and progression of early carotid atherosclerosis: A 3-year follow-up study. Circulation 102(13):1536–1541
111. Lurbe E, Redon J, Kesani A et al (2002) Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. N Engl J Med 347(11):797–805
112. Metoki H, Ohkubo T, Kikuya M et al (2006) Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline: the Ohasama study. Hypertension 47(2):149–154
113. Parati G, Lombardi C, Hedner J et al (2012) Position paper on the management of patients with obstructive sleep apnea and hypertension: joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by the members of European COST (COoperation in Scientific and Technological research) ACTION B26 on obstructive sleep apnea. J Hypertens 30(4):633–646
114. Parati G, Lombardi C, Hedner J et al (2013) Recommendations for the management of patients with obstructive sleep apnoea and hypertension. Eur Respir J 41(3):523–538
115. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G et al (2003) European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens 21(5):821–848. Epub 2003/04/26
116. Oikawa T, Obara T, Ohkubo T et al (2006) Characteristics of resistant hypertension determined by self-measured blood pressure at home and office blood pressure measurements: the J-HOME study. J Hypertens 24(9):1737–1743
117. de la Sierra A, Banegas JR, Oliveras A et al (2012) Clinical differences between resistant hypertensives and patients treated and controlled with three or less drugs. J Hypertens 30(6):1211–1216
118. Pickering TG, Davidson K, Gerin W, Schwartz JE (2002) Masked hypertension. Hypertension 40(6):795–796
119. Parati G, Ulian L, Santucciu C et al (1998) Difference between clinic and daytime blood pressure is not a measure of the white coat effect. Hypertension 31(5):1185–1189

120. Muxfeldt ES, Bloch KV, Nogueira Ada R, Salles GF (2005) True resistant hypertension: is it possible to be recognized in the office? Am J Hypertens 18(12 Pt 1):1534–1540
121. Oliveras A, Armario P, Hernandez-Del Rey R et al (2010) Urinary albumin excretion is associated with true resistant hypertension. J Hum Hypertens 24(1):27–33
122. Pierdomenico SD, Lapenna D, Bucci A et al (2005) Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension. Am J Hypertens 18(11):1422–1428
123. Salles GF, Cardoso CR, Muxfeldt ES (2008) Prognostic influence of office and ambulatory blood pressures in resistant hypertension. Arch Intern Med 168(21):2340–2346
124. Cuspidi C, Macca G, Sampieri L et al (2001) High prevalence of cardiac and extracardiac target organ damage in refractory hypertension. J Hypertens 19(11):2063–2070
125. Moser M, Setaro JF (2006) Clinical practice. Resistant or difficult-to-control hypertension. N Engl J Med 355(4):385–392
126. Johansson K, Hemmingsson E, Harlid R et al (2011) Longer term effects of very low energy diet on obstructive sleep apnoea in cohort derived from randomised controlled trial: prospective observational follow-up study. BMJ 342:d3017
127. Yee BJ, Phillips CL, Banerjee D et al (2007) The effect of sibutramine-assisted weight loss in men with obstructive sleep apnoea. Int J Obes 31(1):161–168
128. Pannain S, Mokhlesi B (2010) Bariatric surgery and its impact on sleep architecture, sleep-disordered breathing, and metabolism. Best Pract Res Clin Endocrinol Metab 24(5):745–761
129. Buchwald H, Avidor Y, Braunwald E et al (2004) Bariatric surgery: a systematic review and meta-analysis. JAMA 292(14):1724–1737
130. Leech JA, Onal E, Lopata M (1992) Nasal CPAP continues to improve sleep-disordered breathing and daytime oxygenation over long-term follow-up of occlusive sleep apnea syndrome. Chest 102(6):1651–1655
131. Kribbs NB, Pack AI, Kline LR et al (1993) Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. Am Rev Respir Dis 147(5):1162–1168
132. Bradley TD, Floras JS (2009) Obstructive sleep apnoea and its cardiovascular consequences. Lancet 373(9657):82–93
133. Alajmi M, Mulgrew AT, Fox J et al (2007) Impact of continuous positive airway pressure therapy on blood pressure in patients with obstructive sleep apnea hypopnea: a meta-analysis of randomized controlled trials. Lung 185(2):67–72
134. Haentjens P, Van Meerhaeghe A, Moscariello A et al (2007) The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome: evidence from a meta-analysis of placebo-controlled randomized trials. Arch Intern Med 167(8):757–764
135. Bazzano LA, Khan Z, Reynolds K, He J (2007) Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. Hypertension 50(2):417–423
136. Becker HF, Jerrentrup A, Ploch T et al (2003) Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. Circulation 107(1):68–73
137. Logan AG, Tkacova R, Perlikowski SM et al (2003) Refractory hypertension and sleep apnoea: effect of CPAP on blood pressure and baroreflex. Eur Respir J 21(2):241–247
138. Dernaika TA, Kinasewitz GT, Tawk MM (2009) Effects of nocturnal continuous positive airway pressure therapy in patients with resistant hypertension and obstructive sleep apnea. J Clin Sleep Med 5(2):103–107
139. Lozano L, Tovar JL, Sampol G et al (2010) Continuous positive airway pressure treatment in sleep apnea patients with resistant hypertension: a randomized, controlled trial. J Hypertens 28(10):2161–2168
140. Hu X, Fan J, Chen S et al (2015) The role of continuous positive airway pressure in blood pressure control for patients with obstructive sleep apnea and hypertension: a meta-analysis of randomized controlled trials. J Clin Hypertens (Greenwich) 17(3):215–222

141. Martinez-Garcia MA, Capote F, Campos-Rodriguez F et al (2013) Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. JAMA 310(22):2407–2415
142. Muxfeldt ES, Margallo V, Costa LM et al (2015) Effects of continuous positive airway pressure treatment on clinic and ambulatory blood pressures in patients with obstructive sleep apnea and resistant hypertension: a randomized controlled trial. Hypertension 65(4):736–742
143. Sekizuka H, Osada N, Akashi YJ (2016) Effect of oral appliance therapy on blood pressure in Japanese patients with obstructive sleep apnea. Clin Exp Hypertens 38(4):404–408
144. Andren A, Hedberg P, Walker-Engstrom ML et al (2013) Effects of treatment with oral appliance on 24-h blood pressure in patients with obstructive sleep apnea and hypertension: a randomized clinical trial. Sleep Breath 17(2):705–712
145. Iftikhar IH, Hays ER, Iverson MA et al (2013) Effect of oral appliances on blood pressure in obstructive sleep apnea: a systematic review and meta-analysis. J Clin Sleep Med 9(2):165–174
146. Coruzzi P, Gualerzi M, Bernkopf E et al (2006) Autonomic cardiac modulation in obstructive sleep apnea: effect of an oral jaw-positioning appliance. Chest 130(5):1362–1368
147. White DP, Shafazand S (2013) Mandibular advancement device vs. CPAP in the treatment of obstructive sleep apnea: are they equally effective in Short term health outcomes? J Clin Sleep Med 9(9):971–972
148. DiBona GF, Kopp UC (1997) Neural control of renal function. Physiol Rev 77(1):75–197
149. Doumas M, Faselis C, Papademetriou V (2011) Renal sympathetic denervation in hypertension. Curr Opin Nephrol Hypertens 20(6):647–653
150. Schlaich MP, Sobotka PA, Krum H et al (2009) Renal sympathetic-nerve ablation for uncontrolled hypertension. N Engl J Med 361(9):932–934
151. Witkowski A, Prejbisz A, Florczak E et al (2011) Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. Hypertension 58(4):559–665
152. Ziegler MG, Milic M, Sun P (2011) Antihypertensive therapy for patients with obstructive sleep apnea. Curr Opin Nephrol Hypertens 20(1):50–55
153. Pimenta E, Calhoun DA (2010) Treatment of resistant hypertension. J Hypertens 28(11):2194–2195
154. Kasiakogias A, Tsioufis C, Thomopoulos C, Andrikou I, Aragiannis D, Dimitriadis K et al (2015) Evening versus morning dosing of antihypertensive drugs in hypertensive patients with sleep apnoea: a cross-over study. J Hypertens 33(2):393–400
155. Kario K, Kuwabara M, Hoshide S et al (2014) Effects of nighttime single-dose administration of vasodilating vs sympatholytic antihypertensive agents on sleep blood pressure in hypertensive patients with sleep apnea syndrome. J Clin Hypertens (Greenwich) 16(6):459–466

# Stress and Hypertension

# 19

Antoinette Marie Schoenthaler
and Diana Margot Rosenthal

## 19.1 Introduction

Psychosocial risk factors—defined broadly as the *influence of social factors on an individual's psychological process and perceptions or behavior and to the interrelation of behavioral and social factors*—have long been implicated as potential contributors to the etiology of hypertension (HTN) [1]. Central to this definition is the premise that psychosocial factors affect HTN through changes in psychobiological processes (i.e., stress tolerance) and/or through changes in individual's behaviors (i.e., adherence to treatment/diet). In recent years, researchers have sought to characterize the pathways through which psychosocial factors operate—the places they emerge, the people they affect, and the positive and negative health outcomes they are associated with—in order to develop intervention strategies targeted at modifying the psychobiological processes and individual behaviors that affect the course of HTN. As a result, national guidelines recommend psychosocial intervention as a means to prevent or delay the onset of HTN [2–4]. Public policymakers have also begun to consider the effects of psychosocial factors on population health in the development of public health strategies to reduce health inequities.

In this book chapter, we provide a synthesis of the literature to enhance our understanding of the psychosocial risk factors that contribute to HTN and provide directions for future research. This chapter is structured based on six major categories of psychosocial stressors: mental health (depression, anxiety, post-traumatic stress disorder [PTSD]), personality factors, occupational stressors, housing instability, interpersonal relationships (social support, racial discrimination, loneliness), and sleep quality (see Table 19.1).

A.M. Schoenthaler (✉) • D.M. Rosenthal
Center for Healthful Behavior Change, NYU School of Medicine, New York, NY, USA
e-mail: Antoinette.schoenthaler@nyumc.org



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_19

**Table 19.1** Characteristics of studies included in the book chapter

| Author | Stressor type | Study type | Psychosocial measure | Study population |
|---|---|---|---|---|
| Mauli et al. [5] | Depression | Prospective | CES-D | 2807 male and female volunteers |
| Everson et al. [6] | Hopelessness | Cohort | Two items on hopelessness | 2682 middle-aged males from Eastern Finland |
| Delaney et al. [7] | Depression | Prospective | CES-D | 3194 African American, Caucasian, Chinese, and Hispanic adults from the Multi-Ethnic Study of Atherosclerosis Study |
| Patten et al. [8] | Depression | Prospective | CIDI-SF | 12,270 normotensive participants from Canadian National Population Health Survey |
| Gangwisch et al. [9] | Depression, insomnia, sleep duration | Prospective | CES-D | 4913 adults from NHANES I |
| Ohira [10] | Depression, hostility | Cohort | Zung Self-Rating Depression Scale; anger Expression Scale; Framingham Tension Scale | 7193 adults from the Circulatory Risk in Communities Study |
| Janal and Roy [11] | Depression, hostility | Prospective | Beck Depression Inventory; Hostility and Direction Hostility Questionnaire | 483 African Americans with type I diabetes |
| Hildrum et al. [12] | Depression, anxiety | Prospective | ADI-12 Index, Hopkins Symptom Checklist-25, HADS | 17,410 males and females aged 20–67 from the Nord-Trøndelag Health Study |
| Ginty et al. [13] | Depression, anxiety | Cohort | HADS | 455 participants from the Dutch Famine Birth Cohort Study |
| Bacon et al. [14] | Anxiety, mood disorder | Prospective | Primary Care Evaluation of Mental Disorders; DSM | 197 normotensive patients |
| Chaudieu et al. [15] | Psychological distress, PTSD | Retrospective | Watson PTSD Inventory; Mini-international Neuropsychiatric Interview | 1662 elderly participants with exposure to trauma |
| Schutte et al. [16] | Psychological distress | Prospective | K6 | 107 South Africans |
| Murakami et al. [17] | Psychological distress | Cross-sectional | Battery of items created for the study | 4311 victims of the 2011 Tohoku tsunami |

| | | | | |
|---|---|---|---|---|
| Paulus et al. [18] | Psychological distress, PTSD | Retrospective | PTSD diagnosis and documented trauma exposure | 186 young male veterans |
| Mommersteeg et al. [19] | Personality factors | Prospective | 14-Item Type D Personality Scale; K6 | 1760 German airline manufacturing employees |
| Turiano et al. [20] | Personality Factors | Prospective | MIDUS Big Five scale | 1054 English-speaking adults living in the USA |
| Trudel-Fitzgerald et al. [21] | Personality factors | Cohort | Emotional vitality (derived from Short Form-36) and optimism indicators | 6384 British civil servants from Whitehall II cohort |
| Joshi et al. [22] | Occupational | Cross-sectional | Questionnaires of occupational status; socioeconomic status | 370 bus conductors |
| Djindjic et al. [23] | Occupational | Cross-sectional | Occupational Stress Index | 439 male professional drivers |
| Johansson et al. [24] | Occupational | Prospective | Number of hours worked per week; telephone interviews | 88 bus drivers |
| Hu et al. [25] | Occupational | Cross-sectional | Occupational stress from the CIDI-SF | 5976 community-dwelling individuals |
| Modrek and Cullen [26] | Occupational | Retrospective | Inpatient claims ICD9 codes, 401–404, or two outpatient claims with the same ICD9 codes | 13,000 employees from large aluminum company |
| Wright et al. [27] | Occupational | Prospective | PSS | 200 law enforcement officers |
| Wiernik et al. [28] | Occupational | Prospective | PSS | 3774 normotensive adults without cardiovascular or renal disease |
| Landsbergis et al. [29] | Occupational | Retrospective | Claims data from sickness, accident, and disability insurance | 9224 automobile employees |
| Smith et al. [30] | Occupational | Prospective | Two physicians claim services with HTN diagnosis within a 2-year period | 6644 workers from the Canadian Community Health Survey |
| Lamy et al. [31] | Occupational | Cohort | NWI-EO Questionnaire; Borg Scale; ERI Questionnaire | 1882 normotensive female hospital registered nurses and nursing assistants |
| Gilbert-Ouimet et al. [32] | Occupational | Prospective | Self-administered questionnaire | 1595 white-collar workers |
| Gebreab et al. [33] | Occupational | Cross-sectional | Global PSS; Weekly Stress Inventory; negative life events | 5301 African Americans from the Jackson Heart Study |
| Leigh and Du [34] | Occupational | Prospective | Hours and annual income | 17,295 employees from the Panel Study of Income Dynamics |

(continued)

**Table 19.1** (continued)

| Author | Stressor type | Study type | Psychosocial measure | Study population |
|---|---|---|---|---|
| Vijayaraghavan et al. [35] | Housing instability | Prospective | Composite measure for housing instability | 5115 males and females from CARDIA study |
| Hawkley et al. [36] | Loneliness | Prospective | UCLA Loneliness Scale-Revised | 229 White, Black, and Hispanic males and females aged 50–68 |
| Momtaz et al. [37] | Loneliness | Cross-sectional | Philadelphia Geriatric Center Morale Scale | 1880 community residents aged ≥60 years |
| Muennig et al. [38] | Social capital and support | Prospective | Social capital form using demographics | 33,994 nationally representative US sample |
| Yang et al. [39] | Social capital and support | Cohort | Clinical Dementia Rating by clinician | 1768 participants enrolled from studies of dementia and healthy aging |
| Davis et al. [40] | Racial discrimination | Cross-sectional | Questionnaire on self-reported experiences of discrimination | 356 African Americans from the Metro Atlanta Heart Disease Study (1999–2001) |
| Krieger and Sidney [41] | Racial discrimination | Prospective | Questionnaire on self-reported experiences of discrimination and unfair treatment | 4086 Black and White males and females from CARDIA study |
| Cozier et al. [42] | Racial discrimination | Prospective | Questionnaire regarding racism | 64,500 females from Black Women's Health Study |
| Clark et al. [43] | Interpersonal relationships | Cohort | Revised Conflict Tactics Scale | 9669 young adults from the National Longitudinal Study of Adolescent Health |
| Capistrant et al. [44] | Interpersonal relationships | Prospective | Care recipient's report of how much assistance they received with activities of daily living and instrumental activities of daily life in the past month | 5708 US adults aged 50+ years and their spouses |
| Vozoris et al. [45] | Insomnia | Cross-sectional | DSM-IV-TR | 12,643 participants from 2005–2006 to 2007–2008 NHANES surveys |
| Fernandez-Mendoza et al. [46] | Insomnia | Cohort | Insomnia; objective short sleep duration; 16-channel polysomnography; electroencephalogram; electroculogram | 1741 males and females randomly selected from Central Pennsylvania |

| | | | | |
|---|---|---|---|---|
| Fung et al. [47] | Sleep disorders and breathing | Prospective | Decreased slow-wave sleep; in-home sleep night polysomnography (PSG); total sleep duration | 3135 elderly males (age ≥ 65 years) |
| Fung et al. [48] | Sleep disorders and breathing | Prospective | Actigraphy-measured sleep variables | 853 elderly males (age ≥ 65 years) |
| Gupta and Knapp [49] | Sleep disorders and breathing | Retrospective | ICD9 codes for obstructive sleep apnea and insomnia | 7234 patients from National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey |
| Bansil et al. [50] | Sleep disorders and breathing | Cross-sectional | Presence of sleep disorders using items from NHANES survey | 10,308 US adults from NHANES (2005–2008) |
| Chouchou et al. [51] | Sleep disorders and breathing | Prospective | Sympathetic sleep fragmentation; Epworth Sleepiness Scales; St. Mary's Hospital Sleep Questionnaire | 780 participants from the PROOF-SYNAPSE study |

*CES-D* Center for Epidemiologic Studies Depression, *CIDI-SF* Composite International Diagnostic Interview-Short Form, *NHANES* National Health and Nutrition Examination Survey, *HADS* Hospital Anxiety and Depression Scale, *DSM Diagnostic and Statistical Manual of Mental Disorders*, *K6* Kessler Screening for Psychological Distress, *MIDUS* Midlife in the United States, *PSS* Perceived Stress Scale, *NWI-EO* Nursing Work Index-Extended Organization, *ERI* Effort-Reward Imbalance Questionnaire

## 19.2 Mental Health

### 19.2.1 Depression

Much of the previous research has focused on the biological and behavioral mechanisms that may explain how depression relates to incident HTN. Specifically, since depression and HTN share common biologic and behavioral characteristics, both diseases tend to be risk factors of each other [3, 4, 52]. For example, several studies have documented higher rates of unhealthy lifestyle behaviors such as physical inactivity, smoking, alcohol abuse, and obesity with an increased risk of HTN among individuals with depressive symptomatology [4, 52, 53]. Gender, age, and race/ethnicity have also been frequently explored as moderators of the depression-HTN association. In a prospective study, women with greater depressive symptomatology (assessed by the Center for Epidemiologic Studies Depression (CES-D) scale) [52] exhibited higher systolic blood pressure (SBP) over the 29-year follow-up; the reverse was true for men [53]. In another study, men reporting high levels of hopelessness, a subcomponent of depression, were three times more likely to develop HTN over a 4-year period than men who were not hopeless (95% confidence interval [95CI], 1.56–6.67) [54]. Using the CES-D or the use of antidepressant medication as a marker of depression, Delaney et al. [55] found no association between depressive symptoms and incident HTN at 2 years among a multiethnic sample [55]. However, a diagnosis of major depression was associated with a 60% increased risk of developing HTN over a 10-year period in the Canadian National Population Health Survey (hazard ratio [HR],1.6; 95CI, 1.2–2.1) [56].

To extend these findings, Gangwisch et al. [57] assessed insomnia and sleep duration as mediators of the depression-HTN link in a prospective cohort from the first National Health and Nutrition Examination Survey (NHANES I). Consistent with predictions, the presence of depression (CES-D) and sleep duration (either short or long) was associated with higher HTN incidence; middle-aged subjects (ages 32–59 years) with depression at baseline had a 44% greater odds of being diagnosed with HTN over the 10-year period [57]. Hostility has also been examined as a potential moderator of the depression-HTN association. Men with "anger-in" scores (i.e., suppressed anger) in the highest tertile had a 1.5-fold age-adjusted relative risk of HTN in the Circulatory Risk in Communities Study as compared with those in the lowest tertile; there was no association in women [58]. High hostility scores were also associated with incident HTN, after adjusting for depression (Beck Depression Inventory) in a prospective study of African Americans with type 1 diabetes [5].

### 19.2.2 Comorbid Anxiety and Depression

HTN incidence has oftentimes been precipitated by the dual effects of anxiety and depression. In a prospective study of adults with three study points (baseline, years 11 and 22), symptoms of anxiety and depression (measured by

the ADI-12 Index, Hopkins Symptom Checklist-25, and Hospital Anxiety and Depression Scale (HADS)) showed a negative association with incident HTN such that higher symptomatology (≥80th percentile) predicted lower SBP and diastolic BP (DBP; odds ratio [OR], 0.80; 95CI, 0.70–0.92) and a higher odds of hypotension (BP < 120/75 mmHg; OR, 1.20; 95CI, 1.05–1.36) after 22 years of follow-up [6]. In contrast, increases in symptom severity, assessed with the HADS, were associated with an increased likelihood of HTN in the Dutch Famine Birth Cohort Study [7]. Finally, the diagnosis of an anxiety disorder was associated with a fourfold increase in the risk of developing HTN 1 year later (95CI, 1.18–14.56) in a cohort of normotensive individuals, while having a mood disorder [8].

### 19.2.3 Psychological Distress

Psychological distress refers to *the unique discomforting, emotional state experienced by an individual in response to a specific stressor or demand that results in harm, either temporary or permanent, to the person* [9]. Exposure to traumatic life events induces high levels of psychological distress including PTSD. In a retrospective study of elderly participants, those who reported reexperiencing trauma-related symptoms exhibited significantly higher rates of HTN than those who reported no symptom reoccurrence (OR, 1.32; 95CI, 0.96–1.82) [10]. Using the short Kessler Screening for Psychological Distress, high levels of distress predicted incident HTN in a South African cohort. Higher levels of "nervousness" in particular were associated with a twofold increase in the risk of developing HTN (95CI, 1.23–3.26) [11].

A cross-sectional study conducted 7–19 weeks after the 2011 Tohoku tsunami showed that a natural disaster creating prolific damages such as disruptions in amenities (i.e., gas supply) and discontinuity of everyday routines (i.e., taking antihypertensive medications) was associated with higher BP levels among victims in areas of more flooding [12]. Among victims not on antihypertensive medications at baseline, there was a dose-dependent association between BP and flooding height above sea level and disruption of the gas supply [12]. In a second study, young male veterans with PTSD referred to outpatient psychiatry in a Veterans Affairs Healthcare System had significantly higher BP compared to those without PTSD (BP, 133.8/87.6 vs. 122.3/78.6 mmHg). The prevalence of HTN was 34.1% among patients with PTSD compared to 16.3% without PTSD [13].

### 19.2.4 Stress-Induced Paroxysmal Hypertension

Paroxysmal hypertension or pseudopheochromocytoma is characterized by sudden onsets of hypertensive paroxysms, BP elevation associated with physical symptoms (i.e., headache, flushing, fatigue, dizziness), and, in many cases, is linked to psychosocial factors such as a history of severe abuse or trauma, panic disorder, or defensive personality [14, 59]. This distinct psychosocial profile provides an important diagnostic clue and enables a confident diagnosis of pseudopheochromocytoma

rather than a diagnosis by default [19]. Despite this, many physicians are unfamiliar with the underlying cause of the condition and feel ill-equipped to treat it [15]. An evaluation of patient's psychosocial profile would prove to be an extremely valuable first step in identifying the appropriate course of treatment to both manage BP and mitigate the psychological problems that perpetuate the condition [21].

## 19.3 Personality Factors

Similar to research on mental health, studies linking attributes of personality to HTN incidence have been inconsistent. Mommersteeg et al. [16] found no association between Type D personality (negative affectivity; social inhibition) and HTN in a 7-year study of German airline manufacturing employees. Alternatively, using "the Big Five personality traits" of neuroticism, extraversion, openness, conscientiousness, and agreeableness, Turiano et al. [17] found that higher levels of conscientiousness predicted lower BP over a 10-year period, while higher levels of neuroticism predicted higher BP. Higher levels of psychological well-being (i.e., feeling full of life, optimism) were associated with 9–11% reduction in HTN risk in a prospective study of British civil servants from the Whitehall II cohort [18].

## 19.4 Occupational Stress

Majority of evidence on occupational stress stems from cross-sectional studies that focus on specific professions and explore common themes including job insecurity, work hours, job strain, job control, and wages. In a study of bus conductors, the prevalence of HTN gradually increased as the duration of service increased, with the highest rate (36.3%) among those with service duration >30 years [19]. A cross-sectional study of male professional drivers (city and intercity bus drivers, truck and taxi drivers) [20] showed associations between the Occupational Stress Index (OSI; i.e., jobs characterized by high demand, conflict/uncertainty, underload, time pressure, aversive exposures) and HTN (OR, 5.5; 95CI, 2.24–7.95). Total OSI had a gradient effect demonstrating that BP readings were highest among city bus drivers and the lowest in truck and taxi drivers. There was also a strong association between total OSI and HTN (OR, 5.59; 95CI, 2.24–7.95). Underload (short-cycle monotonous work) was the strongest individual correlate of HTN (OR, 1.18; 95CI, 1.04–2.58) [20]. Likewise, a prospective study of bus drivers showed that the average number of hours of driving per week predicted higher DBP over a 2-year period [21]. Finally, a cross-sectional study [22] sought to determine the relative contributions of specific types of stressors (work or home) of HTN in a cohort of men and women. In the total sample, general stress was associated with HTN (OR, 1.25; 95CI, 1.08–1.45), accounting for 9.1% of the increased risk [22]. Women showed a greater risk of HTN if they experienced stress at work or at home (OR, 1.29; 95CI, 1.03–1.61 and OR, 1.23; 95CI, 1.00–1.51, respectively); this relationship was not significant in men.

The role of psychosocial stressors on HTN incidence is also dependent on factors concurrent with the occupation itself: working conditions, work environment, and job insecurity. Regarding job insecurity, a retrospective study examined the impact of downsizing on HTN risk over a 5-year period among 13,000 employees from a large aluminum company [23]. While salaried workers had lower rates of HTN overall, individuals that survived layoffs at high-layoff plants exhibited an elevated risk of being diagnosed with HTN at the 5-year follow-up (OR, 1.60; 95CI, 1.04–2.48) [23]. Increases in area-level unemployment were also associated with a higher incidence of HTN. In a prospective study, occupational status related to being a law enforcement officer predicted higher levels of SBP across the 7-year study [24]. Wiernik et al. [25] also analyzed the longitudinal effects of occupational status in combination with sex on HTN incidence. Baseline-perceived stress was associated with a linear increase in HTN incidence over an average of 6 years in women reporting medium or low occupational status [25].

Work organization factors such as high levels of job strain were associated with higher rates of incident HTN in a cohort of automobile manufacturer employees. Specifically, working 10 overtime hours per week was associated with 3.29 more claims for incident HTN per 1000 employees per year [26]. Using claims data from the sickness, accident, and disability insurance, there was a positive correlation among long work hours and psychological distress with incident HTN in a 6-year retrospective study [26]. Overall, skilled workers and assembly plant workers had higher rates of HTN; female production workers conferred the greatest risk. Finally, low job control was more strongly associated with incident HTN among men than women over a 9-year follow-up in the Canadian Community Health Survey [27].

The work environment and interactions between colleagues also significantly contribute to HTN incidence. Lamy et al. [28] examined the association between collective stressors at the work unit level (i.e., low support, poor information exchange, poor relationships with superiors, inability to take paid leave) and the 2-year incidence of HTN among normotensive female hospital registered nurses and nursing assistants. Results showed that organizational work factors influenced the 2-year risk of HTN independently of work factors at the individual level (i.e., workload and occupational stress), baseline BP, age, and body mass index [28]. Occupational stress measured as Effort-Reward Imbalance (ERI)—which suggests that work-related benefits depend upon a reciprocal relationship between efforts and rewards at work—was associated with incident HTN at 3 years in white-collar workers [29]. In women ≥45 years old, the cumulative incidence of HTN was 2.78 (95CI, 1.26–6.10) times higher among those exposed to ERI at both times [29].

Quite commonly, socioeconomic status is associated with or a contributing factor to the aforementioned occupational stressors. In a cross-sectional study of African Americans who participated in the Jackson Heart Study, higher income in women was associated with lower prevalence of HTN and lower levels of stress [30]. In a prospective study [31], low wages were also negatively associated with HTN incidence in employees. Doubling the wage by a 100% increase was associated with a 25–30% decrease in the risk of HTN [31].

## 19.5 Housing Instability

Housing instability—assessed as the frequency of moving, house crowding, and occupying a residence without paying rent or money—has also been associated with an increased risk of HTN. White women participating in the Coronary Artery Risk Development in Young Adults (CARDIA) study with unstable housing had four times the rate of incident HTN than white women with stable housing (incidence rate ratio (IRR), 4.7; 95CI, 2.4–9.2) [32].

## 19.6 Relationship Quality

Beyond the individual and everyday psychosocial stressors, interpersonal relationships or lack thereof increase the likelihood of developing HTN. Such stressors occur in forms of loneliness, social capital, racial discrimination, and caregiver demands.

### 19.6.1 Loneliness

Among a multiethnic sample in the Chicago Health, Aging, and Social Relations Study, higher scores on the UCLA Loneliness Scale-Revised at baseline were associated with a 3.6 mmHg increase in SBP each year of follow-up, which equated to a 14.4 mmHg greater increase in SBP over the 4-year study [33]. The effect of loneliness was independent of other risk factors for HTN including age, race, gender, cardiovascular (CV) medications, comorbid health conditions, depressive symptoms, social support, stress, hostility, and other CV risk factors (i.e., diabetes, stroke). Similarly, a cross-sectional study of 1880 community residents aged ≥60 years found that nearly one-third of respondents reported a high level of loneliness, which was associated with a HTN prevalence rate of 39% [34].

### 19.6.2 Social Capital and Support

Social capital, defined as the number of interactions with friends, neighbors, social clubs, etc., has shown to impact HTN outcomes [35]. Data from the Health and Retirement Study showed a 41% reduced odds (95CI, 0.42–0.84) in developing HTN over the 14-year study among older adults with 4–5 social ties [36]. However, in the Doetinchem Cohort Study, there was no association between negative or positive experiences of social support and risk of incident HTN over a 10-year period among middle-aged participants [37].

### 19.6.3 Racial Discrimination

Racial discrimination has been hypothesized to serve as a chronic psychosocial stressor contributing to the disproportionately higher rates of HTN among African

Americans as compared to Whites [38]. Much of the research to date has examined the effects of individual-level or interpersonal racism on HTN, with a majority employing cross-sectional study designs. While several studies have found no association between perceived racial discrimination and HTN in the cross-sectional studies [39], data from the Metro Atlanta Heart Disease Study [60] found that African Americans who reported moderate to very high levels of stress due to racial discrimination were twice as likely to be hypertensive than those with "no to low" stress. In the CARDIA study [61], experiences of racial discrimination and unfair treatment were associated with a 4–7 mmHg increase in BP among working-class African Americans. Finally, in a prospective study of African American women, positive associations between perceived racism and unfair treatment on incident HTN were only seen in two subgroups of women: those born outside the USA (IRR, 1.6; 95CI, 0.7–3.3) and who grew up in predominantly white neighborhoods (IRR, 1.7; 95CI, 0.9–3.4) [62].

### 19.6.4 Interpersonal Relationships

Interpersonal relationships in the form of positive and negative interactions can also have profound effects on HTN. In the National Longitudinal Study of Adolescent Health [40], adolescent males (grades 7–12) who experienced severe victimization had a 2.66 mmHg (95CI, 0.05–5.28) higher SBP and a 59% increased odds (95CI, 1.07–2.37) of incident HTN in adulthood compared to males who were not exposed. Intimate partner violence was not associated with BP in women. The demands of spousal care giving (assessed by the care recipient's report of how much assistance they need with activities of daily living in the past month) predicted incident HTN (risk ratio (RR), 1.36; 95CI, 1.01–1.83) among caregivers currently experiencing demands as well as those experiencing long-term demands (14+ h/week; RR, 2.29; 95CI, 1.17–4.49) [41].

## 19.7 Sleep Quality

Recent psychosocial literature has examined poor sleep quality and other sleep-related behaviors as risk factors for HTN. Under this umbrella, research includes sleep duration, sleep architecture, sleep disorders, and chronic insomnia.

### 19.7.1 Insomnia

Previous research has theorized that the frequency of insomnia symptoms leads to increased HTN risk. In a test of this hypothesis, Vozoris et al. [42] found no association between BP and insomnia symptoms (i.e., difficulty falling asleep, nocturnal awakenings, undesired early morning awakening, sleep maintenance, etc.) regardless of symptom frequency in the 2005–2006 and 2007–2008 NHANES surveys. In contrast, Fernandez-Mendoza et al. [43] found a significant relationship between

insomnia and HTN incidence in the Penn State Cohort. Individuals with chronic insomnia (duration of ≥1 year) in combination with objective short sleep duration (sleep <6 h during weeknights) exhibited a fourfold increase in incident HTN compared to normal sleepers (sleep ≥6 h; OR, 3.75; 95CI, 1.58–8.95) [43]. Moreover, individuals who reported poor sleep (moderate-to-severe complaint of difficulty falling asleep and/or staying asleep, early awakening, or non-restorative sleep) and had objective short sleep duration exhibited a 1.8 increased odds of developing incident HTN over the 7.5-year follow-up (95CI, 1.04–3.12) [43]. On the other hand, participants that reported chronic insomnia or poor sleep, but who also had objective sleep duration ≥6 h, had no increased risk of HTN.

### 19.7.2 Sleep Disorders and Breathing

Five studies of sleep quality, broadly defined as studies including sleep duration, sleep complaints, and sleep disorders, have examined associations with HTN. In a 2011 study, Fung et al. [44] used home polysomnography to examine the role of sleep-disordered breathing, sleep duration, and sleep architecture in older men (age ≥ 65 years). After adjusting for known CV risk factors and other key sleep variables (i.e., respiratory disturbance index, hypoxemia, central apnea index, total sleep duration in minutes, overall arousal index, sleep efficiency, wake after sleep onset in minutes, and % of time in sleep stages), men with poor sleep architecture (lowest percentile of slow-wave sleep [SWS]) had a 1.8-fold increase in incident HTN compared to men with the highest SWS (95CI, 1.18–2.80). In a second study with the same cohort of men, Fung et al. [45] found no association between total sleep time, percent sleep (estimate of sleep efficiency), sleep latency, wake after sleep onset, and incident HTN. Gupta and Knapp found that patients with obstructive sleep apnea plus insomnia had significantly higher odds of developing HTN (OR, 1.83; 95CI, 1.27–2.65) [46]. In a cross-sectional survey, sleep disorders by itself were not associated with HTN; however, significant associations were observed among adults with concurrent sleep disorders and short sleep (OR, 2.30; 95CI, 1.49–3.56) and with sleep disorders, short sleep, and poor sleep (OR, 1.84; 95CI, 1.13–2.98) [47]. In the PROOF-SYNAPSE study [48], sleep fragmentation measured by the autonomic arousal index was associated with elevated diurnal and 24-h SBP as well as a higher risk of 24-h systolic HTN (OR, 1.70; 95CI, 1.04–2.80).

## 19.8 Discussion

Psychosocial stressors play an important role in advancing our understanding of the etiology of HTN. Overall, there is strong evidence across various study designs, including prospective, retrospective, and cross-sectional cohorts, that occupational stressors, housing instability, loneliness, and stressors related to interpersonal relationships increase the risk of developing HTN. In some cases, the psychosocial stressor is an even more potent risk factor for HTN than traditional CV factors [49].

Despite this evidence, inconsistent results within subsets of psychosocial stressors such as mental health, racial discrimination, personality, and sleep quality persist. Namely, current studies exhibit three main limitations: (1) shortcomings in the study design, (2) confounding of moderating and mediating variables on the stressor-HTN association, and (3) limited inclusion of diverse populations. Below, we discuss each of these limitations in order to stimulate future research.

First, methodological differences across studies—in terms of measurement and study duration—hamper the ability to make definitive conclusions about impact. For example, a 2012 meta-analysis on the depression-HTN association concluded that much of the documented relationships between depression and HTN were based on study duration (longer duration associated with greater incidence) and the inclusion of a baseline depression measure [50]. Adequate length of follow-up is needed to identify a sufficient number of HTN cases in order to avoid type I error [51]. Evidence from this chapter also suggests that it is more advantageous to assess the cumulative effect of psychosocial factors overtime as this has implications for the directionality and significance of the association with HTN.

Studies within each psychosocial stressor also employed a diverse range of measures that limits the ability to decipher which stressor is of greatest relevance to incident HTN. For example, several mental health studies evaluated constructs of depression and anxiety separately (i.e., CES-D), while others used combined measures (i.e., HADS) [6, 57]. Similarly, measures of racial discrimination ranged from global assessments of experiences with discrimination to episodes related to specific settings (i.e., occupational or healthcare) [39, 62]. In examining sleep quality, the use of various measures across studies resulted in conflicting findings even within the same study sample. This was evident in the studies by Fung et al. [45], whereby the study using actigraphy-measured sleep variables resulted in a significant association with incident HTN in contrast to a second study [44] which found no relationship when home measurements were used. These findings suggest that objective measures of sleep duration may be of clinical significance rather than the subjective nature of sleep complaints. Therefore, careful consideration must be given to the variables being assessed as research suggests that there are particular dimensions of stressors that may not be implicated in the etiology of HTN.

Second, it is of utmost importance to examine the moderators and mediators of the stressor-HTN relationship. As shown in this chapter, findings often differed by sex and age of the participants. Thus, inconsistencies across studies may be an artifact of the analytic approach rather than a true null effect. More recently, researchers are examining the interaction between different types of psychosocial stressors such as depression and sleep. Findings indicate that treating sleep complications in depressed individuals may substantially mitigate HTN risk, more so than if they were treated alone. In order to advance the field, such work requires developing a conceptual model of the stressor-HTN associations, based on previous work, so that the extent to which these factors contribute to disease progression overtime may become clearer.

Third, few studies included a diverse cohort of participants that reflect the current demographic shift to an increasingly older and racial/ethnically diverse

population. Such variation is essential to examining whether these factors operate differently based on characteristics of the population. Indeed, studies examining the role of discrimination on the etiology of HTN are sorely absent from the literature. Finally, adequacy of the psychosocial measure may change depending on population being assessed, and selected measures should be carefully evaluated before being employed in the study.

In summary, this chapter calls for a whole-person approach—considering both clinical and psychosocial risk factors—when examining the development and progression of HTN. Psychosocial stress is often complex and multifaceted with stressors occurring across multiple settings and lifestyle behaviors playing a significant role as well. Despite the methodological challenges outlined above, it is critically important for healthcare organizations to work toward systematically screening for and treating patients with high psychosocial stress if we are to make a sustained impact on the relentless burden of HTN.

## References

1. Martikainen P, Bartley M, Lahelma E (2002) Psychosocial determinants of health in social epidemiology. Int J Epidemiol 31:1091–1093
2. Chobanian AV, Bakris GL, Black HR et al (2003) Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 42(6):1206–1252
3. Licht CM, de Geus EJ, Zitman FG et al (2008) Association between major depressive disorder and heart rate variability in the Netherlands Study of Depression and Anxiety (NESDA). Arch Gen Psychiatry 65:1358–1367
4. Jones-Webb R, Jacobs DR Jr, Flack JM, Liu K (1996) Relationships between depressive symptoms, anxiety, alcohol consumption, and blood pressure: results from the CARDIA Study. Coronary Artery Risk Development in Young Adults Study. Alcohol Clin Exp Res 20:420–427
5. Janal MN, Roy A (2011) Medical and psychological risk factors for incident hypertension in type1 diabetic African-Americans. Int J Hypertens 2011:856067
6. Hildrum B, Romild U, Holmen J (2011) Anxiety and depression lowers blood pressure: 22-year follow-up of the population based HUNT study, Norway. BMC Public Health 11:601
7. Ginty AT, Carroll D, Roseboom TJ et al (2013) Depression and anxiety are associated with a diagnosis of hypertension 5 years later in a cohort of late middle-aged men and women. J Hum Hypertens 27(3):187–190
8. Bacon SL, Campbell TS, Arsenault A, Lavoie KL (2014) The impact of mood and anxiety disorders on incident hypertension at one year. Int J Hypertens 2014:953094
9. Ridner SH (2004) Psychological distress: concept analysis. J Adv Nurs 45:536–545
10. Chaudieu I, Norton J, Ritchie K et al (2011) Late-life health consequences of exposure to trauma in a general elderly population: the mediating role of reexperiencing posttraumatic symptoms. J Clin Psychiatry 72(7):929–935
11. Schutte AE, Ware LJ, Huisman HW et al (2015) Psychological distress and the development of hypertension over 5 years in black South Africans. J Clin Hypertens (Greenwich) 17(2):126–133
12. Murakami H, Akashi H, Noda S et al (2013) A cross-sectional survey of blood pressure of a coastal city's resident victims of the 2011 Tohoku Tsunami. Am J Hypertens 26(6):799–807
13. Paulus EJ, Argo TR, Egge JA (2013) The impact of posttraumatic stress disorder on blood pressure and heart rate in a veteran population. J Trauma Stress 26(1):169–172

14. Mann SJ (2008) Severe paroxysmal hypertension (Pseudopheochromocytoma). Curr Hypertens Rep 10(1):12–18
15. Pickering TG, Clemow L (2008) Paroxysmal hypertension: the role of stress and psychological factors. J Clin Hypertens 10:575–581
16. Mommersteeg PM, Herr R, Bosch J et al (2011) Type D personality and metabolic syndrome in a 7-year prospective occupational cohort. J Psychosom Res 71(5):357–363
17. Turiano NA, Mroczek DK, Moynihan J, Chapman BP (2013) Big 5 personality traits and Interleukin-6: evidence for "healthy neuroticism" in a U.S. population sample. Brain Behav Immun 28:83–89
18. Trudel-Fitzgerald C, Boehm JK, Kivimaki M, Kubzansky LD (2014) Taking the tension out of hypertension: a prospective study of psychological well being and hypertension. J Hypertens 32(6):1222–1228
19. Joshi B, Joshi A, Katti SM et al (2013) A study of hypertension and its sociodemographic factors among bus conductors in North Karnataka. Ind J Pub Health Res Develop 4(2):39–43
20. Djindjic N, Jovanovic J, Djindjic B et al (2013) Work stress related lipid disorders and arterial hypertension in professional drivers—a cross-sectional study. Vojnosanit Pregl 70(6):561–568
21. Johansson G, Evans GW, Cederström C et al (2012) The effects of urban bus driving on blood pressure and musculoskeletal problems: a quasi-experimental study. Psychosom Med 74(1):89–92
22. Hu B, Liu X, Yin S et al (2015) Effects of psychological stress on hypertension in middle-aged Chinese: a cross-sectional study. PLoS One 10(6):0129163
23. Modrek S, Cullen MR (2013) Health consequences of the "great recession" on the employed: evidence from an industrial cohort in aluminum manufacturing. Soc Sci Med 92:105–113
24. Wright BR, Barbosa-Leiker C, Hoekstra T (2011) Law enforcement officer versus non-law enforcement officer status as a longitudinal predictor of traditional and emerging cardiovascular risk factors. J Occup Environ Med 53(7):730–734
25. Wiernik E, Nabi H, Pannier B et al (2014) Perceived stress, sex and occupational status interact to increase the risk of future high blood pressure: The IPC cohort study. J Hypertens 32(10):1979–1986
26. Landsbergis PA, Janevic T, Rothenberg L et al (2013) Disability rates for cardiovascular and psychological disorders among autoworkers by job category, facility type, and facility overtime hours. Am J Ind Med 56(7):755–764
27. Smith P, Mustard CA, Lu H, Glazier RH (2013) Comparing the risk associated with psychosocial work conditions and health behaviours on incident hypertension over a nine-year period in Ontario, Canada. Can J Public Health 104(1):e82–e86
28. Lamy S, De Gaudemaris R, Lepage B et al (2014) Psychosocial and organizational work factors and incidence of arterial hypertension among female healthcare workers: results of the organisation des Soins et Sante des Soignants cohort. J Hypertens 32(6):1229–1236
29. Gilbert-Ouimet M, Brisson C, Vezina M et al (2012) Repeated exposure to effort-reward imbalance, increased blood pressure, and hypertension incidence among white-collar workers. Effort-reward imbalance and blood pressure. J Psychosom Res 72(1):26–32
30. Gebreab SY, Diez-Roux AV, Hickson DA et al (2012) The contribution of stress to the social patterning of clinical and subclinical CVD risk factors in African Americans: the Jackson Heart Study. Soc Sci Med 75(9):1697–1707
31. Leigh JP, Du J (2012) Are low wages risk factors for hypertension? Eur J Pub Health 22(6):854–859
32. Vijayaraghavan M, Kushel MB, Vittinghoff E et al (2013) Housing instability and incident hypertension in the CARDIA Cohort. J Urban Health 90(3):427–441
33. Hawkley LC, Thisted RA, Masi CM, Cacioppo JT (2010) Loneliness predicts increased blood pressure: 5-year cross-lagged analyses in middle-aged and older adults. Psychol Aging 25(1):132–141
34. Momtaz YA, Hamid TA, Yusoff S et al (2012) Loneliness as a risk factor for hypertension in later life. J Aging Health 24(4):696–710

35. Muennig P, Cohen AK, Palmer A, Zhu W (2013) The relationship between five different measures of structural social capital, medical examination outcomes, and mortality. Soc Sci Med 85:18–26
36. Yang YC, Li T, Ji Y (2013) Impact of social integration on metabolic functions: evidence from a nationally representative longitudinal study of US older adults. BMC Public Health 13:1210
37. Croezen S, Picavet HSJ, Haveman-Nies A et al (2012) Do positive or negative experiences of social support relate to current and future health? Results from the Doetinchem Cohort Study. BMC Public Health 12:65
38. Brondolo E, Love EE, Pencille M et al (2011) Racism and hypertension: a review of the empirical evidence and implications for clinical practice. Am J Hypertens 24(5):518–529
39. Broman CL (1996) The health consequences of racial discrimination: a study of African Americans. Ethn Dis 6:148–153
40. Clark CJ, Everson-Rose SA, Alonso A et al (2014) Effect of partner violence in adolescence and young adulthood on blood pressure and incident hypertension. PLoS One 9(3):e92204
41. Capistrant BD, Moon JR, Glymour MM (2012) Spousal caregiving and incident hypertension. Am J Hypertens 25(4):437–443
42. Vozoris NT (2014) Insomnia symptom frequency and hypertension risk: a population-based study. J Clin Psychiatry 75(6):616–623
43. Fernandez-Mendoza J, Vgontzas AN, Liao D et al (2012) Insomnia with objective short sleep duration and incident hypertension: the Penn State Cohort. Hypertension 60(4):929–935
44. Fung MM, Peters K, Redline S et al (2011) Decreased slow wave sleep increases risk of developing hypertension in elderly men. Hypertension 58(4):596–603
45. Fung MM, Peters K, Ancoli-Israel S et al (2013) Total sleep time and other sleep characteristics measured by actigraphy do not predict incident hypertension in a cohort of community-dwelling older men. J Clin Sleep Med 9(6):585–591
46. Gupta MA, Knapp K (2014) Cardiovascular and psychiatric morbidity in obstructive sleep apnea (OSA) with insomnia (sleep apnea plus) versus obstructive sleep apnea without insomnia: a case-control study from a Nationally Representative US sample. PLoS One 9(3):e90021
47. Bansil P, Kuklina EV, Merritt RK, Yoon PW (2011) Associations between sleep disorders, sleep duration, quality of sleep, and hypertension: results from the National Health and Nutrition Examination Survey, 2005 to 2008. J Clin Hypertens (Greenwich) 13(10):739–743
48. Chouchou F, Pichot V, Pépin JL et al (2013) Sympathetic overactivity due to sleep fragmentation is associated with elevated diurnal systolic blood pressure in healthy elderly subjects: the PROOF-SYNAPSE study. Eur Heart J 34(28):2122–2131
49. Spruill TM (2010) Chronic psychosocial stress and hypertension. Curr Hypertens Rep 12(1):10–16
50. Meng L, Chen D, Yang Y et al (2012) Depression increases the risk of hypertension incidence: A meta-analysis of prospective cohort studies. J Hypertens 30(5):842–851
51. Markovitz JH, Jonas BS, Davidson K (2001) Psychological factors as precursors to hypertension. Curr Hypertens Rep 3:25–32
52. Radloff LS (1977) The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1:385–401
53. Shah MT, Zonderman AB, Shari R, Waldstein SR (2013) Sex and age differences in the relation of depressive symptoms with blood pressure. Am J Hypertens 26(12):1413–1420
54. Everson SA, Kaplan GA, Goldberg DE, Salonen JT (2000) Hypertension incidence is predicted by high levels of hopelessness in Finnish men. Hypertension 35:561–567
55. Delaney JA, Oddson BE, Kramer H et al (2010) Baseline depressive symptoms are not associated with clinically important levels of incident hypertension during two years of follow-up: the multi-ethnic study of atherosclerosis. Hypertension 55(2):408–414
56. Patten SB, Williams JV, Lavorato DH et al (2009) Major depression as a risk factor for high blood pressure: epidemiologic evidence from a national longitudinal study. Psychosom Med 71(3):273–279

57. Gangwisch JE, Malaspina D, Posner K et al (2010) Insomnia and sleep duration as mediators of the relationship between depression and hypertension incidence. Am J Hypertens 23(1):62–69
58. Ohira T (2010) Psychological distress and cardiovascular disease: the Circulatory Risk in Communities Study (CIRCS). J Epidemiol 20(3):185–191
59. Eisenhofer G, Sharabi Y, Pacak K (2008) Unexplained symptomatic paroxysmal hypertension in pseudopheochromocytoma. Ann N Y Acad Sci 1148:469–478
60. Davis SK, Liu Y, Quarells RC, Din-Dzietharn R (2005) Stress-related racial discrimination and hypertension likelihood in a population-based sample of African Americans: the Metro Atlanta Heart Disease Study. Ethn Dis 15:585–593
61. Krieger N, Sidney S (1996) Racial discrimination and blood pressure: the CARDIA study of young Black and White adults. Am J Public Health 86:1370–1378
62. Cozier Y, Palmer JR, Horton NJ et al (2006) Racial discrimination and the incidence of hypertension in US black women. Ann Epidemiol 16:681–687

# Central Nervous System Disorders: Transient Ischemic Attack and Stroke (Ischemic/Hemorrhagic)

# 20

Shoichiro Sato and Craig S. Anderson

Stroke is the second most common cause of death, accounting for approximately 10% of all deaths, and is the third most common cause of disability, on a global scale in 2010 [1]. About 70% of all strokes occur in low- and middle-income countries.

Stroke includes several diseases which cause occlusion or rupture of cerebral vessels leading to ischemic or hemorrhagic stroke. In the past, the definition of stroke was based on duration of symptoms. Symptoms lasting less than 24 h were considered as transient ischemic attack (TIA). However, advanced brain imaging techniques have led to a reconsideration of ischemic brain injury, such that up to one-third of patients with symptoms lasting less than 24 h actually have cerebral infarction. Subsequently, a new "tissue" definition of TIA has been produced of "a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarction" [2].

Ischemic stroke accounts for about 80–85% of strokes in western populations. It can be classified into several subtypes based on presumed ecology: large vessel atherosclerosis (e.g., artery-to-artery embolism from carotid stenosis or hemodynamic infarction), cardioembolism (e.g., embolism because of atrial fibrillation [AF] or valvular heart disease), cerebral small vessel disease (CSVD or the so-called lacunar stroke), and a heterogeneous mixture of other causes such as arterial dissection and

S. Sato
Neurological and Mental Health Division, The George Institute for Global Health, Faculty of Medicine, UNSW, PO Box M201, Missenden Road, Sydney, NSW 2050, Australia

Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan

C.S. Anderson (✉)
Neurological and Mental Health Division, The George Institute for Global Health, Faculty of Medicine, UNSW, PO Box M201, Missenden Road, Sydney, NSW 2050, Australia

Neurology Department, Royal Prince Alfred Hospital, Sydney, NSW, Australia
e-mail: canderson@georgeinstitute.org.au



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_20

hematological disorders. Hemorrhagic stroke can also be divided into two main types according to the site of the bleeding: spontaneous intracerebral hemorrhage (ICH) which occurs within the parenchyma of the brain, most commonly due to CSVD, or secondary to antithrombotic use (anticoagulation or antiplatelet therapy) or cerebral amyloid angiopathy. ICH can also be caused by structural brain lesions (e.g., arteriovenous malformation, cavernoma, etc.) and systemic diseases that affect platelet function or coagulopathy. Subarachnoid hemorrhage (SAH) is due to extravasation of blood into the subarachnoid space between the pial and arachnoid membranes and is mainly (about 80%) caused by the rupture or "blister" of an intracranial aneurysm.

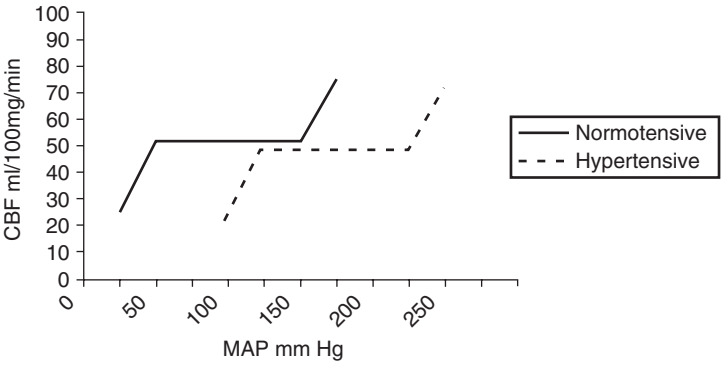
Elevated BP is the important underlying risk factor for all types of stroke, including TIA [3]. In this chapter, we review the acute hypertensive response, cerebral autoregulation, and BP management for ischemic/hemorrhagic stroke and TIA while introducing relevant trial results and highlighting current challenges and future directions.

## 20.1 Acute Hypertensive Response

Acute hypertensive response, which is a physiological response to brain damage [4], is defined as persistent elevation of BP, systolic BP of 140 mmHg or more, or diastolic BP of 90 mmHg or more, typically demonstrated on two recordings taken 5 min apart within the first 24 h of symptom onset [5]. In a systematic review, 52% of patients with stroke were reported to have an acute hypertensive response on admission to hospital. Possible causes of this response include poorly treated or undiagnosed hypertension, activation of the neuroendocrine system, increased cardiac output, pain, dehydration, and mental distress due to the setting of hospitalization. BP in patients with acute stroke gradually decreases by an average systolic BP level of 10 mmHg in the first 24 h and 20 mmHg during the first 10 days after onset, regardless of the use of antihypertensive medication [6].

## 20.2 Cerebral Autoregulation

Cerebral blood flow (CBF) is defined as the volume of blood flowing into a specified amount of brain in a specific time, and cerebral perfusion pressure is defined as the difference between mean arterial pressure and intracranial pressure. CBF is controlled by the cerebral perfusion pressure and the cerebrovascular resistance. Under normal conditions, cerebral perfusion pressure is maintained within a tight range (between 50 and 150 mmHg), despite fluctuations of mean arterial pressure, as shown with a solid curve in Fig. 20.1 [7]. This autoregulation is mediated by change in diameter of cerebral vasculature, which is one of the determinants of cerebrovascular resistance according to the change of BP. When BP decreases under the lower autoregulatory limit, there can be decreased cerebral perfusion pressure, with worsening hypoperfusion and potentially resulting in progression of cerebral ischemia,




CBF=cerebral blood flow; MAP=mean arterial pressure

**Fig. 20.1** Autoregulation maintains cerebral blood flow relatively constant between a mean arterial pressure of between 50 and 150 mmHg. The range may be right shifted in chronically hypertensive patients. *CBF* cerebral blood flow, *MAP* mean arterial pressure [From Ruland S, Aiyagari V (2007) Cerebral autoregulation and blood pressure lowering. Hypertension 49 (5):977–978]

and when BP exceeds the upper the limit, increased cerebral perfusion pressure could cause cerebral edema and hemorrhage. As long-standing high BP, or hypertension, may produce a rightward shift of the autoregulatory curve (*dotted curve* in Fig. 20.1), patients with hypertension are potentially less tolerant of decreased BP [8]. Moreover, as autoregulation may also be impaired after acute stroke, even in patients without history of hypertension, it is important to consider that a patient's cerebral perfusion pressure could change according to changes in systemic BP.

## 20.3 BP Management in Ischemic Stroke and TIA

### 20.3.1 Acute Ischemic Stroke and TIA

Most studies including meta-analysis are consistent in showing significant positive relationships between increasing systolic BP and various adverse outcomes such as death, disability, neurological deterioration, and recurrent ischemic events after stroke [9], whereas some studies suggest that low (<130 mm Hg) and large decreases in BP are also related to poor outcome [10]. However, such associations may not be causal, because patients with more severe stroke may have a more prominent acute hypertensive response and lower BP as a preterminal event. Even so, the concern of clinicians has been that the initiation of intensive BP-lowering treatment early after acute ischemic stroke could reduce cerebral edema and cause hemorrhagic transformation of ischemic tissue, leading to further mass effect and recurrent stroke and other serious cardiovascular events. Therefore, the issue of early intensive BP therapy has been of great interest of stroke trialists as whether it could improve outcomes.

The Scandinavian Candesartan Acute Stroke Trial (SCAST) [11] randomly allocated patients with acute stroke and systolic BP of 140 mmHg or higher and to treatment with the angiotensin-receptor blocker (ARB), candesartan, or placebo. Mean systolic BP difference between treatment groups at 7 days was 5 mmHg, and no differences were observed in the risk of the co-primary outcome, a composite vascular endpoint and functional outcome during 6 months after randomization. The Efficacy of Nitric Oxide in Stroke (ENOS) [12] randomly assigned patients with an acute stroke and systolic BP of 140–220 mmHg to a transdermal glyceryl trinitrate patch group or to an inert glyceryl trinitrate (control) group within 48 h of the onset of symptoms and continued for 7 days. The baseline mean BP of 167/90 mmHg was significantly decreased by 7/4 mmHg after the first dose in glyceryl trinitrate group compared to control group. The result was that the 90-day primary functional outcome did not differ in either treatment comparison nor was there any difference across any of the secondary outcome measures that included activities of daily living, cognition, health-related quality of life, and mood.

Even after these large-scale individual trials and a meta-analysis of them and others [13], controversy persists with regard to optimal BP range and therapeutic benefit of BP lowering in acute ischemic stroke. The Enhanced Control of Hypertension and Thrombolysis in Stroke Study (ENCHANTED) [14] aims to determine the effectiveness of intensive (systolic BP target 130–140 mmHg) vs. standard (<185 mmHg) BP lowering (BP arm) in over 2000 patients with acute ischemic stroke who are treated with recombinant tissue plasminogen activator (rtPA). The results of this study are projected to be available in 2019 and will hopefully provide further evidence regarding hyperacute BP management in thrombolysis-eligible patients with acute ischemic stroke.

As over half of patients who present with an acute stroke are already on antihypertensive treatment, a clinical dilemma has been as to whether to continue or stop these preexisting drugs during the acute phase after stroke. The Continue or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) [15] randomly assigned non-dysphagic patients with acute stroke either to continue taking or to stop the antihypertensive agents for 14 days. Although there were between-group differences in BP (13/8 mmHg) over the 2 weeks, there was no significant difference in the primary outcome of death or dependency at 14 weeks and death and serious cardiovascular events rate at 6 months. In the continue versus stop existing antihypertensive arm of the ENOS trial [12], where a subset of patients were allocated to continue antihypertensive medications as compared to patients who were randomized to stop them, the results were similarly neutral for any difference in functional outcome. Overall, these trials have shown that there is no clear benefit or harm by continuing preexisting antihypertensive drugs in the first few hours or days following acute ischemic stroke.

### 20.3.2 Acute Ischemic Stroke Treated with Thrombolysis

Thrombolytic therapy with intravenous rtPA is an established treatment for acute ischemic stroke despite increasing the early risks of symptomatic ICH and death [16].

Post-hoc analysis of the 624 patients who participated in the pivotal National Institutes of Neurological Diseases and Stroke (NINDS) rtPA trial that demonstrated the efficacy and the license for alteplase indicated that patients with a systolic BP of >185 mmHg and/or a diastolic BP of >110 mmHg before randomization who received BP lowering therapy had worse outcomes compared to those who did not receive such treatment, despite similar levels of elevated BP [17]. A study with another thrombolytic agent (streptokinase), the Australian Streptokinase (ASK) trial in which patients with SBP >185 mmHg were not excluded, showed an association between elevated BP at baseline and increased risk of major ICH [18]. In addition, large international registry studies of thrombolysis with alteplase conducted in 2000s, the Safe Implementation of Thrombolysis in Stroke-Monitoring STudy (SITS-MOST) [19] and the Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR) [20], also showed that elevated baseline systolic BP was associated with symptomatic ICH. Intriguingly, a recent large single-center observational study has shown that BP during the initial 24 h after ischemic stroke treated with intravenous thrombolysis or intra-arterial therapies depended on the vascular recanalization status (reopening or no reopening); a J-shaped association was evident between BP and outcome in no-reopening group, whereas the association was linear in the reopening group (lower BP, good outcome) [21].

The current American Heart Association (AHA)/American Stroke Association (ASA) guidelines recommend target BP levels of ≤185/110 mmHg before administration of intravenous rtPA and afterward of <180/105 mmHg for at least the first 24 h (Class I; Level of Evidence B) but without any recommendations about a lower level of BP control [22]. The previously mentioned BP Arm of the ENCHANTED study is addressing this issue and should elucidate the role of early intensive BP lowering for patients receiving thrombolysis, particularly as to whether the treatment reduces the risk of a poor outcome and symptomatic ICH [23].

### 20.3.3 Secondary Prevention in Ischemic Stroke and TIA

Treatment of hypertension is the most important secondary prevention strategy for patients with a history of ischemic stroke or TIA. The prevalence of hypertension in patients with ischemic stroke is 60–70% [24] and a near linear relationship between level of BP and risk of recurrent stroke and other major cardiovascular events (Fig. 20.2) [25].

Several randomized controlled trials have demonstrated clear benefits of long-term BP lowering for the secondary prevention of stroke. The Perindopril Protection against Recurrent Stroke Study (PROGRESS) [26], in particular, assigned participants with prior any stroke or TIA to the angiotensin-converting enzyme inhibitor (ACE-I), perindopril, alone or in combination with the diuretic, indapamide, or matching placebo(s). During an average of 4 years of follow-up, BP was 9/4 mmHg lower in the active treatment group as compared with the placebo group, and the treatment reduced the risk of fatal or nonfatal stroke (the primary endpoint) by 28%. A greater BP reduction (−12/5 mmHg) and risk reduction (43%) were observed in

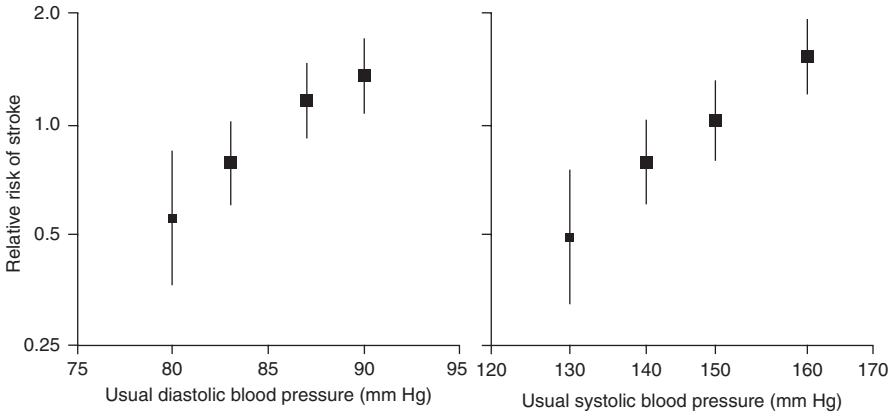



**Fig. 20.2** Relative risk of stroke according to usual diastolic and systolic blood pressure. *Vertical lines* represent 95% confidence intervals (CI), and *solid squares* are proportional to number of strokes in each category [From Rodgers A, MacMahon S, Gamble G et al (1996) Blood pressure and risk of stroke in patients with cerebrovascular disease. BMJ 313 (7050):147]

those patients who received combination therapy, whereas less BP reduction (−5/3 mm Hg) and no significant risk reduction were evident in those who received perindopril alone (Fig. 20.3) [26]. A post-hoc analysis of the trial showed that lower-achieved follow-up BP levels, down to approximately 115/75 mmHg, were associated with greater reduction in the rate of recurrent stroke and without any increased risks (i.e., J-curve) of recurrent events at the lowest BP levels [27]. The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial [28] in which an ARB, telmisartan, and placebo were compared among patients with acute ischemic stroke showed no significant effect on recurrent stroke despite a 4/2 mmHg lower BP in the active treatment group during an average of 2.5 years of follow-up. These two trials indicate that modest BP lowering through inhibition of the renin-angiotensin system does not translate into improved clinical outcomes and reduced short-term risk of recurrent stroke.

A recent updated meta-analysis has shown that every 10 mmHg reduction in systolic BP is associated with a significantly 26% reduced risk of stroke in patients with a history of cerebrovascular diseases [29], which supports an older meta-analysis of reduced recurrent stroke-associated greater magnitude of BP lowering [30]. However, clinical practice is strongly influenced by direct randomized evidence of any benefits and safety of more intensive long-term BP-lowering treatment. The most relevant in this regard is the Secondary Prevention of Small Subcortical Strokes (SPS3) trial [31], which randomized patients with CSVD lacunar stroke into two target systolic BP levels of <130 and 130–149 mmHg. After 1 year, the mean achieved systolic BP levels were 127 mmHg and 138 mmHg in the two groups, but after a mean 3.7 years of follow-up, there was no significant difference in rates of recurrent stroke, fatal or disabling stroke, and the composite outcome of myocardial infarction or vascular death. However, the rate of serious adverse events related to hypotension was similar in the two groups.

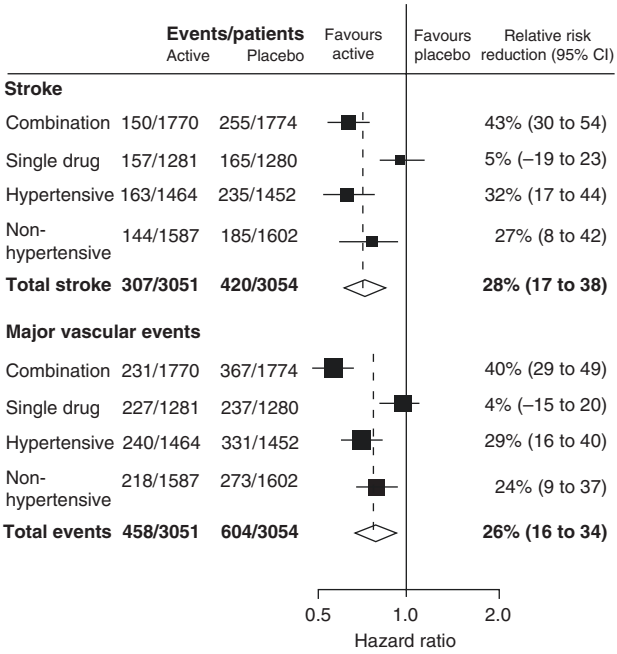



**Fig. 20.3** Effects of study treatment on stroke and major vascular events in subgroups of patients. Hazard ratios (and 95% confidence intervals [CI]) for hypertensive and non-hypertensive subgroups standardised to study-wide proportions of patients for whom combination or single-drug therapy was planned [From PROGRESS Collaborative Group (2001) Randomized trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 358 (9287):1033–1041]

There was also not enough information of a benefit of specific drug classes regarding secondary prevention after ischemic stroke and TIA. A meta-analysis based on 135,715 individuals from 22 trials did not show any substantial differences among different BP-lowering regimens on any of the major cardiovascular events (stroke, coronary heart disease, heart failure, and cardiovascular death) [32].

Most recently, the Systolic Blood Pressure Intervention Trial (SPRINT) [33] demonstrated the benefits of intensive BP control (systolic <120 mmHg) as compared to standard BP control (<140 mmHg) among subjects who were aged ≥50 years with hypertension and at high risk of cardiovascular disease without a history of diabetes mellitus or stroke. The trial showed a significant 25% relative risk reduction in the primary composite outcome of myocardial infarction, acute coronary syndrome, stroke, heart failure, or cardiovascular death). However, given that the treatment benefit of intensive BP control was mainly due to decreased risk of heart failure and death and that patients with prior stroke were excluded, there is uncertainty over the extrapolation of these findings into stricter BP lowering to a target of <120 mmHg in people with ischemic stroke or TIA.

An ongoing clinical trial focused on strict BP control to prevent recurrent vascular events in patients with stroke is the Stroke in Hypertension Optimal Treatment

(SHOT) [34], an open randomized trial with a multifactorial design comparing three different systolic BP targets (<145–135, <135–125, and <125 mmHg) and two different LDL-C targets. The trial aims to enroll 7500 participants who are aged 65 years or more with a history of hypertension and stroke or TIA within the previous 6 months.

## 20.4 BP Management in Hemorrhagic Stroke

### 20.4.1 Acute ICH

Elevated BP is observed in approximately four-fifths of patients with acute ICH [35], and a history of hypertension is associated with more frequent and higher levels of BP on presentation. A population-based study from the UK reported that poststroke BP was markedly elevated compared to usual premorbid levels in patients with acute ICH, whereas BP after major acute ischemic stroke was much closer to premorbid levels [36].

Elevated BP is also related to higher risk of neurological deterioration and poor outcome including death and disability [37]. In terms of increase in hematoma volume (or hematoma growth), which is a strong independent predictor of neurological deterioration and subsequent poor outcome after ICH [38], observational studies demonstrated that patients with elevated BP are more likely to have hematoma growth [39]. Furthermore, it is suggested that elevated BP was related to worsening of brain edema in patients with acute stroke by a prospective observational study of patients with either ischemic or hemorrhagic stroke enrolled within 3 h of onset which reported systolic BP during the initial 24 h was associated with an increased risk of brain edema [40].

There had been a concern against BP lowering in ICH regarding the potential risk of ischemia of brain tissue surrounding hematoma induced by possible depletion of cerebral perfusion pressure [41], particularly in patients with altered cerebral autoregulation [7]. Nevertheless, several observational studies have discredited the concern by showing no significant relationship between BP lowering and perihematomal cerebral blood flow in patients with acute ICH [42], and safety of BP lowering on cerebral blood flow in acute setting was confirmed in the Intracerebral Haemorrhage Acutely Decreasing Arterial Pressure (ICH-ADAPT) trial [43]. In ICH-ADAPT, 75 patients with small- to medium-sized ICH within 24 h of onset were randomized to BP lowering to a systolic BP target of <150 mmHg or <180 mmHg. There was no significant decrease in perihematomal cerebral blood flow measured with computed tomography perfusion imaging at 2 h (the primary outcome) in relation with intensive BP lowering.

The main phase of Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) [44] is the pivotal clinical trial that showed improved functional outcomes with no harm for patients with ICH who received target-driven, early intensive BP-lowering treatment. In INTERACT2, 2839 patients with imaging-confirmed ICH, elevated systolic BP (150–220 mmHg) were

randomly allocated to an intensive BP lowering to <140 mmHg within 1 h and continued for 7 days or standard management of systolic BP to <180 mmHg. The frequency of death or major disability (the primary outcome) was 52% and 56% in the intensive and standard BP-lowering treatment groups, respectively, producing an odds ratio (OR) of 0.87 (95% confidence interval [CI], 0.75–1.01; P = 0.06). Analyses on the prespecified key secondary outcome of an ordinal shift analysis of entire range of modified Rankin Scale demonstrated that the intensive BP-lowering group had significantly higher rates of functional recovery at 90 days (OR for greater disability 0.87; 95% CI 0.77–1.00) and significantly better health-related quality of life as measured on European Quality of Life Scale (EQ-5D) utility score, than the guideline group. Furthermore, the effects of intensive BP lowering were consistent across several prespecified subgroups including age, region of enrollment, time from onset to randomization, baseline severity, and hematoma volume. Although an imaging substudy of INTERACT2 including 967 patients who underwent sequential brain computed tomography demonstrated modest but insignificant reduction in hematoma growth during initial 24 h from intensive BP lowering, the effect becomes significant in a meta-analysis of four randomized controlled trials including INTERACT2 [45].

The most recently completed clinical trial of intensive BP lowering in acute ICH is the Antihypertensive Treatment for Acute Cerebral Hemorrhage (ATACH) II, which compared very early (<4.5 h) and "very intensive" BP lowering (SBP of <140 mmHg) using an intravenous nicardipine-based regime for 24 h and "standard" systolic BP reduction (systolic BP of 140–180 mmHg) [46]. The rate of death and disability at 90 days was 38.7% in the very intensive treatment group and 37.7% of the standard treatment group (adjusted relative risk 1.04, 95% confidence interval 0.85–1.27). Moreover, there was no significant difference between the groups in the distribution of scores on the mRS or the EQ-5D utility metric. While there were no overall significant differences in treatment-related serious adverse events within 72 h, there were significantly more renal-related adverse events in the more intensive group (9.0% versus 4.0%, p = 0.001) and borderline more serious adverse events in this group by 90 days (adjusted relative risk 1.30, 95% CI 1.00–1.69; p = 0.05). Intriguingly, the proportion of patients with hematoma growth, defined as >33% increase in the volume of ICH during the initial 24 h, was 18.9% and 24.4% in the intensive and standard treatment group, respectively (adjusted relative risk 0.78, 95% CI 0.58–1.03; p = 0.08). All the patients enrolled in the ATACH-II trial had elevated systolic BP of >180 mmHg (average at presentation 200 mmHg), while only about a half (48%) of participants in the INTERACT2 had this same level of systolic BP. Mean minimum systolic BP of intensive treatment group in ATACH-II was below 130 mmHg (129 mmHg and 122 mmHg for 0–2 and 2–24 h, respectively). The protocol-defined level for cessation of intravenous BP lowering in INTERACT2 was <130 mmHg whereas <110 mm Hg in the ATACH-II. A subanalysis of INTERACT2 demonstrated that achieved post-randomization systolic BP, which was the mean systolic BP during the initial 24 h, of 130–139 mmHg was associated with better outcomes, and modest increase in the risk of worse outcome was observed for achieved SBP <130 mmHg [47]. The differences between

INTERACT2 and ATACH-II suggest that very intensive and rapid BP lowering to treatment targets <130 mmHg in patients with very high BP could negate the benefit of the treatment.

### 20.4.2 Secondary Prevention in ICH

Poor BP control is related to increased risk of recurrence ICH regardless of subtype (i.e., lobar versus non-lobar) [48]. In PROGRESS trial, of 660 subjects with a history of ICH at baseline, a 49% (95% CI 20–67%) relative risk reduction was observed on recurrent stroke, and lower BP level was continuously associated with lower risk of recurrent ICH [27]. Similar effects of BP lowering for the prevention of ICH were also seen in the SPS3 trial [31], in which there was 63% relative risk reduction on ICH as compared to insignificant reductions in all recurrent stroke and recurrent ischemic stroke. The PRoFESS trial did not show any significant benefits of early initiation of BP lowering for total stroke or ICH [49], but a meta-regression analysis of all these randomized trials suggests that the PRoFESS findings may simply be explained by the very small systolic BP difference achieved between randomized groups, with a clear dose-response relationship apparent for systolic BP and reduction in ICH risk (Fig. 20.4) [50]. These data suggest that much stricter control BP than currently recommended for patients with a history of ICH is safe and could provide large benefits in terms of prevention of recurrent ICH and serious cardiovascular events.

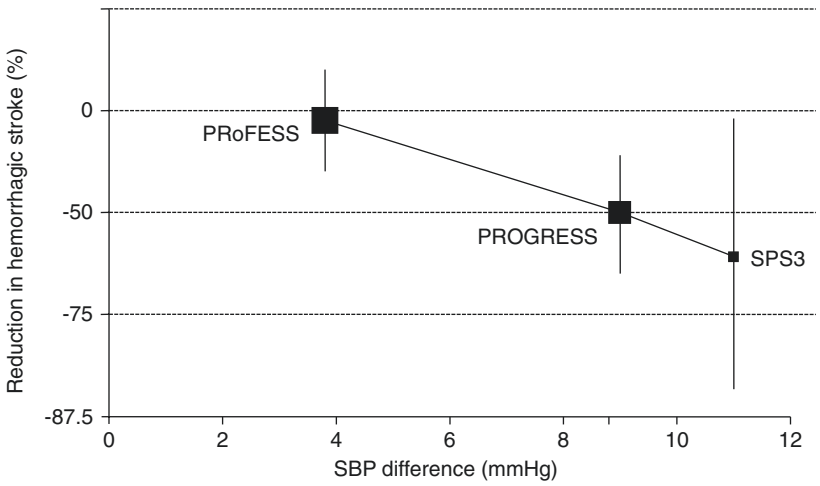



**Fig. 20.4** Reduction in hemorrhagic stroke vs. systolic blood pressure reduction in previous randomized controlled trials [From Sato S, Carcel C, Anderson CS (2015) Blood pressure management after intracerebral hemorrhage. Curr Treat Options Neurol 17 (12):49]

The ideal antihypertensive agent/regime to achieve and maintain good long-term BP control after ICH remains uncertain. Most patients with hypertension require two or more antihypertensive agents to achieve adequate BP control [51], whereas multiple tablets can negatively impact on adherence and/or attendance to scheduled visits [52]. Therefore, a simpler and more tolerable treatment regimen, such as a polypill approach, could achieve higher levels of BP control with adherence in this patient group than is currently being achieved in practice. The ongoing Triple therapy prevention of Recurrent Intracerebral Disease EveNts Trial (TRIDENT), which is a double-blind, placebo-controlled trial, aims to determine the effectiveness of more intensive BP lowering by a fixed low-dose combination of BP-lowering agents (telmisartan, amlodipine, and indapamide–"Triple Pill" strategy) on top of standard of care, on the time to first occurrence of recurrent stroke among over 4200 patients with ICH.

### 20.4.3 SAH

Hypertension is a risk factor for both the occurrence of aneurysmal SAH and its rebleeding. Rebleeding, which is often followed by elevated systolic BP (>150 mmHg), is most likely to occur in the first 24 h of initial bleeding, with a rate of 4–17% [53]. Elevated BP before aneurysm obliteration increases the risk of rebleeding and subsequent worse outcome. The AHA/ASA guidelines [54] recommend that between the time of symptom onset and aneurysm obliteration, BP should be controlled with a titratable agent to balance the risk of stroke, hypertension-related bleeding, and maintenance of cerebral perfusion pressure (Class I; Level of Evidence B). However, the optimal magnitude of BP control to reduce the risk of rebleeding has not been established, although a decrease in systolic BP to 160 mmHg would seem reasonable (Class IIa; Level of Evidence C). A multicenter observational study involving 5612 patients with aneurysmal SAH [55] showed that a systolic BP of between 120 and 140 mmHg was most common prior to rebleeding. It is also reported that despite an aggressive management strategy in which oral nimodipine was given unless systolic BP was less than 120 mmHg, 40 (7%) of 574 patients had rebleeding [56]. Thus, it is an unanswered question as to whether more intensive BP lowering than is currently recommended in guidelines provides any additional benefit to patients.

Delayed cerebral ischemia can be due to vasospasm from reversible narrowing of cerebral arteries. This complication most commonly occurs within 4–14 days after SAH, lasts for 2–4 weeks, and is a major contributor to morbidity and mortality [57]. Despite lacking of evidence from randomized controlled trials, several studies suggest that induced hemodynamic treatment including induced hypertension may increase CBF through the narrowed vessels in the setting of impaired cerebral autoregulation, thereby improving outcome [58]. However, it should be noted that induced hypertension may increase the risk for hypertensive encephalopathy/reversible leukoencephalopathy syndrome and hemorrhagic transformation of ischemia [59].

## 20.5 Summary

Although ischemic/hemorrhagic stroke and TIA could be caused by various underlying pathophysiology, elevated BP is the common and important risk factor for them. There is still no clear evidence that intensive lowering of BP in the setting of acute ischemic stroke or TIA influences outcome. However, emerging evidence in terms of BP management in acute ICH suggests that intensive lowering of BP with a systolic target of 130–140 mm Hg improves functional outcomes. Long-term BP lowering is the most significant intervention for the secondary prevention of stroke, but it still remains to be determined that optimal magnitude of BP lowering or regimens to achieve the BP. As stroke is such a common disease, establishment of optimal BP management, even though which could have relatively small benefit to each patient, could provide a sizable effect in reducing the global burden of stroke.

## References

1. Murray CJ, Vos T, Lozano R et al (2012) Disability-adjusted life years (dalys) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the global burden of disease study 2010. Lancet 380(9859):2197–2223. doi:10.1016/s0140-6736(12)61689-4
2. Easton JD, Saver JL, Albers GW et al (2009) Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 40(6):2276–2293. doi:10.1161/strokeaha.108.192218
3. O'Donnell MJ, Xavier D, Liu L et al (2010) Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 376(9735):112–123. doi:10.1016/s0140-6736(10)60834-3
4. Miller J, Kinni H, Lewandowski C et al (2014) Management of hypertension in stroke. Ann Emerg Med 64(3):248–255. doi:10.1016/j.annemergmed.2014.03.004
5. Qureshi AI (2008) Acute hypertensive response in patients with stroke: pathophysiology and management. Circulation 118(2):176–187. doi:10.1161/circulationaha.107.723874
6. Wallace JD, Levy LL (1981) Blood pressure after stroke. JAMA 246(19):2177–2180
7. Ruland S, Aiyagari V (2007) Cerebral autoregulation and blood pressure lowering. Hypertension 49(5):977–978. doi:10.1161/hypertensionaha.107.087502
8. Strandgaard S (1976) Autoregulation of cerebral blood flow in hypertensive patients. The modifying influence of prolonged antihypertensive treatment on the tolerance to acute, drug-induced hypotension. Circulation 53(4):720–727
9. Willmot M, Leonardi-Bee J, Bath PM (2004) High blood pressure in acute stroke and subsequent outcome: a systematic review. Hypertension 43(1):18–24. doi:10.1161/01.hyp.0000105052.65787.35
10. Tikhonoff V, Zhang H, Richart T et al (2009) Blood pressure as a prognostic factor after acute stroke. Lancet Neurol 8(10):938–948. doi:10.1016/s1474-4422(09)70184-x
11. Sandset EC, Bath PM, Boysen G et al (2011) The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. Lancet 377(9767):741–750. doi:10.1016/s0140-6736(11)60104-9
12. Bath PM, Woodhouse L, Scutt P et al (2015) Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS):

a partial-factorial randomised controlled trial. Lancet 385(9968):617–628. doi:10.1016/s0140-6736(14)61121-1
13. Bath PM, Krishnan K (2014) Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database Syst Rev 10:CD000039. doi:10.1002/14651858.CD000039.pub3
14. Anderson CS, Robinson T, Lindley RI et al (2016) Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke. N Engl J Med 374(24):2313–2323. doi:10.1056/NEJMoa1515510
15. Robinson TG, Potter JF, Ford GA et al (2010) Effects of antihypertensive treatment after acute stroke in the continue or stop post-stroke antihypertensives collaborative study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. Lancet Neurol 9(8):767–775. doi:10.1016/s1474-4422(10)70163-0
16. Wardlaw JM, Murray V, Berge E et al (2012) Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet 379(9834):2364–2372. doi:10.1016/s0140-6736(12)60738-7
17. Brott T, Lu M, Kothari R et al (1998) Hypertension and its treatment in the ninds rt-pa stroke trial. Stroke 29(8):1504–1509
18. Gilligan AK, Markus R, Read S et al (2002) Baseline blood pressure but not early computed tomography changes predicts major hemorrhage after streptokinase in acute ischemic stroke. Stroke 33(9):2236–2242
19. Wahlgren N, Ahmed N, Eriksson N et al (2008) Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST). Stroke 39(12):3316–3322. doi:10.1161/strokeaha.107.510768
20. Ahmed N, Wahlgren N, Brainin M et al (2009) Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). Stroke 40(7):2442–2449. doi:10.1161/strokeaha.109.548602
21. Martins AI, Sargento-Freitas J, Silva F et al (2016) Recanalization modulates association between blood pressure and functional outcome in acute ischemic stroke. Stroke 47(6):1571–1576. doi:10.1161/strokeaha.115.012544
22. Demaerschalk BM, Kleindorfer DO, Adeoye OM et al (2016) Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 47(2):581–641. doi:10.1161/str.0000000000000086
23. Huang Y, Sharma VK, Robinson T et al (2015) Rationale, design, and progress of the ENhanced Control of Hypertension ANd thrombolysis strokE stuDy (ENCHANTED) trial: an international multicenter 2 × 2 quasi-factorial randomized controlled trial of low- vs. Standard-dose rt-pa and early intensive vs. Guideline-recommended blood pressure lowering in patients with acute ischaemic stroke eligible for thrombolysis treatment. Int J Stroke 10(5):778–788. doi:10.1111/ijs.12486
24. Lovett JK, Coull AJ, Rothwell PM (2004) Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. Neurology 62(4):569–573
25. Rodgers A, MacMahon S, Gamble G et al (1996) Blood pressure and risk of stroke in patients with cerebrovascular disease. The United Kingdom Transient Ischaemic Attack Collaborative Group. BMJ 313(7050):147
26. PROGRESS Collaborative Group (2001) Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 358(9287):1033–1041. doi:10.1016/s0140-6736(01)06178-5
27. Arima H, Chalmers J, Woodward M et al (2006) Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial. J Hypertens 24(6):1201–1208. doi:10.1097/01.hjh.0000226212.34055.86
28. Diener HC, Sacco R, Yusuf S (2007) Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose

combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: the prevention regimen for effectively avoiding second strokes trial (PRoFESS). Cerebrovasc Dis 23(5–6):368–380. doi:10.1159/000100105
29. Ettehad D, Emdin CA, Kiran A et al (2016) Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 387(10022):957–967. doi:10.1016/s0140-6736(15)01225-8
30. Rashid P, Leonardi-Bee J, Bath P (2003) Blood pressure reduction and secondary prevention of stroke and other vascular events: a systematic review. Stroke 34(11):2741–2748. doi:10.1161/01.str.0000092488.40085.15
31. Benavente OR, Coffey CS, Conwit R et al (2013) Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. Lancet 382(9891):507–515. doi:10.1016/s0140-6736(13)60852-1
32. Turnbull F (2003) Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 362(9395):1527–1535
33. Wright JT Jr, Williamson JD, Whelton PK et al (2015) A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 373(22):2103–2116. doi:10.1056/NEJMoa1511939
34. Zanchetti A, Liu L, Mancia G et al (2014) Blood pressure and ldl-cholesterol targets for prevention of recurrent strokes and cognitive decline in the hypertensive patient: design of the European Society of Hypertension-Chinese Hypertension League Stroke in Hypertension Optimal Treatment randomized trial. J Hypertens 32(9):1888–1897. doi:10.1097/hjh.0000000000000254
35. Qureshi AI, Ezzeddine MA, Nasar A et al (2007) Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ed in the united states. Am J Emerg Med 25(1):32–38. doi:10.1016/j.ajem.2006.07.008
36. Fischer U, Cooney MT, Bull LM et al (2014) Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study. Lancet Neurol 13(4):374–384. doi:10.1016/s1474-4422(14)70031-6
37. Dandapani BK, Suzuki S, Kelley RE et al (1995) Relation between blood pressure and outcome in intracerebral hemorrhage. Stroke 26(1):21–24
38. Kazui S, Minematsu K, Yamamoto H et al (1997) Predisposing factors to enlargement of spontaneous intracerebral hematoma. Stroke 28(12):2370–2375
39. Broderick JP, Brott TG, Tomsick T et al (1990) Ultra-early evaluation of intracerebral hemorrhage. J Neurosurg 72(2):195–199. doi:10.3171/jns.1990.72.2.0195
40. Vemmos KN, Tsivgoulis G, Spengos K et al (2003) Association between 24-h blood pressure monitoring variables and brain oedema in patients with hyperacute stroke. J Hypertens 21(11):2167–2173. doi:10.1097/01.hjh.0000084798.73547.0c
41. Mayer SA, Lignelli A, Fink ME et al (1998) Perilesional blood flow and edema formation in acute intracerebral hemorrhage: a spect study. Stroke 29(9):1791–1798
42. Powers WJ, Zazulia AR, Videen TO et al (2001) Autoregulation of cerebral blood flow surrounding acute (6 to 22 hours) intracerebral hemorrhage. Neurology 57(1):18–24
43. Butcher KS, Jeerakathil T, Hill M et al (2013) The intracerebral hemorrhage acutely decreasing arterial pressure trial. Stroke 44(3):620–626. doi:10.1161/strokeaha.111.000188
44. Anderson CS, Heeley E, Huang Y et al (2013) Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med 368(25):2355–2365. doi:10.1056/NEJMoa1214609
45. Tsivgoulis G, Katsanos AH, Butcher KS et al (2014) Intensive blood pressure reduction in acute intracerebral hemorrhage: a meta-analysis. Neurology 83(17):1523–1529. doi:10.1212/wnl.0000000000000917
46. Qureshi AI, Palesch YY, Barsan WG et al (2016) Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. N Engl J Med 375(11):1033–1043. doi:10.1056/NEJMoa1603460

47. Arima H, Heeley E, Delcourt C et al (2015) Optimal achieved blood pressure in acute intracerebral hemorrhage: INTERACT2. Neurology 84(5):464–471. doi:10.1212/wnl.0000000000001205
48. Biffi A, Anderson CD, Battey TW et al (2015) Association between blood pressure control and risk of recurrent intracerebral hemorrhage. JAMA 314(9):904–912. doi:10.1001/jama.2015.10082
49. Yusuf S, Diener HC, Sacco RL et al (2008) Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med 359(12):1225–1237. doi:10.1056/NEJMoa0804593
50. Sato S, Carcel C, Anderson CS (2015) Blood pressure management after intracerebral hemorrhage. Curr Treat Options Neurol 17(12):49. doi:10.1007/s11940-015-0382-1
51. Cushman WC, Ford CE, Einhorn PT et al (2008) Blood pressure control by drug group in the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). J Clin Hypertens (Greenwich) 10(10):751–760. doi:10.1111/j.1751-7176.2008.00015.x
52. Shaw E, Anderson JG, Maloney M et al (1995) Factors associated with noncompliance of patients taking antihypertensive medications. Hosp Pharm 30(3):201–203. 206–207
53. Ohkuma H, Tsurutani H, Suzuki S (2001) Incidence and significance of early aneurysmal rebleeding before neurosurgical or neurological management. Stroke 32(5):1176–1180
54. Connolly ES Jr, Rabinstein AA, Carhuapoma JR et al (2012) Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 43(6):1711–1737. doi:10.1161/STR.0b013e3182587839
55. Tanno Y, Homma M, Oinuma M et al (2007) Rebleeding from ruptured intracranial aneurysms in North Eastern Province of Japan. A cooperative study. J Neurol Sci 258(1–2):11–16. doi:10.1016/j.jns.2007.01.074
56. Naidech AM, Janjua N, Kreiter KT et al (2005) Predictors and impact of aneurysm rebleeding after subarachnoid hemorrhage. Arch Neurol 62(3):410–416. doi:10.1001/archneur.62.3.410
57. Schmidt JM, Wartenberg KE, Fernandez A et al (2008) Frequency and clinical impact of asymptomatic cerebral infarction due to vasospasm after subarachnoid hemorrhage. J Neurosurg 109(6):1052–1059. doi:10.3171/jns.2008.109.12.1052
58. Sen J, Belli A, Albon H et al (2003) Triple-H therapy in the management of aneurysmal subarachnoid haemorrhage. Lancet Neurol 2(10):614–621
59. Amin-Hanjani S, Schwartz RB, Sathi S et al (1999) Hypertensive encephalopathy as a complication of hyperdynamic therapy for vasospasm: report of two cases. Neurosurgery 44(5):1113–1116

# Part VI

# Hypertension Phenotypes: The Kidney

# Chronic Kidney Disease

# 21

Silvio Borrelli, Luca De Nicola, Giuseppe Conte, and Roberto Minutolo

## 21.1 Introduction

Hypertension and chronic kidney disease (CKD) are global public health challenges due to their growing prevalence worldwide [1–3] and the associated higher risk for fatal and nonfatal cardiovascular (CV) events [4, 5]. These two conditions are strictly interrelated because elevated blood pressure (BP) not only is a main complication of CKD [6, 7] but can also act as its determinant [8].

A recent meta-analysis provides evidence that in the general population [8], over a median of 6 years of follow-up, the adjusted risk of GFR <60 mL/min/1.73 $m^2$ is more than 75% greater in hypertensive versus normotensive individuals. Similarly, in individuals with prehypertension (systolic BP of 120–139 mm Hg and/or diastolic BP of 80–89 mm Hg), risk of developing low GFR is increased by 25%. When systolic and diastolic BP was considered as continuous variables, risk of CKD increased by about 10% for each 10 mm Hg higher level of either BP component.

In patients with overt CKD, GFR decline is associated with a higher prevalence of hypertension and worse control rates. Indeed, BP is elevated in approximately 80–85% of patients with non-dialysis CKD [9], and the prevalence of hypertension increases progressively from 65% to 95% as the GFR falls from 85 to 15 mL/min/1.73 $m^2$ [10].

Hypertension constitutes a major risk factor for the progression of renal disease, especially in proteinuric patients [7, 11], as well as for the high CV risk observed since the early stages of CKD independently of proteinuria level [5]. Therefore, the

S. Borrelli • L. De Nicola • G. Conte • R. Minutolo, M.D. (✉)
Division of Nephrology, Department of Scienze Mediche, Chirurgiche, Neurologiche, Metaboliche e dell'Invecchiamento, University of Campania Luigi Vanvitelli, Via M. Longo 50, 80138 Naples, Italy
e-mail: roberto.minutolo@unina2.it



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_21

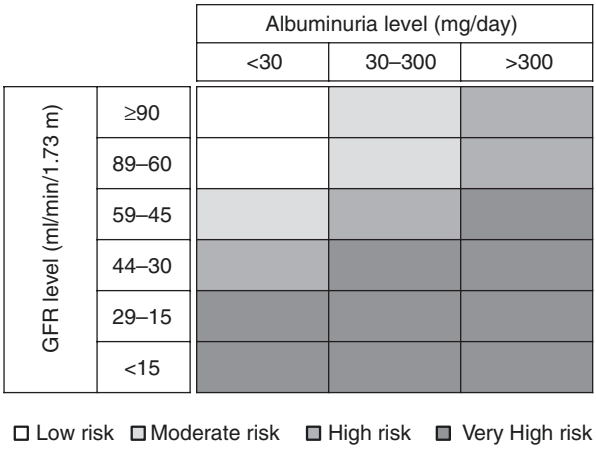



**Fig. 21.1** Classification of CKD according to K/DIGO guidelines [18]

antihypertensive therapy in CKD aims at slowing progression of kidney failure and reducing CV risk. However, in these patients, hypertension is often refractory to the treatment [12–16]. Therefore, BP-lowering strategies must take into account the complex pathogenesis of hypertension in CKD and, especially, the concomitant presence of albuminuria that substantially modifies the prognosis of CKD patients [17]. This latter concept is highlighted by the new classification of CKD (Fig. 21.1), where improved risk stratification is attained by combining GFR levels with albuminuria category (normal to mild, moderate, and severe) [18].

## 21.2 Pathogenesis of Hypertension in CKD

A variety of factors account for the high prevalence of hypertension in CKD, including the reduction of sodium excretion, the increased activity of the renin-angiotensin-aldosterone system (RAAS), and the sympathetic nervous system [19–21].

The main disorder in CKD is the salt and water retention that occurs in the majority of patients with reduced glomerular filtration rate (GFR). The resulting expansion of the extracellular volume (ECV) allows preserving the external balance of sodium but causes the development of persistent hypertension. In these patients, entity of ECV expansion strictly depends on the severity of GFR impairment and corresponds to approximately 5–10% of body weight, even in the absence of peripheral edema [19]. Of note, salt sensitivity of BP is not a feature limited to the advanced stages of CKD but begins before the development of clear hypertension and severe GFR decline [22, 23]. The common impairment of sodium excretion in renal patients may also explain the higher prevalence of nocturnal hypertension in CKD versus essential hypertension [24, 25].

Furthermore, in CKD patients, systemic hypertension is maintained by the activation of RAAS, which is inappropriate when considering the ECV expansion [20]. The ensuing glomerular hyperfiltration may contribute to the progressive kidney

injury [20]. Finally, hypoxemia of renal tissue due to kidney damage activates the central nervous system via afferent nerves that in turn increases sympathetic activity thus contributing to the genesis of hypertension [21].

Notably, CKD is associated with premature vascular aging, characterized by accelerated arteriosclerosis and/or endothelial dysfunction caused by impaired nitric oxide synthesis [26, 27]. Rigidity of arterial wall attenuates baroreceptor control of efferent sympathetic activity and vagal activation. Reduced baroreflex sensitivity maintains high sympathetic activity directed to the heart, blood vessels, and kidney, which contributes to increasing BP [28, 29].

Additional pathogenetic mechanisms of hypertension in CKD are secondary hyperparathyroidism (leading to vasoconstriction and hypertension by means of increased intracellular calcium concentration) [30] and eventual treatment with erythropoietin (by means of increased blood viscosity and/or release of vasoconstrictive factors).

## 21.3 Optimal BP Target in CKD

BP control is a cornerstone of management of CKD patients. However, the BP target for this population remains ill defined since there is no solid evidence on the optimal BP goal [31].

For many years international guidelines have recommended a BP < 130/80 mmHg in all patients with CKD patients in attempt to slow the renal progression and to reduce the high CV risk [32–34]. However, this BP goal has not been validated in randomized controlled trials being mainly driven by data obtained in either observational and post-hoc analyses of trials [35–40] or meta-analyses [41, 42]. In particular, MDRD study [35–37], AASK trial [38, 39], and REIN-2 trial [40] failed to show benefit for clinical outcomes from the low versus usual blood pressure targets. Only MDRD study follow-up (post-trial observational study) showed a 23% reduction of the risk for kidney failure in the group assigned to the low target [12]. More recently, the randomized Systolic Blood Pressure Intervention Trial (SPRINT) has shown that intensive BP control (<120 mmHg), as compared to standard control (<140 mmHg), did not reduce the CV and renal risk in the subgroup of patients with CKD [43]. Conversely, intensive treatment was associated with higher rates of hypotensive episodes and acute renal injury.

The inconclusive results on the prognostic role of BP target in patients with CKD might relate to the limited ability of clinic BP readings to adequately stratify the global risk of this high-risk population [44–46]. This hypothesis will be verified by the ancillary study of SPRINT trial in 600 patients undergone to ABPM [47].

Although there are far less data in CKD patients to inform the best approach, current guideline recommendations suggest that no single BP target is optimal for all CKD patients and encourage individualization of treatment depending on age, severity of albuminuria, and comorbidities, in contrast with the “one size fits all” viewpoint that has previously been endorsed. Table 21.1 summarizes the BP goals in each CKD subpopulation proposed by K/DIGO [48]. Briefly, because proteinuria

**Table 21.1** BP goals recommended by K/DIGO in CDK patients with and without diabetes [48]

| | Albuminuria levels | | |
|---|---|---|---|
| | <30 mg/day | 30–300 mg/day | >300 mg/day |
| Diabetics | ≤140/90 | ≤130/80 | ≤130/80 |
| Non-diabetics | ≤140/90 | ≤130/80 | ≤130/80 |

amplifies both cardiac and renal risks [17, 49–52], current guidelines suggest a lower target of ≤130/80 mmHg for patients with CKD and albumin excretion rate of ≥30 mg/24 h (i.e., those with either micro- or macroalbuminuria), whereas in patients without albuminuria, BP should be ≤140/90 mm Hg. Recommendations are almost identical in CKD patients with diabetes [53–58] and without diabetes [11, 12, 36, 59] (Table 21.1). Current guidelines suggest to pay particular attention in elderly patients, which constitute the most rapidly growing population of CKD patients, despite evidence-based recommendations for elderly CKD patients are scarce and inconclusive. Nonetheless, BP levels <140/90 mm Hg have been recommended in all CKD patients by American College of Cardiology Foundation and American Heart Association (ACCF/AHA) and National Institute for Health and Clinical Excellence (NICE) as well [59, 60].

## 21.4 Which BP Measurement in CKD Patients?

Hypertension is usually diagnosed and treated based on BP readings obtained in the clinic; however, BP may considerably differ when measured at home. Out-of-office BP measurements include ABPM lasting 24 h and home BP monitoring (HBPM) in which patients record BP at home while seated and resting. Both assessments allow disclosing abnormal pressor profiles, as white coat hypertension (high clinic BP but normal ABPM or HBPM) or masked hypertension (normal clinic BP but high ABPM or HBPM), while ABPM also provides an accurate picture of circadian rhythm of BP and the evaluation of nocturnal dip. Indeed, BP is physiologically 10–20% lower during sleep as compared to daytime. Accordingly, a night/day BP ratio between 0.8 and 0.9 is considered normal, and patients are defined as "dipper," while the lack of nighttime BP reduction of at least 10% allows diagnosing the " non-dipper" status. More specifically, a decline of nocturnal BP between 0 and 10% (night/day BP ratio 0.9–1.0) defines patients as "non-dipper," whereas if nocturnal BP is higher than diurnal BP (night/day BP ratio > 1.0), it defines patients as "reverse dipper." Occasionally, some patients, defined as "extreme dipper," experience a marked reduction of night BP greater than 20% (night/day BP ratio < 0.8) [61].

Several observational studies in CKD population have found that ABPM is superior to office-based measurements in predicting end-stage renal disease (ESRD), cardiovascular events, and death [62–65]. In particular, Agarwal and Andersen demonstrated in a cohort of 217 veterans with CKD followed for a median of 3.5 years, the superiority of ABPM over clinical BP for predicting a composite endpoint of death or ESRD [63]. Similar results were obtained when considering HBPM versus

office BP in the same cohort [65]. Furthermore, an analysis of 617 CKD patients in the African American Study of Kidney Disease and Hypertension (AASK) study confirmed the superiority of ABPM for predicting both CV events and a composite of death, ESRD, or doubling of serum creatinine over a median follow-up of 5 years [64]. Finally, Minutolo et al. reported that in a cohort of 436 CKD patients followed for a median of 4.2 years, office BP did not predict CV events or composite of death and ESRD, while high BP at ABPM, and in particular nighttime values, increased the risk of adverse outcome [65]. In that study, the cardiorenal risk increased significantly when daytime or nighttime BP exceeded 135/85 and 120/70 mmHg, respectively. These data confirmed that normality thresholds for daytime and nighttime BP proposed for essential hypertension might be confidently applied also to patients with CKD [65].

## 21.5 Out-of-Office BP Measurements in CKD

### 21.5.1 Altered BP Profiles in CKD

A meta-analysis evaluating prevalence of altered BP profiles in CKD patients [66] reported that WCH was more frequent (18%) than hypertensive population (13%), whereas MH was less prevalent in CKD (8%) with respect to essential hypertension (11%) [67, 68]. However, recent studies not included in the meta-analysis have provided discrepant prevalence rates of abnormal BP profiles [69–74]. Indeed, as reported in Table 21.2, the prevalence of WCH ranged between 5% and 29%, whereas MH occurred in 5–31% patients. This variability may be explained by the ethnicity of cohorts, since the prevalence of WCH is higher than that of MH in Caucasian patients [69–71], while the opposite was found in studies enrolling Afro-American or Asian patients [72–74].

Given the technical and economic barriers to routine implementation of ABPM, a critical question is on the timing of these measurements, that is, when to perform an out-of-office measurement of BP to detect altered BP profiles or, alternatively, what clinical and demographic conditions may predict the presence of WCH or MH and therefore indicate the need of ABPM. Two studies addressed this issue in CKD patients [75, 76]. Minutolo et al. reported that, among 228 CKD patients stages 2–5 with high-office BP, 40% of patients had a WCH, and this condition was

**Table 21.2** Prevalence of white coat hypertension and masked hypertension in CKD cohorts

| | Thresholds for defining BP profiles (mmHg) | | | |
|---|---|---|---|---|
| Cohort | Office BP | ABPM | WCH (%) | MH (%) |
| Italian cohort [69] | <140/90 | Day/night <135/85/<120/70 | 22.1 | 14.5 |
| Spanish registry [70] | <140/90 | 24 h BP <130/80 | 28.8 | 7.0 |
| Veterans cohort [71] | <130/80 | Awake BP <130/80 | 24.6 | 4.7 |
| AASK study [74] | <140/90 | Daytime BP <135/85 | 5.3 | 25.1 |
| JAC-CKD cohort [72] | <140/90 | 24 h BP <130/80 | 5.6 | 30.9 |
| Chinese cohort [73] | ≤140/90 | 24 h BP ≤130/80 | 9.7 | 18.2 |

significantly associated to proteinuria >1 g/day (odds ratio 3.12) and higher-office BP (odds ratio 1.61 for each 10 mmHg) [75]. Agarwal et al. in a cohort of 333 CKD patients (stages 2–4) with normal clinic BP (<140/90 mmHg) found that MH was a common condition whose prevalence varied from 27% (using daytime BP) to 33% (using 24 h BP) and should be suspected when clinic BP is in the prehypertensive range [76].

The more accurate estimates of hypertensive status offered by ABPM with respect to clinic BP translate into better risk stratification. Indeed, when using the two BP measurements (office and ambulatory) to detect altered BP profiles, renal and cardiovascular prognosis of CKD patients with sustained hypertension (office and ABPM not at goal) was worse than that of normotensive patients (both office and ABPM at goal). Similarly, cardiorenal risk of patients with MH (office at goal and ABPM not at goal) was similar to those with sustained hypertension and higher than normotensive patients. Conversely, having WCH (office not at goal and ABPM at goal) was not associated with higher risk for any event. These findings clearly suggest that the different prognosis can be ascribed to poor control of the ambulatory BP (as occurs in sustained hypertension and MH) rather than to higher-office BP (WCH). The prognosis associated with pressor profiles was independent from the office and ambulatory thresholds used to define BP profiles [69]. It is important to note that classifying patients based on both clinic and out-of-office BP has relevant therapeutic implications. Indeed, physicians should avoid therapy intensification in WCH in order to prevent harmful ischemia-induced episodes affecting renal, cerebral, and cardiac function, particularly at nighttime [75] and in elderly patients [77], but they must reinforce antihypertensive therapy in MH to reduce their higher risk due to uncontrolled ambulatory BP.

The importance of combining clinic and out-of-office BP appears also in CKD patients with resistant hypertension (RH), in which out-of-office BP monitoring allows to distinguish between pseudoresistance (WCH) and true RH. Indeed, while 30% of patients were defined as resistant on the basis of only clinic BP measurements, pseudoresistance (ABP at goal in RH patients) was common (24% of these patients and 7% of whole cohort). Also in this setting, better estimate of hypertensive status by ABPM translates into a better risk stratification. Indeed, patients with normal ABPM (controls and pseudoresistant patients) had the best prognosis for either outcome independent of their RH status, while the higher risk for cardiorenal events was observed only in true RH [15].

### 21.5.2 Altered Circadian Profile in CKD

The distinctive characteristic of ABPM is its ability of obtaining information on nighttime BP that is now considered the ABPM component more strictly linked to adverse outcome [78]. Indeed, even when daytime BP is well controlled, the presence of nocturnal hypertension portends a greater risk of renal progression [62].

The lack of physiological BP decline during nighttime (non-dipping status) occurs frequently in CKD patients being consistently above 50% in all cohorts

considered [69, 71–74], with increasing rates in elderly and advanced CKD [77]. In a group of 459 CKD patients regularly followed in renal clinics, the risk of being non-dipper was significantly associated to older age, diabetes, left ventricular hypertrophy, and anemia [77]. In a large Japanese cohort of CKD patients, non-dipping status has been associated also to more advanced CKD, seasonal variation and, as expected, to nocturia [72]. Altered circadian profiles are strongly associated with adverse clinical outcomes in CKD [62–64], similarly to what was reported in general population and essential hypertension [79]. In particular, non-dippers and reverse dippers with CKD displayed a twofold greater CV risk and a 60–70% higher risk of renal events [62]. Agarwal and Andersen reported similar results in a cohort of veterans with CKD and highlighted that a similar risk of CV outcomes occurred by using day or night versus awake or sleep BP and that dipping defined as a ratio confers a greater CV risk compared to dipping when defined as absolute change [64]. Nocturnal hypertension also represents a potential target for therapy; indeed non-dippers may benefit of a "chronotherapeutic" antihypertensive approach. This intervention consists in the administration of drugs at bedtime in order to restore the physiologic BP decline at night. This approach has been tested in a pilot uncontrolled study, in which one antihypertensive drug was switched to bedtime in 32 CKD non-dipper patients [24]. ABPM was repeated at 8 weeks, and 87.5% of the subjects became dippers. Of note, restoring the normal nocturnal dip was associated with a significant reduction of proteinuria [24]. More recently, a randomized controlled open-label crossover trial was performed in 147 participants to the AASK study, 76% being non-dipper. This study did not confirm a significant BP reduction at night when either one antihypertensive drug or all drugs were administered at bedtime as compared with administration of therapy in the morning [80]. Finally, a randomized trial tested effectiveness of chronotherapy in 661 CKD patients (66% non-dippers at baseline) and reported a surprising 65% reduction in the relative risk of the composite endpoint of death or CV events [81].

In patients with uncontrolled daytime and nighttime systolic BP, the reassessment of ABPM may be helpful. Specifically, a second ambulatory monitoring, obtained 1 year after the first one, allows to correctly reclassifying as at risk from 15% to 22% of patients [82]. In particular, CKD patients not reaching the goal at the two ABPM had the worst renal prognosis, while patients not at goal at baseline but reaching the goal at second ABPM were not exposed to a greater renal risk.

## 21.6 Treatment of Hypertension in CKD Patients

### 21.6.1 Low-Salt Diet

Generally, the first step in the BP management is lifestyle modifications, such as achieving or maintaining a healthy weight (BMI 20–25 kg/m$^2$), limiting salt and alcohol intake, and increasing physical exercise [48]. Because of volume expansion occurring in CKD patients, the pivotal intervention is certainly represented by the restriction of sodium intake below 100 mmol/day (corresponding to less than 6 g of

salt). In patients with CKD, moderate reduction of salt intake allows a much greater BP decrease in comparison with hypertensive patients with normal GFR undergoing major restriction of salt intake (salt sensitivity of BP) [22, 83, 84]. Specifically, Koomans et al. found that a mean decrease of sodium intake of about 6 g/d led to a decrease of mean BP of about 12 mm Hg [84]. More recently, data from Chronic Renal Insufficiency Cohort (CRIC) study showed that among 3757 patients with CKD, higher urinary sodium excretion was associated with increased risk of CVD [85]. Furthermore, dietary sodium restriction may also act indirectly by enhancing the antihypertensive effects of angiotensin-converting enzyme inhibitors (CEIs) [86].

However, this dietary measure is scarcely implemented in CKD population regularly followed in nephrology clinics (<20% of patients have a salt intake below 6 g/day) [87, 88]. This is a paradoxical condition if one considers that, as mentioned above, CKD is typically characterized by high-salt sensitivity [84] that becomes evident from early CKD stages [22].

### 21.6.2 Diuretics

Due to the poor adherence to low-salt diet, diuretics are needed to decrease volume expansion and ameliorate BP control in the majority of CKD patients. Two critical points in the diuretic treatment of CKD patients are the selection of the class of diuretic and titration of the dosage according to degree of kidney failure [89]. Indeed while patients with mild renal impairment (GFR >40 mL/min/1.73 $m^2$) may respond to thiazide diuretics, those with more advanced CKD require the use of more potent loop diuretics; furthermore, the lower is the GFR, the higher must be the dose of furosemide or torasemide [89]. In a clinical trial performed in patients with GFR in the range 10–40 mL/min, correction of volume expansion (evidenced by body weight reduction of 2.0 kg coupled with a marked reduction in BP) was safely induced by oral administration of furosemide at the following daily doses: 1.0, 2.5, and 4.0 mg/kg body weight in patients with GFRs of 40–31, 30–20, and 19–10 mL/min, respectively [90]. Therefore, to improve the diuretic management is helpful to start diuretic treatment with a low dose that can be progressively increased if body weight does not decrease. The lack of a significant body weight reduction (0.4–0.6 kg/day) despite increasing diuretic doses likely suggests the presence of diuretic resistance that can be overcome by adding other agents (such as metolazone) in order to limit the breaking phenomenon (sodium over-reabsorption in the distal segments of renal tubule) [91].

In the cases of the hypertension refractory to the treatment, it may be helpful to use spironolactone at the dose of 25–100 mg/day that is efficacious in non-CKD patients with diagnosis of RH [92]. However, assessment of spironolactone efficacy has not been tested in patients with renal impairment that are at higher risk of hyperkalemia. Disappointingly enough, nephrologists are today still reluctant to use adequately loop diuretics in their hypertensive CKD patients. This erroneous attitude cannot be justified by the fear of side effects, which are infrequent, usually reversible and predictable when the patient is regularly followed [93].

### 21.6.3 Inhibitors of RAAS

The CEIs or angiotensin receptor blockers (ARBs) are more effective than other antihypertensive drugs in slowing the progression of proteinuric diabetic [54–59] and nondiabetic CKD [11, 36, 60]. This specific renoprotective effect significantly exceeds that associated with antihypertensive drugs not active on RAAS and appears to be essentially caused by their specific antiproteinuric effect. Experimental studies, in fact, have demonstrated for anti-RAAS agents a decrease in intraglomerular pressure by predominant vasodilation of the efferent arteriole resistance and improved glomerular permselectivity [94, 95]. Antiproteinuric effect is more prominent when patients are kept on a low-sodium diet [96] or are treated with diuretics [97] because relative volume depletion results in enhanced angiotensin II dependence of the glomerular microcirculation.

A critical (actual) issue is the role of CEI-ARB combination therapy. Additive antiproteinuric effect and concomitant increased efficacy in terms of slowing CKD progression have been reported only in proteinuric nondiabetic CKD patients affected by IgA nephropathy [98]. Conversely, ONTARGET trial showed that in high-risk vascular disease/diabetes patients, the combination of the CEI plus ARB was associated with more adverse events with no additional benefit [99]. However, the very low prevalence of significant albuminuria among participants was indicative of ischemic nephropathy as leading cause of renal disease; in these conditions, dual blockade of RAAS is not required (no need of proteinuria reduction) and may expose patients to greater risk of worsening of renal function especially in the setting of clinical trial in which drug withdrawal is not allowed [99].

It is important to emphasize that although the benefits of RAAS inhibitors hold true also in patients with advanced CKD [100], the safety of CEIs or ARBs therapy in the advanced CKD needs a tight control of volume status, changes of GFR, and serum potassium. In fact, clinically significant hyperkalemia and reductions in GFR can occur in patients receiving ACE-Is or ARBs, particularly when these agents are used together with NSAIDs, COX-2 inhibitors, or potassium-sparing diuretics. Furthermore, in patients who develop intercurrent illnesses that lead to dehydration as a result of diarrhea, vomiting, or fever, it is recommended to have temporary withdrawal of CEIs or ARBs until recovery.

At variance with proteinuric CKD, in patients with non-proteinuric renal disease, RAAS inhibitors are not specifically indicated; under these conditions, in fact, CEIs have not been found to be superior to standard therapy in slowing progression of the renal disease [101] despite there is some evidence that inhibitors of the RAAS system might prevent an increase in albuminuria [102, 103]. However, such studies have not been performed in patients with reduced GFR but normal urinary albumin excretion. Therefore, in patients with non-proteinuric nephropathy (i.e., ischemic or hypertensive renal diseases), therapy should be primarily based on achievement of optimal BP control to ameliorate renal and cardiovascular prognosis with a careful evaluation of the balance of risks and benefits of the use of CEIs or ARBs [48].

### 21.6.4 Other BP-Lowering Agents

Multidrug regimens are usually necessary to achieve BP goals by interfering with the different pathways involved in the complex pathogenesis of hypertension in patients with CKD. There is no evidence on the class of antihypertensive drugs to be used in CKD as third line, that is, after optimization of treatment with anti-RAAS and diuretics. All classes of antihypertensives may be used in CKD patients, keeping in mind the pharmacokinetics of each drug, in order to avoid the accumulation of drug or active metabolites that could exacerbate concentration-dependent side effects. Furthermore, most of these drugs are effective vasodilators that may exacerbate fluid retention of CKD patients; for that reason their use should be postponed once euvolemia is achieved by dietary salt restriction or adequate diuretic therapy.

In summary, in CKD patients with albuminuria >30 mg/day, it is recommended to use CEIs or ARBs as first-line drugs taking into account their protective effects on CKD progression [7, 11] and CV outcomes [103, 104]. In non-albuminuric patients, there is no solid evidence to suggest one specific class of antihypertensive, besides and beyond diuretics. Therefore, after a low-salt diet is implemented and anti-RAAS and adequate doses of loop diuretics have been used, additional antihypertensive agents can be decided on the basis of comorbidities (heart failure, myocardial infarction, asthma, chronic obstructive pulmonary disease, etc.).

## References

1. Yoon SS, Burt V, Louis T, Carroll MD (2012) Hypertension among adults in the United States, 2009–2010. NCHS Data Brief 107:1–8
2. Coresh J, Selvin E, Stevens LA et al (2007) Prevalence of chronic kidney disease in the United States. JAMA 298(17):2038–2047
3. Levey AS, Coresh J (2012) Chronic kidney disease. Lancet 379(9811):165–180
4. Lewington S, Clarke R, Qizilbash N et al (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 360(9349):1903–1913
5. Go AS, Chertow GM, Fan D et al (2004) Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351(13):1296–1305
6. Klag MJ, Whelton PK, Randall BL et al (1996) Blood pressure and end-stage renal disease in men. N Engl J Med 334(1):13–18
7. Jafar TH, Stark PC, Schmid CH et al, for the AIPRD Study Group (2003) Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition. Ann Intern Med 139:244–253
8. Garofalo C, Borrelli S, Pacilio M et al (2016) Hypertension and prehypertension and prediction of development of decreased estimated GFR in the general population: a meta-analysis of cohort studies. Am J Kidney Dis 67(1):89–97
9. Whaley-Connell AT, Sowers JR, Stevens LA et al, Kidney Early Evaluation Program Investigators (2008) CKD in the United States: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999–2004. Am J Kidney Dis 51(4 Suppl 2):S13–S20
10. Buckalew VM Jr, Berg RL, Wang SR et al (1996) Prevalence of hypertension in 1,795 subjects with chronic renal disease: the modification of diet in renal disease study baseline cohort. Modification of Diet in Renal Disease Study Group. Am J Kidney Dis 28(6):811–821

11. Sarnak MJ, Greene T, Wang X et al (2005) The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the Modification of Diet in Renal Disease Study. Ann Intern Med 142:342–351
12. Muntner P, Anderson A, Charleston J et al (2010) Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis 55:441–451
13. Tanner RM, Calhoun DA, Bell EK et al (2013) Prevalence of apparent treatment-resistant hypertension among individuals with CKD. Clin J Am Soc Nephrol 8:1583–1590
14. Sim JJ, Bhandari SK, Shi J et al (2015) Comparative risk of renal, cardiovascular, and mortality outcomes in controlled, uncontrolled resistant and nonresistant hypertension. Kidney Int 88(3):622–632
15. De Nicola L, Gabbai FB, Agarwal R et al (2013) Prevalence and prognostic role of resistant hypertension in Chronic Kidney Disease. J Am Coll Cardiol 61(24):2461–2467
16. De Nicola L, Borrelli S, Gabbai FB et al (2011) Burden of resistant hypertension in hypertensive patients with non-dialysis chronic kidney disease. Kidney Blood Press Res 34(1):58–67
17. Coresh J, Twin TC, Matsushita K et al, for the CKD Prognosis Consortium (2014) Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA 311:2518–2531
18. KDIGO (2013) KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl 3(1):1–150
19. De Nicola L, Minutolo R, Bellizzi V et al (2004) Achievement of target blood pressure levels in chronic kidney disease: a salty question? Am J Kidney Dis 43(5):782–795
20. Remuzzi G, Perico N, Macia M, Ruggenenti P (2005) The role of renin-angiotensin-aldosterone system in the progression of chronic kidney disease. Kidney Int Suppl 99:S57–S65
21. Neumann J, Ligtenberg G, Klein II et al (2004) Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment. Kidney Int 65(5):1568–1576
22. Cianciaruso B, Bellizzi V, Minutolo R et al (1996) Renal adaptation to dietary sodium restriction in moderate renal failure resulting from chronic glomerular disease. J Am Soc Nephrol 7(2):306–313
23. Konishi Y, Okada N, Okamura M et al (2001) Sodium sensitivity of blood pressure appearing before hypertension and related to histological damage in IgA nephropathy. Hypertension 38(1):81–85
24. Minutolo R, Gabbai FB, Borrelli S et al (2007) Changing the timing of antihypertensive therapy to reduce nocturnal blood pressure in CKD: an 8-week uncontrolled trial. Am J Kidney Dis 50(6):908–917
25. Sachdeva A, Weder AB (2006) Nocturnal sodium excretion, blood pressure dipping and sodium sensitivity. Hypertension 48:527–533
26. Briet M, Boutouyrie P, Laurent S, London GM (2012) Arterial stiffness and pulse pressure in CKD and ESRD. Kidney Int 82:388–400
27. Passauer J, Pistrosch F, Büssemaker E et al (2005) Reduced agonist-induced endothelium-dependent vasodilation in uremia is attributable to an impairment of vascular nitric oxide. J Am Soc Nephrol 16(4):959–965
28. Chesterton LJ, Sigrist MK, Bennett T et al (2005) Reduced baroreflex sensitivity is associated with increased vascular calcification and arterial stiffness. Nephrol Dial Transplant 20:1140–1147
29. Studinger P, Lénárd Z, Mersich B et al (2006) Determinants of baroreflex function in juvenile end-stage renal disease. Kidney Int 69:2236–2242
30. Raine AE, Bedford L, Simpson AW et al (1993) Hyperparathyroidism, platelet intracellular free calcium and hypertension in chronic renal failure. Kidney Int 43(3):700–705
31. Upadhyay A, Earley A, Haynes SM, Uhlig K (2011) Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. Ann Intern Med 154:541–548
32. Chobanian AV, Bakris GL, Black HR et al, National High Blood Pressure Education Program Coordinating Committee (2003) The Seventh Report of the Joint National Committee on

prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 289:2560–2572
33. Mancia G, De Backer G, Dominiczak A et al, Management of Arterial Hypertension of the European Society of Hypertension, European Society of Cardiology (2007) 2007 Guidelines for the Management of Arterial Hypertension: The task force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 25:1105–1187
34. Kidney Disease Outcomes Quality Initiative (K/DOQI) (2004) K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 43:S1–S290
35. Lazarus JM, Bourgoignie JJ, Buckalew VM et al (1997) Achievement and safety of a low blood pressure goal in chronic renal disease. The Modification of Diet in Renal Disease Study Group. Hypertension 29:641–650
36. Klahr S, Levey AS, Beck GJ et al (1994) The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med 330:877–884
37. Peterson JC, Adler S, Burkart JM et al (1995) Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. Ann Intern Med 123:754–762
38. Wright JT Jr, Bakris G, Greene T et al (2002) African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 288:2421–2431
39. Norris K, Bourgoigne J, Gassman J et al (2006) Cardiovascular outcomes in the African American Study of Kidney Disease and Hypertension (AASK) Trial. Am J Kidney Dis 48:739–751
40. Ruggenenti P, Perna A, Loriga G et al (2005) Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. Lancet 365:939–946
41. Lv J, Ehteshami P, Sarnak MJ et al (2013) Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ 185:949–957
42. Lv J, Neal B, Ehteshami P et al (2012) Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: a systematic review and meta-analysis. PLoS Med 9:e1001293
43. Wright JT Jr, Williamson JD, Whelton PK et al, SPRINT Research Group (2015) A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 373(22):2103–2116
44. Lewis JB (2010) Blood pressure control in chronic kidney disease. Is less really more? J Am Soc Nephrol 21:1086–1092
45. Borrelli S, De Nicola L, Minutolo R et al (2012) Limitations of blood pressure target in non-dialysis chronic kidney disease: a question of method? G Ital Nefrol 29(4):418–424
46. Agarwal R (2010) Debate: CON position. People with chronic kidney disease should have a blood pressure lower than 130/80 mm Hg. Am J Nephrol 32:374–376
47. ClinicalTrials.gov Identifier:NCT01835249
48. KDIGO (2012) KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl 2(5):337–414
49. Hallan SI, Ritz E, Orth SR (2009) Combining GFR and albuminuria to classify CKD improves prediction of ESRD. J Am Soc Nephrol 20:1069–1077
50. Hemmelgarn BR, Manns BJ, Lloyd A et al (2010) Relation between kidney function, proteinuria, and adverse outcomes. JAMA 303:423–429
51. Hillege HL, Piddler V, Diercks GF et al (2002) Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation 106:1777–1782
52. Wachtell K, Ibsen H, Olsen MH et al (2003) Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. Ann Intern Med 139:901–906

53. Parving HH, Lehnert H, Bröchner-Mortensen J et al, Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group (2001) The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 345(12):870–878
54. Brenner BM, Cooper ME, de Zeeuw D et al (2001) Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 345(12):861–869
55. Lewis EJ, Hunsicker LG, Claske WR et al (2001) Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 345(12):851–860
56. Bakris GL et al (2003) Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. Arch Intern Med 163(13):1555–1565
57. de Zeeuw D, Weir MR, Shanifar S et al (2004) Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney Int 65(6):2309–2320
58. Appel LJ, Wright JT, Greene T et al (2010) Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med 363(10):918–929
59. Aronow WS, Fleg JL, Pepine CJ et al (2011) ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. J Am Soc Hypertens 5:259–352
60. National Clinical Guideline Center, British Hypertension Society (2011) Hypertension. The Clinical Management of Primary Hypertension in Adults. Clinical Guideline 127. Commissioned by the National Institute for Health and Clinical Excellence
61. Pickering TG, Shimbo D, Haas D (2006) Ambulatory blood-pressure monitoring. N Engl J Med 354:2368–2374
62. Minutolo R, Agarwal R, Borrelli S et al (2011) Prognostic role of ambulatory blood pressure monitoring in patients with non-dialysis CKD. Arch Intern Med 171(12):1090–1098
63. Agarwal R, Andersen MJ (2006) Prognostic importance of ambulatory blood pressure recordings in patients with chronic kidney disease. Kidney Int 69(7):1175–1180
64. Agarwal R, Andersen MJ (2006) Blood pressure recordings within and outside the clinic and cardiovascular events in chronic kidney disease. Am J Nephrol 26(5):503–510
65. Gabbai FB, Rahman M, Hu B et al (2012) Relationship between ambulatory BP and clinical outcomes in patients with hypertensive CKD. Clin J Am Soc Nephrol 7(11):1770–1776
66. Bangash F, Agarwal R (2009) Masked hypertension and white coat hypertension in chronic kidney disease: a meta-analysis. Clin J Am Soc Nephrol 4(3):656–664
67. Pickering TG, James GD, Boddie C et al (1988) How common is white coat hypertension? JAMA 259(2):225–228
68. Pickering TG, Davidson K, Gerin W, Schwartz JE (2002) Masked hypertension. Hypertension 40(6):795–796
69. Minutolo R, Gabbai FB, Agarwal R et al (2014) Assessment of achieved clinic and ambulatory blood pressure recordings and outcomes during treatment in hypertensive patients with CKD: a multicenter prospective cohort study. Am J Kidney Dis 64(5):744–752
70. Gorostidi M, Sarafidis PA, de la Sierra A et al, Spanish ABPM Registry Investigators (2013) Differences between office and 24-hour blood pressure control in hypertensive patients with CKD: a 5,693-patient cross-sectional analysis from Spain. Am J Kidney Dis 62(2):285–294
71. Andersen MJ, Khawandi W, Agarwal R (2005) Home blood pressure monitoring in CKD. Am J Kidney Dis 45(6):994–1001
72. Iimuro S, Imai E, Watanabe T et al, Chronic Kidney Disease Japan Cohort Study Group (2013) Clinical correlates of ambulatory BP monitoring among patients with CKD. Clin J Am Soc Nephrol 8(5):721–730
73. Wang C, Gong WY, Zhang J et al (2015) Disparate assessment of clinic blood pressure and ambulatory blood pressure in differently aged patients with chronic kidney disease. Int J Cardiol 183:54–62

74. Pogue VA, Rahman M, Lipkouitz M et al (2009) Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. Hypertension 53(1):20–27
75. Minutolo R, Borrelli S, Scigliano R et al (2007) Prevalence and clinical correlates of white coat hypertension in chronic kidney disease. Nephrol Dial Transplant 22:2217–2223
76. Agarwal R, Pappas MK, Sinha AD (2016) Masked uncontrolled hypertension in CKD. J Am Soc Nephrol 27(3):924–932
77. Minutolo R, Borrelli S, Chiodini P et al (2007) Effects of age on hypertensive status in patients with chronic kidney disease. J Hypertens 11:2325–2333
78. Sinha AD, Agarwal R (2015) The complex relationship between CKD and ambulatory blood pressure patterns. Adv Chronic Kidney Dis 22:102–107
79. Fagard RH, Celis H, Thijs L et al (2008) Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. Hypertension 51(1):55–61
80. Rahman M, Greene T, Phillips RA et al (2013) A trial of 2 strategies to reduce nocturnal blood pressure in blacks with chronic kidney disease. Hypertension 61(1):82–88
81. Hermida RC, Ayala DE, Mojón FJR (2011) Bedtime dosing of antihypertensive medications reduces cardiovascular risk in CKD. J Am Soc Nephrol 22(12):2313–2321
82. Minutolo R, Gabbai FB, Chiodini P et al (2015) Reassessment of ambulatory blood pressure improves renal risk stratification in nondialysis chronic kidney disease: Long-Term Cohort Study. Hypertension 66(3):557–562
83. He FJ, MacGregor GA (2002) Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials. Implications for public health. J Hum Hypertens 16(11):761–770
84. Koomans HA, Roos JC, Dorhout Mees EJ, Delawi IM (1985) Sodium balance in renal failure. A comparison of patients with normal subjects under extremes of sodium intake. Hypertension 7(5):714–721
85. Mills KT, Chen J, Yang W et al (2016) Sodium excretion and the risk of cardiovascular disease in patients with chronic kidney disease. JAMA 315(20):2200–2210
86. Slagman MCJ, Waanders F, Hemmelder MH et al, Holland Nephrology Study Group (2011) Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. BMJ 343:d4366
87. De Nicola L, Minutolo R, Gallo C et al (2005) Management of hypertension in chronic kidney disease: the Italian multicentric study. J Nephrol 18(4):397–404
88. De Nicola L, Provenzano M, Chiodini P et al (2015) Independent role of underlying kidney disease on renal prognosis of patients with chronic kidney disease under Nephrology Care. PLoS One 10(5):e0127071
89. Rose BD (1991) Diuretics. Kidney Int 39(2):336–352
90. Dal Canton A, Fuiano G, Conte G et al (1985) Mechanism of increased plasma urea after diuretic therapy in uraemic patients. Clin Sci 68(3):255–261
91. Fliser D, Schröter M, Neubeck M, Ritz E (1994) Coadministration of thiazides increases the efficacy of loop diuretics even in patients with advanced renal failure. Kidney Int 46(2):482–488
92. Vaclavík J, Sedlák R, Plachý M et al (2011) Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomized, double-blind, placebo-controlled trial. Hypertension 57:1069–1075
93. Moser M (1998) Why are physicians not prescribing diuretics more frequently in the management of hypertension? JAMA 279(22):1813–1816
94. Remuzzi A, Puntorieri S, Battaglia C et al (1990) Angiotensin converting enzyme inhibition ameliorates glomerular filtration of macromolecules and water and lessens glomerular injury in the rat. J Clin Invest 85:541–549
95. Yoshioka T, Rennke HG, Salant DJ et al (1987) Role of abnormally high transmural pressure in the permselectivity defect of glomerular capillary wall: a study in early passive Heymann nephritis. Circ Res 61:531–538

96. Houlihan CA, Allen TJ, Baxter AL et al (2002) A low-sodium diet potentiates the effects of losartan in type 2 diabetes. Diabetes Care 25(4):663–671
97. Vogt L, Waanders F, Boomsma F et al (2008) Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. J Am Soc Nephrol 19(5):999–1007
98. Russo D, Minutolo R, Pisani A et al (2001) Coadministration of losartan and enalapril exerts additive antiproteinuric effect in IgA nephropathy. Am J Kidney Dis 38(1):18–25
99. Yusuf S, Teo KK, Pogue J et al, for ONTARGET Investigators (2008) Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 358:1547–1559
100. Hou FF, Zhang X, Zhang GH et al (2006) Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med 354:131–140
101. Rahman M, Pressel S, Davis BR et al (2005) Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med 165(8):936–946
102. Ibsen H, Olsen MH, Wachtell K et al (2006) Does albuminuria predict cardiovascular outcomes on treatment with losartan versus atenolol in patients with diabetes, hypertension, and left ventricular hypertrophy? The LIFE study. Diabetes Care 29:595–600
103. Ruggenenti P et al (2004) Preventing microalbuminuria in type 2 diabetes. N Engl J Med 351:1941–1951
104. Yusuf S, Sleight P, Pogue J et al (2000) Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 342:145–153

# Calculus Renal Disease

# 22

Attilio Losito

## 22.1 Epidemiology

Nephrolithiasis is widespread across the world with incidence and prevalence that vary among different geographical areas, as does the composition of kidney stones. The majority of stones are made of calcium (>80%) complexed with oxalate and/or phosphate. The presence of oxalate ranges between 45 and 73% and that of phosphate between 10 and 25%. Stones made of uric acid range between 7 and 14% [1]. In industrialized nations, the historical annual incidence was reported between 0.5% and 1.9% [2, 3]. During the last decades a trend toward increased incidence and prevalence has been observed worldwide. The lifetime prevalence in the United States has increased from 2.62%, observed in years 1964–1972, to 5.2% in years 1988–1994. Germany, Spain, and Italy have shown the same trend [4–6].

In broad terms it is generally thought that kidney stone formation is the result of interaction between genetic and environmental factors. The increase in incidence and prevalence of nephrolithiasis has developed in such a short time that is not compatible with a genetic change. Lifestyle, instead, appears to have played an important role in this trend. This is clearly shown in pediatric experience. Nephrolithiasis has become more common in children over the past few decades as a result of rapid variations in habits and increasing affluence. Changing socio-economic conditions have generated changes in the incidence and type of nephrolithiasis with respect to the site and the physicochemical composition of the calculi. Especially changes in dietary practices may be a key driving force [7].

A. Losito
Struttura Complessa Nefrologia and Dialisi, Ospedale Santa Maria Della Misericordia, Piazzale G. Menghini 1, 06132 Perugia, Italy
e-mail: atlosito@tin.it



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_22

In adults, the present increase in the prevalence of KSD has been associated with the parallel increase in obesity. The last, in turn, is considered a consequence of the exaggerated consumption of starchy foods and high-fructose corn syrup. Consumption of animal protein has also increased in a number of countries, paralleling the acceleration of stone disease [8]. Furthermore an increased intake of sodium and sodium-rich foods has been shown in some groups of stone formers [9]. All these factors act synergically with an individual genetic susceptibility to contribute to stone formation. Therefore, presently, in the epidemiology of nephrolithiasis, obesity and diet (particularly sodium intake and fructose-rich drinks) play an important role.

### 22.1.1 Association of Hypertension with Nephrolithiasis

Epidemiological data show a singular overlapping between hypertension and nephrolithiasis in terms of the age of prevalence and associated risk factors. Furthermore, the two conditions show a non-dissimilar epidemiological trend, a continuous increase in the last decades. The sharing of risk factors between the two conditions is only one of the elements that in the last few decades have raised the attention of researchers toward the relationship between hypertension and nephrolithiasis.

In 1967, Tibblin reported the results of a survey on 50-year-old men, randomly selected from the general population in Göteborg, Sweden. In this report an association of hypertension with kidney stone was shown for the first time [10]. In the following years, only few studies dealing with the association of hypertension with nephrolithiasis were published [11, 12]. The first study, formally designed to test the hypothesis that kidney stone disease is more frequent among hypertensive, was performed on 688 male workers of the Olivetti factory near Naples [13]. The results showed that the risk of nephrolithiasis in treated hypertensive men was significantly higher than that in the normotensive group. The prevalence of a history of nephrolithiasis was 13.4% in the normotensive subjects, 20.3% in the untreated hypertensives, and 32.8% in the treated hypertensives. In the 8 years follow-up study on the same cohort, the prevalence of kidney stone was 16.7% in hypertensive subjects versus 8.5% in normotensive [14].

Although no answer was provided on what might be the pathogenetic factor linking nephrolithiasis with hypertension, a hypothetical role for hypercalciuria was put forward.

An attempt to get an insight into factors linking hypertension to kidney stones formation was made by Borghi et al. [15]. They studied stone risk profile in a cohort of essential hypertension patients in comparison with normotensive controls. Hypertensive subjects had a greater risk of renal stone formation, especially when hypertension is associated with excessive body weight. During the follow-up hypertensive patients had more stone episodes than controls (14.4% vs. 2.9%). Higher oxaluria and calciuria as well as supersaturation of calcium oxalate and uric acid were the differentiating factors between hypertensive and normotensive subjects. The urine of hypertensive women differed from that of control women in having higher excretion of calcium, phosphorus, and oxalate and in supersaturation of calcium oxalate. For the first time urinary excretion of lithogenic compound was

reported in association with essential hypertension. Most of the factors highlighted in this study, supposedly linking hypertension to nephrolithiasis, became the most investigated in the following years. Thenceforth the investigational approach changed and the association between nephrolithiasis and hypertension was assessed, studying patients affected by nephrolithiasis and looking in these for the prevalence of hypertension and hypothetical linking factors.

Examining a cohort of 258 stone formers, Cupisti et al. did not find a higher prevalence of hypertension than the general population [16]. In a following investigation, Madore et al. studied 4111 patients with nephrolithiasis and found in men a significant association of this condition with hypertension [17]. Moreover in 79.5% of patients, nephrolithiasis was prior or concomitant with the diagnosis of hypertension. More recently a follow-up study in stone formers has shown that the presence of hypertension is significantly associated with the recurrence of stone formation [18]. High blood pressure has also been shown in women with nephrolithiasis and coronary heart disease, confirming the relevance of this association [19]. Notable studies showing an association between hypertension and KSD are shown in Table 22.1.

### 22.1.2 Factors Linking Hypertension to Nephrolithiasis

The approach to investigate the association of nephrolithiasis with hypertension starting from stone formers cohorts promoted research based not only on stone composition but also on urine excretion of lithogenic solutes and supersaturation and on more general predisposing factors (Table 22.2). In this setting, several lithogenic solutes have been studied individually and in association.

**Table 22.1** Association between hypertension and nephrolithiasis

| Prevalence of hypertension in nephrolithiasis | | |
|---|---|---|
| *Author* | *Year* | *Prevalence vs. non-stone formers* |
| Madore | 1998 | 24% Higher |
| Strazzullo | 2001 | 57% Higher |
| Prevalence of nephrolithiasis in hypertension | | |
| *Author* | *Year* | *Prevalence vs. non-hypertensive** |
| Tibblin | 1967 | ~30% Higher |
| Cirillo | 1988 | ~50% Higher |
| Cappuccio | 1990 | ~70% Higher |
| Borghi | 1999 | ~100% Higher |

*Approximate estimates deduced from original papers

**Table 22.2** Factors linking nephrolithiasis to hypertension

| General factors | Urine components |
|---|---|
| BMI, obesity, metabolic syndrome | Calcium |
| Female sex | Sodium |
| Uricemia | Oxalate |
| Genetics | Citrate |
| Dietary fructose | Acids |
| Dietary sodium | |
| Reduced GFR | |

### 22.1.3 Calcium and Sodium

The first singled-out component was calcium. This is not only the most common component of kidney stones, but it is also involved in the pathogenesis of hypertension [20, 21]. It has been proposed that in patients with essential hypertension, renal calcium handling is altered in such a way that urinary calcium excretion is increased at each level of sodium output [22]. This renal alteration is the consequence of a diffuse cell membrane defect in the cellular handling of sodium and calcium at a number of sites. An indirect evidence of hypercalciuria in hypertension comes also from studies on bone mineralization. Essential hypertension is associated with reduced bone density in the elderly [23]. Clinical studies have also confirmed hypercalciuria as a link between hypertension and nephrolithiasis [24]. In a retrospective study on a large cohort of stone formers, Eisner et al. found that hypertension was associated only with significantly increased urine calcium and not with other urinary components [25]. The evidence at genetic level, supporting the link between calciuria and hypertension, was found both in animals and humans. The molecular defect linking $Na^+$ and $Ca^{2+}$ renal reabsorption has been detected in mice [26]. At clinical level the use of a classical genetic approach has produced further evidence on the link between hypertension and nephrolithiasis. The investigation of the aggregation of hypertension and KSD in families of patients with KSD and hypercalciuria has shown that the disturbance in calcium metabolism in hypertension and KSD has a genetic basis [27]. Although rare, Gordon syndrome, a genetic syndrome characterized by hypertension, hyperkalemia, and hypercalciuria, is a good example in which nephrolithiasis and hypertension are linked by hypercalciuria based on a genetic defect [28].

Dietary sodium has been linked to the process of kidney stone formation for many years. It was shown experimentally in normal subjects in whom a high sodium diet produced an increased tendency for the crystallization of calcium salts in urine [29]. Moreover, in calcium stone-forming patients, high sodium chloride intake was associated with low bone density and hypercalciuria [30]. The link between the risk of stone forming and sodium intake is clearly established. The underlying pathophysiological mechanisms may lie either within the kidney itself or in a more general derangement. In fact these changes may be secondary to a primary renal tubular defect (“renal calcium leak” hypothesis) or to the effect of central volume expansion often seen in hypertension that in turn may be one consequence of the excess of sodium in the diet [31]. In a reanalysis of cohort of kidney stone formers, we found that higher blood pressure was associated with higher renal excretion of sodium (Fig. 22.1). Therefore sodium intake and high calcium excretion are an example of how hypertension and calcium stone formation are intertwined and linked. These findings suggest also a dietetic approach to these conditions aimed at definite pathophysiological targets [32].

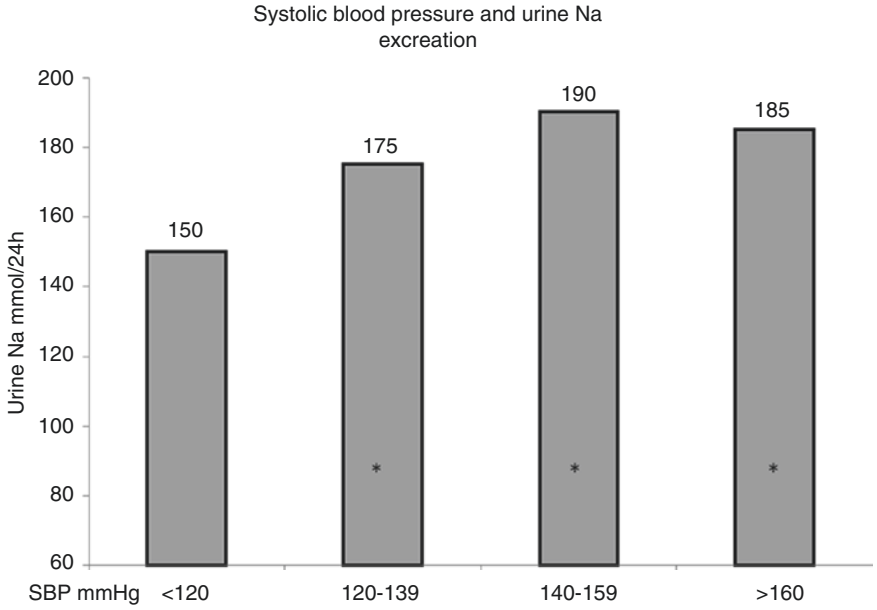



**Fig. 22.1** Renal sodium excretion in 234 patients with different types of stones. Patients are grouped by systolic blood pressure. *Significant difference with the reference group (SBP <120 mmHg). Unpublished analysis of reported data [35]

### 22.1.4 Citrate and Acids

New information on the association of hypertension with nephrolithiasis comes from studies on large cohorts. The Nurses' Health Study I (older women; N = 1284), Nurses' Health Study II (younger women; N = 952), and the Health Professionals Follow-up Study (men; N = 788) are three cohorts followed for years. In participants with nephrolithiasis, urinary calcium levels were not related consistently to hypertension. Instead, lower urinary citrate excretion was associated independently with prevalent hypertension [33]. Other studies confirmed the association of low urinary citrate with hypertension, but highlighted other potential factors [34]. Following investigations were addressed to factors that regulate urinary citrate excretion and may play a role in hypertension. Taylor suggested that hypocitraturia is due to increased citrate reabsorption in proximal tubules as a consequence of subclinical metabolic acidosis in hypertensive individuals. In fact animal and human studies have shown in salt-sensitive hypertension an increased acid excretion as a consequence of metabolic acid over production [35, 36]. In a study in stone formers in whom a complete set of urinary components and oversaturation was performed, citraturia was lower in patients with higher blood pressure [34] (Fig. 22.2). On the whole, low urine pH and citrate appear to be not only markers of hypertension associated with nephrolithiasis but also part of the pathophysiological process [36].

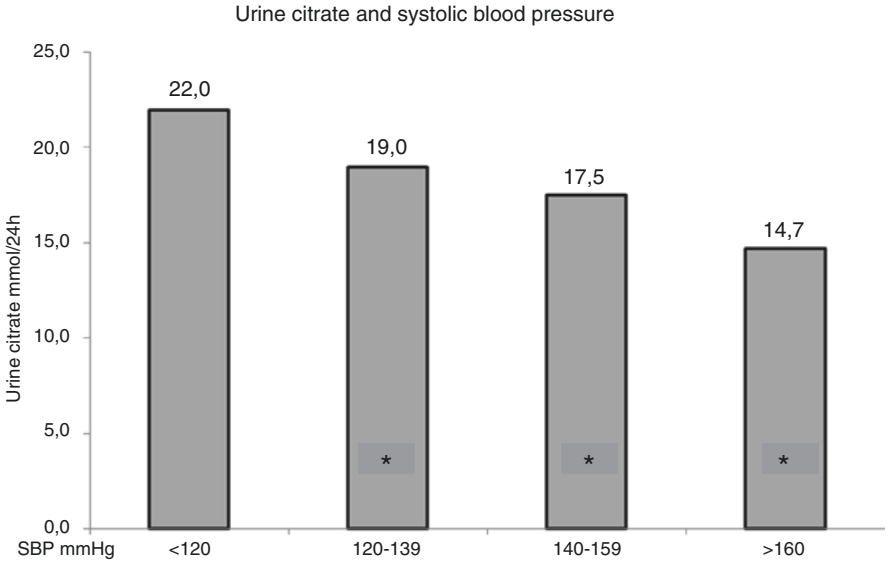



**Fig. 22.2** Urine citrate and systolic blood pressure. Patients are grouped by systolic blood pressure. *Significant difference with SBP <120 mmHg. Unpublished analysis of reported data [35]

### 22.1.5 Lifestyle, Diet, and Systemic Factors

Urinary citrate excretion is regulated by several factors. In stone formers, they themselves might also play a role in the development of hypertension.

Among those are insulin resistance and lifestyle. Studies have shown that higher level of insulin resistance is associated with lower urinary citrate excretion and that hypocitraturic patients show a greater insulin resistance than normocitraturic calcium stone formers [37]. With respect to lifestyle, there are many factors associated with citrate excretion. Hypertension is independently associated with lower 24-h urinary citrate excretion, but other several dietary and lifestyle factors and medical conditions are associated with hypo- and hypercitraturia [38]. Some constitutional factors, such as body mass index, are also associated with hypocitraturia [39]. This makes things less clear since it is well established that high BMI is strongly associated with hypertension [40]. Therefore many lifestyle and constitutional factors associated with hypocitraturia are also associated with hypertension.

Among the dietary factors potentially responsible of stone formation and hypertension is fructose. The consumption of this artificial sweetener is associated with an increased risk of kidney stones [41]. The underlying mechanism seems to be the effect of consumption of fructose on the level of supersaturation in the urine, but no clear-cut evidence has been produced yet.

On the other hand, a cross-sectional analysis using the data collected from the National Health and Nutrition Examination Survey has shown that high fructose intake, in the form of added sugar, independently associates with higher BP levels among US

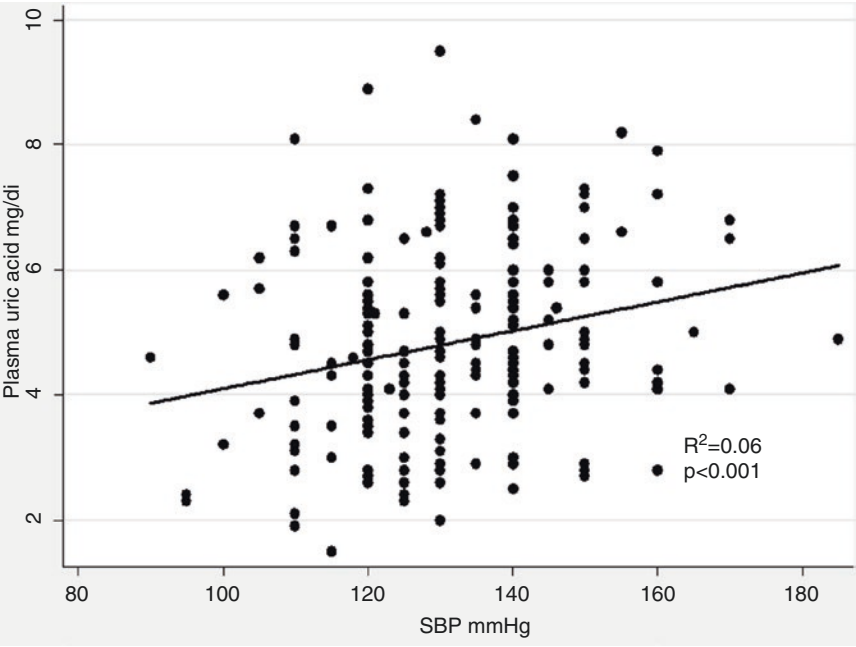



**Fig. 22.3** Plasma uric acid and systolic blood pressure in KSD. There is a direct and significant correlation between plasma uric acid and systolic blood pressure. Unpublished analysis of reported data [35]

adults without a history of hypertension [42]. Also in this case, the mechanism linking fructose intake to hypertension has not been clearly established. Yet studies in animals have shown that fructose may raise BP via several mechanisms, including stimulation of uric acid, inhibition of endothelial nitric oxide synthase system, and stimulation of the sympathetic nervous system, or by directly increasing sodium absorption in the gut [42]. Uricemia is one of the most suspected links. In the general population, a direct relationship between serum uric acid levels and BP has been shown [43, 44]. This relationship is also present in nephrolithiasis. In stone formers the association between hypertension and uric acid has been repeatedly reported [45, 46]. We found a direct relationship between uricemia and blood pressure in a cohort of stone formers [34] (Fig. 22.3). The supposed mechanism lies in uricemia-induced microvascular changes that in turn lead to endothelial dysfunction, a precursor to both coronary artery disease and hypertension. Among the several hypothetical explanations for this association in stone formers, there is one pointing specifically at a reduction of kidney function. In a retrospective analysis, uric acid stone formers had a small, significant reduction of creatinine clearance [47].

### 22.1.6 Obesity and BMI

We have seen that some dietary habits, such as high sodium and fructose intake, are associated with hypertension in nephrolithiasis. Yet inappropriate diet, and lifestyle, may also play a role indirectly, increasing BMI and promoting obesity.

The association between overweight and obesity and the prevalence of high BP has been known for some time [48].

The finding of an association between increased BMI and history of kidney stones is more recent. Curham et al. analyzed the data from the Nurses' Health Study II and the Health Professionals Follow-Up Study including a total of 140,905 subjects and looked for an association of body size and risk of kidney stones [49, 50]. They found an association of prevalence and incidence of kidney stones with weight and BMI. The magnitude of risk was higher in female than in male. These separated data showed a sharing of a risk factor between hypertension and nephrolithiasis, in the presence of increased BMI or obesity. A subsequent analysis of data from the Third National Health and Nutrition Examination Survey was addressed to estimating the association between the history of stone disease and hypertension [51]. In women, it was estimated that stone formers had a 69% increase in risk of hypertension. The risk increased with body mass index in both sexes, but was more pronounced in women. These findings therefore support the link between kidney stone disease and hypertension and suggest that overweight women stone formers may be at significantly increased risk for hypertension. The association of obesity with hypertension in women was confirmed in a following study investigating metabolic syndrome and nephrolithiasis in an inpatient population [52]. On the whole there is adequate evidence to support a role for inappropriate diet and obesity in the association of nephrolithiasis with hypertension [53]. There are also strong suggestions that some individual component of the metabolic syndrome, particularly insulin resistance, might play the same role [54]. A clear-cut evidence of this relationship has not been provided yet. In this setting we must take into account a recent investigation of autonomic dysfunction in idiopathic recurrent kidney stone formers [55]. The results showed that patients with recurrent stone formation have a subtle autonomic dysfunction resulting in increased blood BP and abnormal cardiovascular control. This study introduces further a component in the already complex picture of the relationship between nephrolithiasis and hypertension.

In conclusion, we have a certainty that kidney stone formers have a high probability of becoming hypertensive, and conversely, hypertensive subjects are at risk of nephrolithiasis. We now know that there are several links between the two conditions. Or, more precisely, we know that there are risk factors shared by the two conditions and that in different instances, different factors appear to link hypertension to nephrolithiasis. Finally, the association with hypertension contributes to the increased risk of cardiovascular disease recently reported in kidney stone formers.

## References

1. Bushinsky DA, Coe FL, Moe OW (2008) Nephrolithiasis. In: Brenner BM (ed) The Kidney, 8th edn. Saunders, Philadelphia, pp I299–1349
2. Stamatelou KK, Francis ME, Jones CA et al (2003) Time trends in reported prevalence of kidney stones in the United States: 1976–1994. Kidney Int 63:1817–1823
3. Lieske JC, Peña de la Vega LS, Slezak JM et al (2006) Renal stone epidemiology in Rochester, Minnesota: an update. Kidney Int 69:760–764

4. Hesse A, Brändle E, Wilbert D et al (2000) Study on the prevalence and incidence of urolithiasis in Germany comparing the years 1979 vs. 2000. Eur Urol 44:709–713
5. Sánchez-Martín FM, Millán Rodríguez F, Esquena Fernández S et al (2007) Incidence and prevalence of published studies about urolithiasis in Spain: a review [article in Spanish]. Actas Urol Esp 31:511–520
6. Amato M, Lusini ML, Nelli F (2004) Epidemiology of nephrolithiasis today. Urol Int 72(suppl 1):1–5
7. López M, Hoppe B (2010) History, epidemiology and regional diversities of urolithiasis. Pediatr Nephrol 25:49–59
8. Galal OM (2002) The nutrition transition in Egypt: obesity, undernutrition and the food consumption context. Public Health Nutr 5:141–148
9. Engstrom A, Tobelmann RC, Albertson AM (1997) Sodium intake trends and food choices. Am J Clin Nutr 65(suppl):704S–707S
10. Tibblin G (1967) High blood pressure in men aged 50-a population study of men born in 1913. Acta Medica Scand Suppl 470:1–84
11. Robertson WG, Peacock M, Baker M et al (1983) Studies on the prevalence and epidemiology of urinary stone disease in men in Leeds. Br J Urol 55:595–598
12. Al C, Laurenzi MN (1988) Elevated blood pressure and positive history of kidney stones: results from a population-based study. J Hypertens 6(suppl 4):485–486
13. Cappuccio FP, Strazzullo P, Mancini M (1990) Kidney stones and hypertension: population based study of an independent clinical association. BMJ 300:1234–1236
14. Cappuccio FP, Siani A, Barba G et al (1999) A prospective study of hypertension and the incidence of kidney stones in men. J Hypertens 17:1017–1022
15. Borghi L, Meschi T, Guerra A et al (1999) Essential arterial hypertension and stone disease. Kidney Int 55:2397–2406
16. Cupisti A, Morelli E, Meola M et al (1996) Hypertension in kidney stone patients. Nephron 73:569–572
17. Madore F, Stampfer MJ, Rimm EB, Curhan GC (1998) Nephrolithiasis and risk of hypertension. Am J Hypertens 11:46–53
18. Kim YJ, Park MS, Kim WT et al (2011) Hypertension influences recurrent stone formation in non obese stone formers. Urology 77:1059–1063
19. Ferraro PM, Taylor EN, Eisner BH, Gambaro G, Rimm EB, Mukamal KJ, Curhan GC (2013) History of kidney stones and the risk of coronary heart disease. JAMA 310:408–415
20. McCarron DA, Pingree PA, Rubin RJ et al (1998) Enhanced parathyroid function in essential hypertension:a homeostatic response to a urinary calcium leak. Hypertension 2:162–168
21. Strazzullo P, Nunziata V, Cirillo M et al (1983) Abnormalities of calcium metabolism in essential hypertension. Clin Sci 65:137–141
22. Strazzullo P (1991) The renal calcium leak in primary hypertension: pathophysiological aspects and clinical implications. Nutr Metab Cardiovasc Dis 1:98–103
23. Cappuccio FP, Meilahn E, Zmuda JM, Cauley JA (1999) High blood pressure and bone-mineral loss in elderly white women: a prospective study. Lancet 354:971–975
24. Timio F, Kerry SM, Anson KM et al (2003) Calcium urolithiasis, blood pressure and salt intake. Blood Press 12:122–127
25. Eisner BH, Porten SP, Bechis SK, Stoller ML (2010) Hypertension is associated with increased urinary calcium excretion in patients with nephrolithiasis. J Urol 183:576–579
26. Pan W, Borovac J, Spicer Z et al (2012) The epithelial sodium/proton exchanger, NHE3, is necessary for renal and intestinal calcium (re)absorption. Am J Physiol Ren Physiol 302:F943–F956
27. Mente A, Honey RJ, McLaughlin JM et al (2006) High urinary calcium excretion and genetic susceptibility to hypertension and kidney stone disease. J Am Soc Nephrol 17:2567–2575
28. Stratton JD, McNicholas TA, Farrington K (1998) Recurrent calcium stones in Gordon's syndrome. Br J Urol 82:925
29. Sakhaee K, Harvey JA, Padalino PK et al (1993) The potential role of salt abuse on the risk for kidney stone formation. J Urol 150:310–312

30. Martini LA, Cuppari L, Colugnati FA et al (2000) High sodium chloride intake is associated with low bone density in calcium stone-forming patients. Clin Nephrol 54:85–93
31. Adrogué HJ, Madias NE (2007) Sodium and potassium in the pathogenesis of hypertension. N Engl J Med 356:1966–1978
32. Taylor EN, Fung TT, Curhan GC (2009) DASH-style diet associates with reduced risk for kidney stones. J Am Soc Nephrol 20:2253–2259
33. Taylor EN, Mount DB, Forman JP, Curhan GC (2006) Association of prevalent hypertension with 24-hour urinary excretion of calcium, citrate, and other factors. Am J Kidney Dis 47:780–789
34. Losito A, Nunzi EG, Covarelli C et al (2009) Increased acid excretion in kidney stone formers with essential hypertension. Nephrol Dial Transplant 24:137–141
35. Batlle DC, Sharma AM, Alsheikha MW et al (1993) Renal acid excretion and intracellular pH in salt-sensitive genetic hypertension. J Clin Invest 91:2178–2184
36. Sharma AM, Kribben A, Schattenfroh S et al (1990) Salt sensitivity in humans is associated with abnormal acid-base regulation. Hypertension 16:407–413
37. Cupisti A, Meola M, D'Alessandro C et al (2007) Insulin resistance and low urinary citrate excretion in calcium stone formers. Biomed Pharmacother 61:86–90
38. Mandel EI, Taylor EN, Curhan GC (2013) Dietary and lifestyle factors and medical conditions associated with urinary citrate excretion. Clin J Am Soc Nephrol 8:901–908
39. Eisner BH, Eisenberg ML, Stoller ML (2010) Relationship between body mass index and quantitative 24-hour urine chemistries in patients with nephrolithiasis. Urology 75:1289–1293
40. Brown CD, Higgins M, Donato KA et al (2000) Body mass index and the prevalence of hypertension and dyslipidemia. Obes Res 8:605–619
41. Taylor EN, Curhan GC (2008) Fructose consumption and the risk of kidney stones. Kidney Int 73:207–212
42. Soleimani M (2011) Dietary fructose, salt absorption and hypertension in metabolic syndrome: towards a new paradigm. Acta Physiol (Oxford) 201:55–62
43. Feig DI, Kang DH, Johnson RJ (2008) Uric acid and cardiovascular risk. N Engl J Med 359:1811–1821
44. Whelton A (2012) Hyperuricemia and hypertension: a confluence of concepts. Hypertension 60:1112–1113
45. Cannon PJ, Stason WB, Demartini FE et al (1966) Hyperuricemia in primary and renal hypertension. N Engl J Med 275:457–464
46. Johnson RJ, Feig DI, Herrera-Acosta J, Kang DH (2005) Resurrection of uric acid as a causal risk factor in essential hypertension. Hypertension 45:18–20
47. Worcester EM, Parks JH, Evan AP, Coe FL (2006) Renal function in patients with nephrolithiasis. J Urol 176:600–603
48. Mac Mahon S, Cutler J, Brittian E, Higgins M (1987) Obesity and hypertension: epidemiological and clinical issues. Eur Heart J 8:57–70
49. Curhan GC, Willett WC, Rimm EB et al (1998) Body size and risk of kidney stones. J Am Soc Nephrol 9:1645–1652
50. Taylor EN, Stampfer MJ, Curhan GC (2005) Obesity, weight gain, and the risk of kidney stones. JAMA 293:455–462
51. Gillen DL, Coe FL, Worcester EM (2005) Nephrolithiasis and increased blood pressure among females with high body mass index. Am J Kidney Dis 46:263–269
52. Rendina D, Mossetti G, De Filippo G et al (2009) Association between metabolic syndrome and nephrolithiasis in an inpatient population in southern Italy: role of gender, hypertension and abdominal obesity. Nephrol Dial Transplant 24:900–906
53. Obligado SH, Goldfarb DS (2008) The association of nephrolithiasis with hypertension and obesity: a review. Am J Hypertens 21:257–264
54. Cupisti A, D'Alessandro C, Samoni S et al (2014) Nephrolithiasis and hypertension: possible links and clinical implications. J Nephrol 27:477–482
55. Domingos F, Escalda A (2012) Causes of autonomic dysfunction in idiopathic recurrent kidney stone formers. Int Urol Nephrol 44:873–882

# Uric Acid-Hypertension Relationships

# 23

Adel E. Berbari, Najla A. Daouk, and Giuseppe Mancia

## 23.1 Introduction

It is well established that high serum uric acid levels are associated with deposition of uric acid crystals in tissues of several target organs and formation of urinary calculi and nephrolithiasis [1]. Further there is increasing evidence that chronic hyperuricemia is a major risk for future hypertension, cardiorenal disease, and metabolic disorders [2–9].

Serum uric acid levels in the population tend to increase [10]. Several factors contribute to the increase in serum uric acid levels, namely, changing dietary patterns, increasing body weight and obesity, chronic administration of certain classes of therapeutic agents, and improved life expectancy [2].

The aim of this chapter is to summarize relevant studies concerning uric acid and possible links to hypertension and renal and cardiovascular diseases.

## 23.2 Uric Acid-Cardiorenal Relationship

### 23.2.1 Historical Background

Uric acid was first associated with primary hypertension in 1874 by Mohamed [11]. Mohamed, who noted that many of his hypertensive patients had a family history of gout, proposed that uric acid might play an important role in the

A.E. Berbari, M.D. (✉) • N.A. Daouk
Department of Internal Medicine, American University of Beirut Medical Center,
Riad El Solh, 1107 2020 Beirut, Lebanon
e-mail: ab01@aub.edu.lb

G. Mancia
Emeritus Professor of Medicine, University of Milano-Bicocca,
Monza, Italy



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_23

pathogenesis of essential hypertension [12]. Several years later, Haig linked uric acid to elevated blood pressure (BP) [13, 14]. Further, in an address to the American Medical Association in 1897, Davis contented that gout was a major cause of hypertension and manifested renal tubulointerstitial and arteriolar vascular diseases and ventricular hypertrophy [15]. In 1913, a French group of investigators reported that the injection of uric acid into rabbits could increase BP [16].

Although the association between increased serum uric acid and hypertension was repeatedly reported in the early part of the twentieth century, it received little attention by scientific organizations and documents [17, 18]. Serum uric acid was even ignored in clinical practice [18, 19]. However, from the late 1980s, a large number of clinical and experimental studies were published, documenting the prognostic significance of serum uric acid, reviving the interest in this parameter as a major risk for hypertension, and cardiorenal diseases [20].

### 23.2.2 Uric Acid: Generation, Excretion, and Biochemical Reactions

Uric acid (7,9-dihydro-1H-purine-2,6,8(3H)-trione; 8-hydroxyxanthine; purine-2,6,8-triol; 2,6,8-trioxypurine) is a weak, odorless, colorless, and tasteless organic acid. It is poorly soluble at urinary physiological pH = 5.0–6.0 with a concentration not exceeding 15 mg/dL [21]. However, at a urinary pH = 7.0 and in non-acidic solutions, uric acid solubility increases significantly with a concentration often equal to or exceeding 200 mg/dL [21]. At pH = 7.4 and at 37 °C, about 98% of uric acid is ionized as monosodium urate [22]. At the uric acid concentration of the extracellular fluid, serum is supersaturated with monosodium urate at uric acid concentration more than 6.5 mg/L [23].

Serum uric acid levels follow a circadian rhythm with higher uric acid levels during the night and first morning hours.

Uric acid is not regularly ingested, although dietary intake appears to provide a significant source of urate precursors [24].

The liver is the major site of uric acid production from both exogenous and endogenous purines, which are derived from dietary sources and nucleic acid metabolism [25]. Biochemical reactions catalyzed by two enzyme systems, xanthine dehydrogenase and xanthine oxidase, mediate the breakdown of purines into xanthine and hypoxanthine [2, 25]. In turn, the latter two compounds are metabolized to the poorly soluble uric acid [25]. In most mammals, uric acid is further degraded to allantoin, a very soluble and easily eliminated product by uricase, an oxidative enzyme located in the peroxisomes of the hepatocytes (Fig. 23.1) [25]. In contrast, in humans and great apes, due to the lack of hepatic uricase from genetic mutation, the poorly soluble uric acid is the final breakdown product of purine metabolism [25].

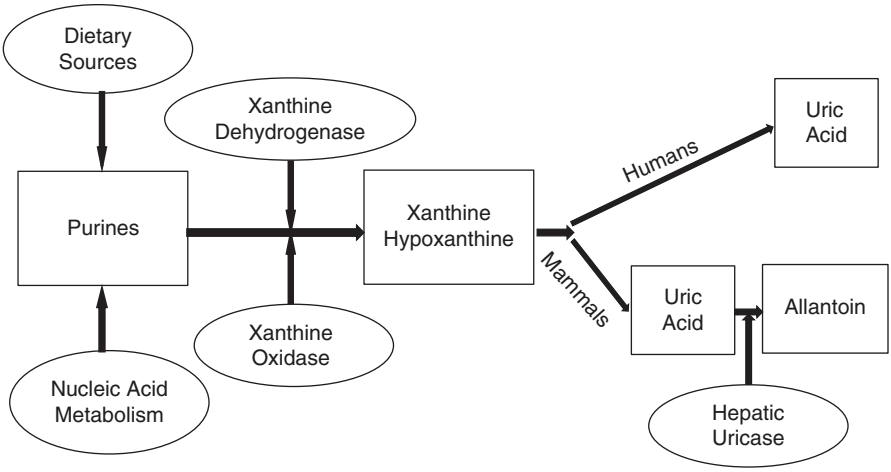



**Fig. 23.1** Genesis of uric acid/allantoin production

As a result of these biochemical and functional differences, serum uric acid levels are significantly higher in humans than in other mammalians [21].

#### 23.2.2.1 Homeostasis

With a functional pKa of about 5.75 and an arterial blood pH = 7.40, uric acid, the poorly soluble end product of purine metabolism, dissociates and circulates as the urate anion:

$$\text{Uric acid} \underset{\text{pH}=7.40}{\overset{\text{pKa}=5.75}{\rightarrow}} \text{urate} + \text{H}$$

The body urate pool in an adult male is about 1200 mg, representing about twice the amount in an adult female [26]. This gender difference has been attributed to the greater renal urate excretion in premenopausal females due to the biologic effects of estrogenic hormones [26].

#### 23.2.2.2 Uric Acid Elimination

Homeostasis of serum uric acid is maintained by two mechanisms, namely, renal and gastrointestinal [25]. Under normal physiologic conditions, metabolism of urate by human tissues is negligible.

The poorly soluble intracellular uric acid is transported into the circulation by a complex mechanism [27]. Upon reaching the circulation, serum uric acid is excreted by the kidneys and the gastrointestinal tract [25].

##### Renal Clearance

About 2/3 of the daily turnover of urate in humans is excreted by the kidneys through glomerular filtration and tubular processes [25].

Protein binding accounts for only about 5% of the circulating urate [22]. Thus, almost all of the circulating urate is freely filterable at the glomerulus [22].

Tubular handling of urate takes place at the proximal tubule and is characterized by three processes, namely, presecretory reabsorption, secretion, and postsecretory reabsorption [21, 22].

Most of the filtered urate is reabsorbed in the early part of the proximal tubule (the so-called presecretory reabsorption phase) [21, 22]. This process is followed by secretion which occurs in the $S_2$ segment of the proximal tubule and returns about 50% of the filtered urate back into the tubular lumen [28]. The secreted urate undergoes further reabsorption (the so-called postsecretory reabsorption) and occurs in $S_3$ segment of the proximal tubule [28].

About 90% of the secreted urate undergoes postsecretory reabsorption [22, 28]. Thus, only about 7–12% of the filtered urate is excreted [22].

#### Gastrointestinal Degradation

The remaining 1/3 of the urate load is excreted by the gastrointestinal tract [25].

Recent evidence suggests that the entry of urate into the intestines is both passive and active [29]. In the gut, urate is almost completely degraded by intestinal bacteria, with little being found in the stools [30].

### 23.2.2.3 Biologic Effects of Uric Acid

Serum urate is not an inert molecule, but possesses several biological actions that could be either beneficial or detrimental [25].

#### Antioxidant Properties

Urate may act as an aqueous antioxidant. Along with ascorbate, urate is one of the most important antioxidants in the plasma reacting with a large number of oxidants [31]. In particular, by scavenging superoxide anions, it blocks the reaction of superoxide with nitric oxide and prevents the formation of peroxynitrite which is a very toxic product to the cells [32]. Uric acid may also prevent the degradation of extracellular superoxide, an extracellular enzyme which is critical in blocking the reaction and inactivation of nitric oxide by superoxide anions [25].

#### Adverse Reactions

In contrast to its beneficial actions, urate has a large number of adverse effects on vascular structures.

*Endothelial dysfunction*: Urate may contribute to endothelial dysfunction. Uric acid infusions in healthy human subjects result in impaired acetylcholine-induced vasodilatation in the forearm, documenting impaired endothelial nitric oxide (NO) release [33]. In experimental animals, mild hyperuricemia inhibits the NO system in the kidney [33].

The mechanism by which uric acid (urate) impairs endothelial function may be related to a pro-oxidative action under certain conditions [2].

*Proliferation of vascular smooth muscle cells*: Uric acid (urate) also stimulates proliferation of vascular muscle cells by activating intracellular protein metabolism

resulting in proliferative and pro-inflammatory reactions which produce growth factors, vasoconstriction, and pro-inflammatory molecules [2, 34–36].

### 23.2.3 Hyperuricemia

#### 23.2.3.1 Definition

Hyperuricemia is generally defined as serum urate levels of >6.5–7.0 mg/dL in males and >6 mg/dL in females [31]. However, the definition of hyperuricemia has been difficult to assess around the mean of serum urate levels in the population [22].

Different criteria have been used to determine which levels of serum urate define hyperuricemia. First, based in its physiochemical properties, serum urate is supersaturated at a concentration greater than 6.5 mg/dL in the extracellular fluid [22]. It has been recommended to consider serum urate levels greater than 7.0 and 6.0 mg/dL in males and females, respectively, to represent hyperuricemia [22]. Second, age has a significant effect on serum urate levels. Serum urate levels are lower in children than in adults [22, 25, 38]. With the entry into male puberty, values increase toward normal adult male range [22, 25, 38]. Further, compared to their male counterparts, premenopausal females have lower serum urate values, attributed to the higher renal urate handling [22, 38]. However, with the onset of menopause, serum urate levels tend to increase, approaching those in males of corresponding age [22, 38].

Third, several studies have demonstrated that serum uric acid levels cluster in families, suggesting that genetic factors modulate the regulation of this molecule [39]. Twin studies, path analysis and segregation analysis methods, estimate that the heritability of serum uric acid ranges between 0.40 and 0.73 [39–41].

Genome-wide association studies revealed that numerous candidate genes are involved in the regulation of serum uric acid levels [42]. About thirty gene variants have been identified, explaining about 7% of the variation in serum uric acid levels [42].

The gene most strongly associated with serum uric acid resides on chromosome 4 and codes for SLC2A9 (also known as GLUT9), a key urate transporter which localizes to both apical and basolateral membranes of the human renal proximal tubular cells in vitro [43]. Recent studies have shown that SLC2A9 is involved in renal and gastrointestinal excretion of uric acid and is implicated in antioxidant defense [44].

The causality of serum uric acid and cardiovascular disease has been explored by genome-wide association and Mendelian randomization studies. However, the results of these studies have been contradictory.

Investigating the association between a missense nucleotide polymorphism in the LC2A9 gene and BP, Passa found that a decrease in serum uric acid levels correlated with lower systolic BP, depending on the salt intake [43]. On the other hand, using a genetic score approach in the Rotterdam Study, Sedaghat et al. reported that in thirty gene variants higher serum uric acid was associated with lower systolic and diastolic blood pressure levels, but only in the subgroup of

subjects responsive to diuretics [45]. In contrast, in a family-based study which included 449 subjects in a homogenous population, Mallamaci et al. reported that there was a strong correlation between a variant GLUT9 (SLC2A9) gene, hyperuricemia, and increase in some BP components, namely, clinic systolic BP (SBP) and white coat effect (defined as the difference between clinic SBP and daytime systolic ambulatory BP) [46]. However, not all studies demonstrated a relation between genetic factors, serum uric acid, and BP. In their study, Pelinor et al. reported no evidence for causal association for a variant SLC2A9 gene, with serum uric acid and systolic and diastolic BP [47].

Several other chromosome regions that influence serum uric acid have been identified [48, 49]. Nath et al. identified a major locus on chromosome 6q22–23 for serum uric acid using data from 644 participants in the San Antonio Family Heart Study [49]. In this cohort, serum uric acid was found to exhibit a significant heritability of 0.42 [49].

The association of a variant gene on chromosome 6q22–23 with serum uric acid is of particular interest. Studies have indicated that 6q22–23 chromosome region contains genes that influence familial IgA nephropathy (IgAN) [50]. Hyperuricemia appears to predispose the progression of familial IgAN [51]. Further, serum uric acid levels correlate with histologic and immunochemical glomerular and tubulointerstitial changes in IgAN [51].

Fourth, epidemiologic studies have reported that both environmental health traits and pharmacologic agents may account for variation in serum uric acid levels [22, 52, 53].

High serum uric acid levels are strongly associated with a large number of health traits such as obesity, waist circumference, insulin resistance, type 2 diabetes, and renal disease [52–54]. Further, these health traits are characterized by a high heritability, suggesting that a set of common genes may influence serum uric acid and these health traits [49]. These observations suggest that both environmental health conditions and genetic background influence serum uric acid levels [2, 49].

In the San Antonio Family Heart Study, significant genetic correlations were observed between uric acid and cardiovascular risk traits such as obesity, waist circumference, body mass index (BMI), and systolic and pulse pressures with correlations spanning from 0.37 to 0.68 [49]. The strongest evidence for linkage with serum uric acid occurred between two genetic variants on chromosome 6q22–23 [49].

Hyperuricemia can be caused by a small number of inherited enzyme defects which lead to purine overproduction such as overactivity of phosphoribosylpyrophosphate synthase, decreased activity of hypoxanthine phosphoribosyltransferase, and glycogen storage disease [2, 22]. Additional causes of hyperuricemia include food products and pharmacologic agents and drugs (Table 23.1) [2, 22, 55, 56].

As discussed in previous sections, there is no universally accepted definition of hyperuricemia. For purposes related to crystal deposition disease (gout, nephrolithiasis), a physicochemical definition of hyperuricemia based upon solubility properties of urate in body fluids is recommended [57–59]. This definition corresponds to a serum urate concentration of equal to or greater than 7 mg/dL [57–59]. However, a definition of hyperuricemia appropriate to the non-crystal deposition disorders

**Table 23.1** Determinants of elevated serum uric acid levels

| Production | Excretion |
|---|---|
| • Rare enzymatic defects | • Impaired renal excretion |
| • High cell turnover | |
| • Alcohol ingestion | |

(hypertension, cardiorenal disease) has been more problematic for two reasons: (1) the high prevalence of asymptomatic hyperuricemia, using serum urate concentrations exceeding saturation but within two standard deviations of the population mean [60], and (2) the association of serum urate levels with cardiovascular disorders (hypertension, cardiorenal disease) occurring at subsaturation concentrations [61, 62].

Other experts recommend using a serum urate concentration exceeding 6 mg/dL as a definition of hyperuricemia [61–64]. This recommendation is based on the assumption that goal serum urate concentration of less than 6 mg/dL appears to be associated with reduction in both clinical consequences of hyperuricemia and recurrence of gout [61–64].

#### 23.2.3.2 Prevalence

As mentioned in other sections of this chapter, several factors influence the levels of serum uric acid, making it difficult to recommend a normal set of values (Table 23.2). However, based on epidemiologic and clinical studies, the following cutoff values of serum uric acid levels have been considered to denote an upper limit reference range, with 5 mg/dL for children, 7 mg/dL for men, and 6 mg/dL for women [37, 61].

Hyperuricemia is a very common abnormal laboratory test encountered in clinical practice.

In the general population, hyperuricemia is present in 17% of adult males in France, in 7% of adult males in Spain, and in 13.7% of men in North China [22, 65, 66]. In the USA, the estimated prevalence of hyperuricemia as reported in the US National Health and Nutrition Examination Survey (NHANES) 2007–2008 is about 23%, with rates higher in Afro-Americans than in other American ethnic groups [10]. Certain aboriginal populations in the Pacific regions exhibit very high prevalent rates of 41% [67].

Further, worldwide, the prevalence of hyperuricemia has increased substantially in recent decades [68]. The progressive increase in serum uric acid levels has been attributed to the increasing prevalence of obesity and increased consumption of sugar-sweetened beverages, foods rich in purines, and alcohol [69–74].

In a recent Italian survey, using a cutoff uric acid level of 6 mg/dL, the prevalence of hyperuricemia increased from 8.5% in 2005 to 11.9% in 2009 [75]. Likewise, a study from Japan revealed an increased prevalence of hyperuricemia over a 10-year follow-up [76].

Hyperuricemia is a frequent finding in hypertension in adults, adolescents, and children (Table 23.3).

**Table 23.2** Causes of secondary hyperuricemia

| Drugs/pharmacologic agents |
|---|
| • Diuretics |
| • Cyclosporine |
| • Low-dose salicylates |
| • Beta blockers |
| • Ethambutol |
| • Pyrazinamide |
| • Levodopa |
| • Laxative abuse |
| • Ethanol |
| • Salt restriction |
| Dietary products |
| • Meat |
| – Beef lamb, pork |
| – Internal organs |
| Liver |
| Kidney |
| Heart |
| • Seafood |
| – Mussels |
| – Crab |
| – Shrimps |
| – Sardines |
| – Caviar |
| – Anchovies |
| • Poultry |
| – Chicken |
| – Duck |
| • Dried peas/beans/legumes |
| – Baked beans |
| – Kidney beans |
| – Peas |
| • Vegetables |
| – Asparagus |
| – Cauliflower |
| – Spinach |
| – Mushrooms |
| • Whole grains |
| • Fructose |

**Table 23.3** Incidence of increased serum uric acid levels in various population

| Phenotype | Rate (%) |
|---|---|
| US general population | 5 |
| Untreated hypertension | 25 |
| Treated hypertension | 50 |
| General hypertensive population | 40–60 |
| Malignant hypertension ± renal failure | 75–100 |

Among the earliest studies linking serum uric acid to hypertension, Cannon reported the coexistence of hyperuricemia in 25–50% of untreated primary adult hypertension and in 75% of renal and/or malignant hypertension [77]. Following these early reports, several studies documented that the relationship between serum

uric acid and BP is continuous and is observed in Afro-Americans, whites, and Asians [78–80]. In one study, 50% of adults with asymptomatic hyperuricemia (defined as serum uric acid >7 mg/dL in males and >6.5 mg/dL in females) were hypertensive [20, 81]. Likewise, about 60–65% of patients with gout have hypertension [82]. In addition, the incidence of hyperuricemia appears to correlate with antihypertensive therapy and severity indices of the hypertensive process [77, 83, 84].

However, the association of serum uric acid with BP appears to be age dependent and weakens with aging. The relation of serum uric acid, BP, and age was evaluated in a study of over 45,000 healthy Koreans who underwent a routine health examination and never received any uricosuric or antihypertensive agents [85]. In subjects younger than 60 years of both genders, an increase in serum uric acid was strongly associated with an elevation in both systolic and diastolic blood pressures [85]. The association was stronger in females [85]. In contrast, in subjects 60 years or older, the association of serum uric acid and BP weakens and may even be lost [85].

Hyperuricemia is commonly observed also in pediatric and adolescent hypertension.

Forty to 70% of hypertensive children and adolescents have primary hypertension without an identifiable etiology [86]. Feig et al. evaluated 125 hypertensive children with never previously treated hypertension, with an age range of 6 to 18 years and a mean of 13.4 years and 40 age-matched normotensive controls [61]. Serum uric acid levels of >6.5 mg/dL were found in 89% in primary hypertension, in 30% in secondary hypertension, and in none in white coat hypertension and normotensive controls (Table 23.4) [61]. The association of serum uric acid and BP was also examined in the National Survey 1999–2006, a large nationally representative cohort of US adolescents, a population with a low prevalence of cardiovascular disease and risk factors [62]. Among 6036 adolescents, with an age range of 12–17 years and mean of 14.7 years, 17% were obese, 3.3% were hypertensive (defined as systolic and diastolic blood pressure ≥95% for age, sex, and height), and 34% had an elevated serum uric acid levels >5.5 mg/dL [62]. Compared with serum uric acid levels <5.5 mg/dL, participants with a serum uric acid level of >5.5 mg/dL had two times greater risk of having increased blood pressure [62].

### 23.2.3.3 Hypertension

#### Epidemiology

Human and animal studies have repeatedly indicated an independent association between serum uric acid and the risk of hypertension [61, 62]. Several epidemiologic and clinical studies have examined the link between hyperuricemia and risk of hypertension.

**Table 23.4** Incidence of hyperuricemia in new onset hypertension in adolescents (serum uric acid >5.5 mg/dL) [83]

| Hypertension phenotype | Prevalence (%) |
|---|---|
| Essential hypertension | 89 |
| Secondary hypertension | 30 |
| White coat hypertension | 0 |
| Normotensive controls | 0 |

A cohort of 125 children, with an age range of 6–18 years and a mean of 13.4 ± 3.3 years, was evaluated for never-treated new onset hypertension [61]. Compared to normotensive controls (mean BP = 108 ± 11.4/62.4 ± 6.4 mmHg), hypertensive subjects with primary (essential) hypertension (mean BP = 146 ± 10.7 /82.2 ± 11.2 mmHg) had significantly higher serum uric acid levels (6.7 ± 1.3 vs. 3.6 ± 0.8 mg/dL) [61]. In this study, there was a tight and linear correlation between serum uric acid levels and systolic and diastolic blood pressures [61]. Each 1 mg/dL increase in serum uric acid level was associated with an average increase of 14 mmHg in systolic BP and 7 mmHg in diastolic BP [61]. Similar findings were reported in larger cross-sectional studies. In a study which included 501 children at high cardiovascular risk with an age range of 6–18 years and a mean of 10.8 years referred for evaluation, 33.3% and 40.5% were overweight or obese, respectively, 17.4% had prehypertension, and 27.1% were hypertensive [87]. Serum uric acid levels were directly related to systolic and diastolic blood pressures. Compared to normotensive children, the risk of prehypertension or hypertension increased by at least 50% for each 1 mg/dL increase in serum uric acid level and doubled for children in the gender-specific top serum uric acid quartile [87]. The Bogalusa Heart Study examined the association between increased serum uric acid and BP levels in childhood and primary hypertension in early adulthood [88]. This study enrolled 577 whites and blacks as children aged 5–17 years and adults aged 18–33 years with a follow-up period of 12 years [88]. Childhood serum uric acid was significantly correlated with both childhood and adult systolic and diastolic blood pressures [88]. In a multivariate regression analysis, adjusting for age, sex, race, and childhood body index, serum uric acid levels were significant predictors of adult diastolic BP, whereas change of serum uric acid was a significant predictor of systolic BP [88]. These findings suggest that increased serum uric acid levels in childhood are associated with an elevation in BP which persists into adulthood [88].

A number of recent studies have examined the association between uric acid, BP, and incident hypertension in middle-aged and elderly subjects. In a large meta-analysis of 18 cohort studies representing data from 55,607 subjects, hyperuricemia was associated with an increased risk of incident hypertension (adjusted risk ratio—RR—1.41) [89]. For every 1 mg/dL increase in serum uric acid level, the pooled RR for incident hypertension, after adjusting for potential confounding, was 1.13 [89]. The risk was more pronounced in younger individuals and in women [89]. The Brisighella Heart Study confirmed the association between serum uric acid and hypertension [4]. In this landmark study which enrolled 619 male and female participants, aged 14–84 years, free of cardiovascular disease and not receiving any antihypertensive, antidiabetic, or uricosuric medications, the prevalence of hypertension was strongly related to quartiles of serum uric acid [4]. After adjustment for a large number of parameters, significant differences in the prevalence of hypertension were reported between second and third quartiles (23% vs. 36.4%) and between third and fourth quartiles (36.4% vs. 56.3%) [4]. The PAMELA (Pressioni Arteriose Monitorate E Loro Associazioni) study which enrolled 9045 participants from an urban population tested the relation between baseline serum uric acid, cardiovascular disease, metabolic variables, and new onset office and out-of-office (home and

ambulatory) hypertension [90]. After 10 years of follow-up, baseline serum uric acid was associated with an abnormal metabolic profile, target organ involvement, and independently predicted new onset of out-of-office systolic BP values [90]. For every 1 mg/dL increase in serum uric acid, after adjustment for all potential confounders, the increased risk of developing new onset home and ambulatory hypertension was 34% and 29%, respectively [90]. An increase in serum uric acid of 1 mg/dL also independently predicted cardiovascular and all-cause mortality [90].

Most of the studies that assessed the correlation between hyperuricemia and new onset hypertension included younger subjects, namely, children, adolescents, and young adults [86–88]. The Health Professionals Follow-Up study, a cohort study of 59,529 males, examined the independent association between serum uric acid and risk for incident hypertension among older men aged 47–81 years [91]. Serum uric acid was associated positively and significantly with risk of incident hypertension among men younger than 60 years (RR = 1.38) but not among men who were ≥60 years of age (RR = 0.9). In the quartile analysis, a trend toward a positive association between serum uric acid and risk for hypertension was observed among younger but not among older men [91]. Comparing participants in the highest uric acid quartile with those in the lowest, the multivariable RR was 2.01 for men <60 years of age and 0.81 for men ≥60 years of age [91]. A large Korean study confirmed the lack of association between serum uric acid and BP in male and female participants >60 years of age [85].

Preeclampsia is characterized by a marked increase in serum uric acid levels in both mother and fetus [92]. However, the relation of hyperuricemia to the outcome of pregnancy in preeclampsia, a phenotype of severe gestational hypertension, remains inconclusive [92]. A case-control study examined fetal outcome data from 972 pregnancies collected from 1999 to 2002 [93]. In women with gestational hypertension, hyperuricemia was associated with shorter gestations and small infant birth weight centiles and increased risk of preterm birth and small-for-gestational-age infants [93]. The risk of these outcomes was increased even in the absence of proteinuria and, occasionally, even in the absence of hypertension [93]. Women with hypertension, hyperuricemia, and proteinuria were at a greater risk than those with hypertension and proteinuria alone [93]. In another study, the relation between maternal uric acid and maternal and fetal outcome was evaluated prospectively in 206 primiparas and singleton pregnancy with recent onset of gestational hypertension [94]. After a follow-up to 1-month postdelivery, the maternal serum uric acid at 5.20 mg/dL (309 μmol/L) cutoff was a predictor of preeclampsia with an adjusted odds ratio of 7.1 ($p$ <0.001) and delivery of a small-for-gestational-age infant, with an adjusted odds ratio of 1.6 ($p$ <0.02) [94].

These observations suggest that hyperuricemia may identify a phenotype of gestational hypertension associated with significant risk [95]. In a study of 62 pregnant women with gestational hypertension but without proteinuria, the characteristic preeclamptic renal lesion, referred to as glomeruloendotheliosis, was found only in women with hyperuricemia [95].

Serum uric acid appears to be a risk, not only for hypertension but also for milder degrees of elevated BP levels. In a community-based study of 14,451 Chinese

subjects, a linear interaction was observed between serum uric acid and risk of prehypertension, especially at serum uric acid levels between 3.4 mg/dL (200 μmol/L) and 6.4 mg/dL (380 μmol/L) [96]. In contrast, in this study as well as in others, this correlation was lost in subjects older than 60 years of age [89, 96].

Studies in recent past decades indicate that increased serum uric acid is associated with novel cardiovascular risk markers such as blood pressure variability (BPV), insulin resistance, and salt sensitivity.

BPV obtained by 24-h ambulatory BP monitoring is associated with target organ involvement, cardiovascular events, and mortality in hypertensive patients [97, 98]. In a study of 300 patients (mean age 57.3 ± 13.6 years) with untreated essential hypertension, log serum uric acid was positively correlated with 24-h systolic BPV, day and night systolic and diastolic BPV (Pearson's coefficients of 0.246, 0.280, and 0.353, respectively) [99].

Reduced insulin sensitivity and hyperinsulinemia have been postulated to participate in the pathogenesis of uric acid-associated incident hypertension [100–102]. The interaction between serum uric acid, serum insulin, and incident hypertension has been evaluated in 1496 nonobese healthy women, aged 32–52 years without hypertension, diabetes mellitus, or coronary artery disease at baseline from the second Nurses' Health Study [100]. After simultaneous control of all biomarkers, estimated glomerular filtration rate, and total cholesterol levels, only serum uric acid and serum insulin levels were independently associated with incident hypertension [102]. Comparing the highest and lowest quartiles of serum uric acid levels, the odds ratio of incident hypertension was 1.89 [102]. A similar comparison yielded an odds ratio of 2.03 for serum insulin levels [102]. Assuming an estimated annual basal incidence of 14.6 per 1000, 30.8% of hypertension in young women occurred with a serum uric acid of 3.4 mg/dL (304 μmol/L) or greater and in 24.2% with serum insulin levels of 2.9 mg/dL (174 μmol/L) or greater [102].

In experimental animals, chronic and persistent hyperuricemia is associated with hypertension, renal parenchymal and microvascular lesions, and salt sensitivity [103]. The relationship between uric acid metabolism and renal tubular sodium handling was assessed in the Olivetti Factory study which included 592 men aged 32–68 years and represented a sample of the general population. The clearance of lithium was used as a proxy for segmental renal tubular sodium handling [104]. Serum uric acid level was inversely and significantly associated with fractional excretion of lithium ($r = -22$) indicating that the higher the serum uric acid level the greater the amount of sodium reabsorbed at nephron sites proximal to the distal tubule [104]. These findings demonstrate a link between hyperuricemia and increased proximal tubular sodium reabsorption, possibly through hyperinsulinemia [104].

### Mechanisms

It is well established that increased serum uric acid levels correlates with incident hypertension [85–89]. However, the observation that serum uric acid appears to be a good predictor of hypertension does not necessarily imply an etiologic role as both hypertension and hyperuricemia may be the result of a common underlying pathology [105].

Numerous hypotheses have been postulated to explain the causal link between serum uric acid levels and hypertension. Evidence supporting a causal role of uric acid in hypertension comes from experimental studies in laboratory animals [106, 107]. To determine the effect of uric acid on BP in laboratory animals, serum uric acid levels were increased by administration of oxonic acid, a uricase inhibitor [106, 107]. Rats develop hypertension which is characterized by two phases, an early phase of reversible BP elevation and a late phase contributing to irreversible hypertension [106, 107]. In rats treated with oxonic acid, the uric acid inhibitor, serum uric acid increases leading to a gradual rise in BP over a period of 2–3 weeks, proportional to the degree of increase in serum uric acid [106, 107]. The renin-angiotensin system is stimulated, and nitric oxide synthesis is inhibited, causing systemic and renal vasoconstriction [106, 107]. This early phase of hypertension can be reversed by withdrawal of oxonic acid or administration of uric acid-reducing drugs (allopurinol or benziodarone) or blockers of renin-angiotensin system [106].

In contrast, the second phase of hypertension is characterized by prolonged and persistent elevation in serum uric acid levels, renal microvascular lesions and tubulointerstitial changes, chronic renal impairment, and irreversible hypertension [106, 107]. Tissue culture models have demonstrated that uric acid enters vascular smooth muscle cells inciting a cascade of biochemical reactions [108]. This cascade results in proliferation of vascular smooth muscle cells, reduced compliance of the renal afferent arterioles, and a sodium-sensitive hypertension [103, 108–110]. In rats, these histopathologic changes and the hypertension persist for several years and cannot be reversed by urate-lowering therapy [108].

In humans, epidemiologic and cross-sectional studies and clinical trials lend support for the causal link between hyperuricemia and incident hypertension [85–89]. Further, the etiologic association between serum uric acid and BP elevations appear to be stronger in younger than older hypertensive populations and in women [62, 89].

Several older and more recent studies have shown that hyperuricemia is a frequent biochemical finding in hypertensive children, adolescents, and young adults [61, 89, 108]. In the Moscow Children's Hypertension Study, elevated serum uric acid levels (>8 mg/dL) were reported in 9.5% of children with normal BP, in 49% in children with borderline hypertension, and in 73% of those with moderate to severe hypertension [108]. In the Hungarian Children's Study which included 17,624 children followed up for 13 years, hyperuricemia was a strong risk factor for the development of hypertension [111]. In a small study, hypertensive adolescents, aged 13–18 years, had increased serum uric acid levels (>6.5 mg/dL) and peripheral plasma renin activity [112]. In a more recent study which classified hypertension into phenotypes, hypertension was more common in primary (essential) than in secondary hypertension [61]. Elevated serum uric acid levels (>5.5 mg/dL) were reported in about 90% of adolescents with essential hypertension (serum uric acid = 6.7 ± 1.3 mg/dL), whereas serum uric acid levels were significantly lower in those with secondary hypertension (serum uric acid = 4.3 ± 1.4 mg/dL) and in white coat hypertension (serum uric acid = 3.6 ± 0.7 mg/dL) [61].

Hyperuricemic children and adolescents with new onset essential hypertension are generally overweight or obese and exhibit normal renal function and several

features of the metabolic syndrome, although the latter may be absent in some patients [62, 113].

Uric acid-lowering therapy has been recently used to test the causal role of serum uric acid in hypertension in both younger (children, adolescents) and older (middle-aged and elderly subjects) populations.

In one study, 30 adolescents with new onset essential hypertension received either allopurinol or placebo in a randomized, double-blinded, crossover trial [114]. In the 20 of the 30 participants, while on allopurinol, their BP became normal, and their serum uric acid levels fell to <5.5 mg/dL compared to 3% while on placebo; of the ten children who remained hypertensive, their serum uric acid levels did not reach target serum uric acid reduction [114].

In the follow-up clinical trial, obese children with prehypertension/grade 1 hypertension were randomized into three groups to receive placebo; allopurinol, a uricosuric and xanthine oxidase inhibitor; or probenecid, a uricosuric agent [114]. Children on placebo had a slight but insignificant fall in systolic BP. In contrast, patients on active treatment experienced a marked reduction in office-measured SBP/DBP, with an average fall of −10.1/−8.0 and −10.2/−8.8 mmHg for allopurinol- and probenecid-treated groups, respectively [115]. Ambulatory 24-h BP monitoring revealed the same pattern [115].

These data indicate that the mechanism of BP lowering is associated with serum uric acid reduction, independently of allopurinol-induced xanthine oxidase inhibition [115].

The pathophysiologic mechanism of hyperuricemia in recent onset childhood/adolescent essential (primary) hypertension has not been completely elucidated.

Serum uric acid concentration is frequently increased in adult borderline, mild and moderately severe hypertension [77, 116]. The hyperuricemia has been attributed to increased renovascular resistance and reduced renal blood flow [116]. In support of this hypothesis, several investigations demonstrated that in normotensive subjects, infusion of norepinephrine or angiotensin II is associated with an elevation in BP, hyperuricemia, and reduced renal blood flow [117]. Discontinuation of the pressor infusions leads to normalization of BP, serum uric acid concentration, and renal blood flow [117].

The phenotype of childhood/adolescent new onset essential hypertension may be reminiscent of the early phase of oxonic-induced hyperuricemia which is characterized by hypertension, enhanced renin-angiotensin system, inhibition of nitric oxide systems, and reversible renovascular hemodynamic alterations [106, 107].

It has been postulated that, in addition to elevated serum uric acid concentrations, disturbances in uric acid production may contribute to BP elevation and hypertension [118, 119]. Overactivity of xanthine oxidase, the rate-limiting enzyme in purine metabolism, may lead to a relative decrease in the more upstream purine metabolites, characterized by higher ratios of xanthinic/hypoxanthine, uric acid/xanthine, and uric acid/hypoxanthine [118].

A study which included 246 healthy school-age children, with a mean age of 7.1 ± 0.4 years, from the KOALA Birth Cohort Study, evaluated the association between purine metabolite ratios, serum uric acid concentrations, and BP [118].

The findings revealed that in school-age children with a high BP, increased serum uric acid concentration and purine metabolite ratios are associated with higher diastolic BP $z$ scores, a hemodynamic evidence of increased systemic vascular resistance, lending further support to causal role of serum uric acid in the development of hypertension [118, 120].

Whether serum uric acid has a direct causal role in the development of hypertension in older adults is not clear. A recent analysis of 6984 patients receiving treatment for hypertension did not reveal a relationship between baseline serum uric acid concentration and long-term BP changes, although higher uric acid concentration was associated with a decline in renal function [121]. Further, it is not clear whether uric acid-reducing therapy lowers BP in hypertensive adults. A metaanalysis which combined data from ten clinical trials of 738 participants revealed that allopurinol administration was associated with a small reduction in systolic BP (3.3 mmHg) [122]. A recent study evaluated changes in BP after initiation of allopurinol therapy in hypertensive patients, aged >65 years using data from the UK Clinical Practice Research Datalink [123]. The study, which included 365 allopurinol treated and 6678 controls, demonstrated that allopurinol-treated participants had a mild but significant reduction in both systolic and diastolic blood pressures (2.1/1.7 mmHg, respectively) [123]. There was a trend toward a greater fall in BP in the high-dose allopurinol group [123]. Further, the change in BP was not related to baseline serum uric acid concentrations [123].

## Classification

The pathophysiologic mechanisms that define the relationship between serum uric acid levels and the development of hypertension have not been completely elucidated [105]. However, it is postulated that different pathologic factors underlie different phenotypes of hyperuricemia-associated hypertension.

### Hyperuricemia-Hypertension Phenotype in Younger Populations

In hypertensive children, adolescents, and young adults, a population with minimal vascular disease, hyperuricemia is both a marker and a causal factor in new onset incident hypertension [85, 87–89, 108]. Normalization of both serum uric acid and BP levels with uric acid-reducing therapy provides support for this hypothesis [114, 118, 120].

The phenotype of hyperuricemic hypertension in the young, which is reminiscent of the early phase of oxonic-induced hyperuricemia BP elevation in experimental animals, is characterized by overweight/obesity, features of the metabolic syndrome, enhanced renal renin-angiotensin system, inhibited endothelial nitric oxide synthesis, increased renovascular resistance and impaired renal blood flow and a potentially reversible BP elevation with uricosuric therapy, and/or blockade of the renin-angiotensin system [52, 53].

### Hyperuricemia-Hypertension Phenotype in Older Populations

In middle-aged and elderly hypertensive populations, hyperuricemia is a frequent laboratory manifestation and a major risk for cardiorenal conditions [77]. It is

however unclear whether serum uric acid plays any role in the initiation or maintenance of BP elevation in this age group [85, 91, 121]. Further, studies have reported that the association between serum uric acid and BP weakens with age and with the duration of hypertension [85].

Several factors have been postulated to participate in the increase in serum uric acid concentrations in older populations including ischemia, reduced renal blood flow and impaired renal function, metabolic factors, drugs, and dietary products [2, 22, 55, 56]. In turn, hyperuricemia increases the levels of tissue-toxic reactive oxygen species through enhanced activity of xanthine oxidoreductase enzyme [122, 124]. In addition, it induces alterations in the structural and functional properties of the vascular wall and stimulates the vascular renin-angiotensin system [125]. These reactions lead to target organ damage and cardiovascular complications [87, 121].

Allopurinol administration improves cardiorenal outcome and causes BP reduction, which is of lesser magnitude than that observed in younger hyperuricemic hypertensive populations [123]. However, higher doses of allopurinol are required to achieve these therapeutic effects [122, 123, 126].

Gestational Hyperuricemia-Hypertension Phenotype (Preeclampsia)

Among the hypertensive disorders of pregnancy, preeclampsia remains one of the most important causes of maternal and fetal morbidity and mortality [94]. Increased serum uric acid concentration is both one of the characteristic features and a predictor of preeclampsia [93, 94].

In women with gestation hypertension, hyperuricemia is associated with shorter gestations and increased risk of preterm birth and small-for-gestational-age infants [93].

Although preeclampsia is characterized also by hypertension and proteinuria, hyperuricemia portends a greater risk of poor pregnancy outcome than elevated BP levels, increased urinary protein excretion, or even both [93].

Hyperuricemia appears as effective as proteinuria in identifying gestational hypertensive pregnancies at risk [93].

The pathophysiologic association between hyperuricemia and preeclampsia has not been completely elucidated. It has been postulated that hyperuricemia may participate in the development of preeclampsia by mediating both systemic and glomerular hypertension and renal pathological lesions [127].

#### 23.2.3.4 Cardiovascular Diseases

Serum uric acid is frequently elevated in subjects at cardiovascular risk [37]. Hypertensive patients with hyperuricemia have a three- to fivefold increased risk of coronary or cerebrovascular disease compared with hypertensive patients with normal serum uric acid levels [128]. Further, there is a clear epidemiologic association between asymptomatic hyperuricemia and incident hypertension, heart failure, myocardial infarction, stroke, obesity, metabolic syndrome, and diabetes [37, 77, 129–131]. The relation between serum uric acid concentration and endovascular disease is not limited to frank hyperuricemia defined as >7 mg/dL (420 μmol/L) in men and >6 mg/dL (360 μmol/L) in women but is also observed with serum uric

acid levels considered to be in the normal to high range (>5.2–5.5 mg/dL = 310–330 μmol/L) [61, 132]. However, it remains controversial whether serum uric acid plays a causal role in the development of cardiovascular disease or is simply a marker of traditional cardiovascular disease risk factor [37].

Recent reports from the Framingham Heart Study and Atherosclerotic Risk in Communities (ARIC) Study which collectively involve over 200,000 men and women claim no association between serum uric acid and incident cardiovascular disease in multivariable models [133, 134]. In contrast, other studies documented an independent association of serum uric acid with cardiovascular disease. Reanalysis of the SHEP (Systolic Hypertension in the Elderly Program) trial found that serum uric acid levels determine outcome independent of other parameters such as BP [135]. Patients treated successfully for hypertension with diuretics who also had an increase in their serum uric acid levels >10 mg/dL (600 μmol/L) while on treatment failed to show any benefit in cardiovascular event rates when compared to placebo [135]. In a large cohort of individuals taking part in the Third National Health and Nutrition Survey, an increased risk of all-cause and cardiac mortality was associated with increasing serum uric acid levels during a 10-year follow-up [136]. Likewise, a prospective study reported that serum uric acid was an independent predictor of cardiovascular and all-cause mortality as well as development of new onset hypertension [90]. The results of the LIFE Study provided additional support for an association between baseline serum uric acid and increased risk of cardiovascular events [137]. Attenuation of the increase in serum uric acid by losartan over 4.8 years reduced cardiovascular events in the high-risk population [137].

In contrast to its adverse effects on the cardiovascular system, serum uric acid appears to provide a protective action on certain neurologic disorders such as neurodegenerative disease, Parkinson's disease, multiple sclerosis, and Alzheimer's disease/dementia [138–140]. In addition, elevated serum uric acid concentrations have been associated with lower all-cause and cardiovascular mortality in patients receiving hemodialysis treatment [128].

It has been postulated that these beneficial actions of hyperuricemia in neurologic disorders may be due, at least partly, to the antioxidant properties of uric acid [141].

Target organ involvement is a known risk for cardiovascular outcome. In a study which was part of a larger trial (MAGIC—Microalbuminuria: A Genoa Investigation on Complications), the relation between serum uric acid and target organ damage was evaluated in 425 middle-aged (age range 20–67 years) untreated patients with essential hypertension [142]. Patients with target organ damage had significantly higher serum uric acid levels [142]. Each standard deviation increase in serum uric acid was associated with a 75% higher risk of having left ventricular hypertrophy and a two-times greater risk of having carotid abnormalities (increased carotid intima-media thickness) and 12% prevalence of microalbuminuria [142].

#### 23.2.3.5 Kidney Disease

Hyperuricemia is highly prevalent in patients with chronic kidney disease, reflecting reduced efficiency of renal excretion of uric acid and associated with hypouricosuria [143]. Hyperuricemia as defined as a serum uric acid of >6.5 mg/dL

(390 μmol/L) in women and >7 mg/dL (420 μmol/L) in men occurs in many renal diseases [3].

The role of uric acid in the initiation and progression of chronic kidney disease remains controversial. Recent epidemiological and experimental evidence suggests a role for uric acid, not only by a marker of reduced kidney function but also as a causal risk for the development and progression of renal disease.

Several epidemiological surveys and prospective studies have documented an association between hyperuricemia and risk of new onset kidney disease. In the Okinawa General Health Maintenance Association study, which included 6400 Japanese participants with normal renal function at baseline, serum uric acid levels >8 mg/dL (480 μmol/L) were associated with a 2.9 and tenfold increased risk of developing chronic kidney disease (defined as serum creatinine levels >1.4 mg/dL in men and >1.2 mg/dL in women) within 2 years in men and women, respectively [144]. An elevated serum uric acid level was even more predictive for the development of renal insufficiency than proteinuria [144]. The relations between serum uric acid levels and incident kidney disease (defined as glomerular filtration rate-GFR-decrease of ≥15 mL/min/1.73m$^2$ with a final GFR <60 mL/min/1.73m$^2$) were also evaluated in over 13,000 participants with intact kidney function in two community-based cohorts [134]. During a follow-up period of 8.5 years, each 1 mg/dL greater uric acid level at baseline was associated with an approximately 10% increase in risk of kidney disease in multivariable adjusted models [134].

The association among longitudinal BP, renal function, and cardiovascular outcomes was also explored in a large cohort of treated hypertension, attending the Glasgow BP clinic [121]. The study which included over 6000 patients revealed that serum uric acid was independently associated with decline in renal function. Comparing patients in the first quartile of serum uric acid, the relative decrease in GFR in the fourth quartile was 10.7 mL/min/1.73 m$^2$ in men and 12.2 mL/min/1.73 m$^2$ in women [121]. Further, serum uric acid was independently associated with cardiovascular and all-cause mortality only in women [121]. On the other hand, there was no relationship between longitudinal BP control and uric acid level, suggesting that hyperuricemia does not alter the efficacy of contemporary hypertension management [121]. Hyperuricemia has been reported to be an independent risk factor for progression of IgA nephropathy [145]. The association between serum uric acid and risk of incident chronic kidney disease may be dose response dependent [146]. A prospective study of over 21,000 patients followed up for a median of 7 years with different serum uric acid levels but same baseline estimated glomerular filtration rate (eGFR) [146]. Mild hyperuricemia (7–8.9 mg/dL/420–534 μmol/L) nearly doubled the risk for incident kidney disease, while more severe hyperuricemia (≥9 mg/dL / ≥540 μmol/L) tripled the risk [146]. The association of serum uric acid—incident chronic kidney disease—persisted despite multiple adjustments by statistical models [146]. These data indicate that hyperuricemia precedes reduction in GFR [146].

In a randomized clinical trial in 54 hyperuricemic patients with stages 3 and 4 CKD, allopurinol therapy, compared to placebo, during a 1-year follow-up was associated with a significant reduction in serum uric acid levels and delay in progression of CKD (defined as an increase in serum creatinine level >40% of baseline

or the need for replacement therapy suggesting that hyperuricemia may be nephrotoxic in CKD, accelerating progression to end-stage renal disease) [147].

In contrast, other studies failed to substantiate a relationship between serum uric acid concentrations and chronic kidney disease. In a separate analysis of 5800 participants from the Cardiovascular Health Study (CHS), there was no association between serum uric acid concentrations and incident CKD defined as eGFR <60 mL/min/1.73 $m^2$ [143]. Likewise in a cohort of patients with predominantly nondiabetic stages 3 and 4 CKD, hyperuricemia was not an independent predictor of progression to end-stage renal failure [8].

Experimental studies on rodents provide support for the causal role of serum uric acid in initiation of chronic kidney disease. Oxonic-induced hyperuricemia in rats caused a slow development of albuminuria, preglomerular arteriopathy, glomerulosclerosis, tubulointerstitial changes, and hypertension [107]. Controlling hyperuricemia with hypouricosuric agents, in the early phase of the process, prevents microvascular and histopathologic injury and preserves renal function in these animals [106, 107].

The question of whether a specific gouty or chronic urate nephropathy exists has been posed frequently [148]. The current evidence cannot definitely prove or refute the hypothesis [148].

Kidney disease and hypertension are highly prevalent in gout and hyperuricemia [134]. Using data from over 5700 participants aged 20 years or older in the National Health and Nutrition Examination Survey 2007–2008, 74% had hypertension, and 71% had chronic kidney disease stage ≥2 [149]. With increasing levels of hyperuricemia, there was a graded increase in prevalence of these comorbidities [149]. The histopathologic alterations in the kidneys of patients with chronic hyperuricemia were obtained from reports of kidney biopsies or autopsies performed before the advent of uricosuric therapy. Microscopically, the lesions consist of microtophi of uric acid, usually located in the medulla or papilla associated with a chronic interstitial inflammation, arteriolar nephrosclerosis, and glomerulosclerosis [150]. However, there was little correlation between the development of gouty or urate nephropathy and either clinical and laboratory abnormalities or level of serum uric acid [37, 150]. This has been attributed to the fact that these patients often have hypertension, diabetes mellitus, dyslipidemia, and older age, all of which by themselves can cause renal injury, nephrosclerosis, and renal failure [150].

#### 23.2.3.6 Acute Urate Nephropathy

In addition to its role in the pathogenesis of chronic kidney disease, hyperuricemia may cause acute kidney injury leading to acute renal failure [151]. Experimental and clinical data provide support for the direct and indirect role for uric acid in the development of acute kidney injury [152].

##### Acute Hyperuricemic Obstructive Nephropathy (Crystal-Dependent Mechanism of Kidney Injury)

This type of acute renal failure, a complication of tumor lysis syndrome, is caused by intrarenal deposition of crystals leading to tubular obstruction [152].

Administration of cytotoxic therapy to large volume, rapidly proliferating hematologic malignancies and some solid tumors, causes release and degradation by the liver of nucleic acids with production of uric acid and acidic metabolites [152]. Serum uric acid rises acutely and rapidly to levels often >12 mg/dL (>720 μmol/L) resulting in marked uricosuria, acidic urine, intravascular volume contraction and intraluminal formation, and deposition of macro- and microcrystals of uric acid in the distal tubules and collecting ducts with obstruction of tubular lumina [152].

The aim of therapy is prevention of acute renal failure prior to and during chemotherapy by adequate hydration, alkalinization of the urine, and administration of allopurinol, a xanthine inhibitor, and urate oxidase inhibitors [152, 153].

Despite recent advances in therapy, 5–6% of at risk pediatric and adult patients receiving chemotherapy develop acute renal failure [151]. About 40–50% of these patients require dialysis treatment with associated all-cause mortality in excess of 50% [151].

### Ischemic Acute Hyperuricemic Acute Renal Failure (Crystal-Independent Mechanism of Acute Kidney Injury)

There is increasing experimental and clinical evidence that uric acid may cause acute kidney injury and acute kidney failure by crystal independent mechanisms [106]. Several studies have reported that acute kidney injury may be precipitated by milder degrees of elevation of serum uric acid concentration [152]. In subjects undergoing elective but high risk cardiovascular surgery, serum uric acid levels of >6.1 mg/dL (366 μmol/L) increased the risk of postoperative acute kidney injury by fourfold, independently of baseline serum uric acid level and other classical cardiovascular risk factors or previous cardiac surgery [152, 154]. Further, in none of the patients who developed acute kidney injury, the preoperative serum uric acid concentration was >10 mg/dL (600 μmol/L) [152, 154]. In a retrospective analysis of two large randomized studies of patients with coronary artery bypass surgery {(GUARDIAN: Guard during Ischemia Against Necrosis: 11,590 patients) and (EXPEDITION: Sodium-Proton Exchange Inhibition to Prevent Coronary Events in Acute Cardiac Conditions: 5761 patients)}, the presence of preoperative or postoperative serum uric acid level >7.5 mg/dL (450 μmol/L) was associated with a two to fourfold increased risk of developing acute kidney injury, after controlling several other factors [151, 152].

Several pathophysiologic pathways have been implicated in the pathogenesis of crystal-independent acute kidney injury. Inflammatory responses, oxidative stress, endothelial dysfunction, and enhanced renin-angiotensin system contribute to renal vasoconstriction, preglomerular arteriopathy, and impaired renal autoregulation [151, 152]. Several of these pathologic factors have been documented in oxonic-mediated hyperuricemia in animal models and in the human [54, 106].

The management of crystal-independent acute kidney injury remains unclear. Diuretics do not appear to protect against the development of acute renal failure, but may even prolong recovery of renal function [151, 155].

## 23.3 Association of Fructose Consumption, Hyperuricemia, Metabolic Disorders, and Cardiorenal Diseases

The prevalence of hyperuricemia has doubled worldwide [68, 156]. Hyperuricemia has been associated with the metabolic syndrome and implicated as a risk factor in the etiology of hypertension, atherosclerosis, insulin resistance, diabetes mellitus, and kidney disease [4, 6–8]. Among dietary products, consumption of sugar-sweetened beverages can induce hyperuricemia [157–159]. Although these beverages do not contain purines, they contain large amounts of sweeteners including sucrose (composed of 50% fructose and 50% glucose), fructose, and high-fructose corn syrup (composed of 55% fructose and 45% glucose) [73, 160]. Both fructose and high-fructose corn syrup have been associated with elevated levels of serum uric acid [161].

Fructose is an isomer of dextrose synthesized from corn syrup and is currently used as a sweetener in preference to naturally occurring sucrose [161]. Fructose is unique among sugars in that it rapidly causes depletion of ATP and increases both the generation and release of uric acid [162].

Experimental studies in animals support a link between fructose intake, hyperuricemia, and hypertension. Administration of fructose is associated with enhanced sympathetic nervous and renin-angiotensin systems, increased heart rate, hyperuricemia, sodium retention, renal structural and functional alterations, and hypertension [162–165]. In addition, fructose feeding induces also insulin resistance and the metabolic syndrome [165]. However, fructose does not increase BP effectively in rats except during active ingestion [162]. This observation has been attributed, at least partly, to the presence of uricase enzyme in rats which blunts the BP response to uric acid [162].

Epidemiological, cross-sectional, and clinical studies reported an association between fructose intake, hyperuricemia, hypertension, and chronic kidney disease. In the NHANES (1999–2004), a strong association between sugar-sweetened drinks, uric acid levels, and hypertension was observed in adolescents [74]. Adolescents with higher sugar-sweetened beverage consumption had higher serum uric acid levels and systolic BP [74]. Similarly, a correlation between fructose from added sugars and elevated BP levels was reported in the NHANES (2003–2006) [166].

Another cross-sectional study from Brazil examined the association between type of soft drink consumption and BP in Brazilian adolescents [167]. Adolescents consuming diet soft drinks had the highest BP levels compared to nonconsumers and consumers of regular sugar-sweetened beverages [167]. Further, consumers of sugar-sweetened beverages had greater values of BP compared to nonconsumers [167].

Consumption of fructose-rich drinks is associated with BP elevation. Acute ingestion of 60 g of fructose (which is comparable to 12 ounces of soft drinks) caused an increase in BP in healthy young adults [162]. Similarly, administration of 200 g of fructose per day for 2 weeks increased both fasting serum uric acid levels and clinic and 24-h ambulatory BP in healthy adult men [162, 168]. Allopurinol administration reduced both serum uric acid levels and BP [162, 168].

In contrast to the other studies, the Nurse and Health Professionals study could not document an association between fructose and BP elevation [169]. Further in that study, the risk of hypertension and cardiovascular disease was attributed to factors other than or in addition to fructose [170].

There is increasing evidence that fructose may have a role in the development of chronic kidney disease. In the NHANES (1999–2004) study, consumption of one or more sugar containing beverages was associated with an increased risk of albuminuria [171]. Further, in the Atherosclerotic Risk in Communities (ARIC) study, the odds ratio for chronic kidney disease (eGFR <60 mL/min/1.73 $m^2$) increased significantly to 2.59 among participants who drank more than one sugar-sweetened soda per day and had a serum uric acid level of >9 mg/dL (540 μmol/L) [159].

## 23.4 Thiazide Diuretics, Hyperuricemia, and Target Organ Involvement

Thiazide diuretics, first introduced in 1957, remain the mainstay of antihypertensive therapy as monotherapy or in combination with other agents [172–174]. Clinical trials have demonstrated the effectiveness of thiazide diuretics in reducing BP and cardiovascular morbidity and mortality in uncomplicated essential hypertension [173, 174]. However, the use of these medications is associated with serious adverse reactions including hyperuricemia, hypokalemia, metabolic disturbances, and target organ involvement [175].

In this section, discussion will be limited to adverse reactions of the thiazide-induced hyperuricemia.

Thiazide diuretics can induce hyperuricemia even at low dose (Table 23.5) [176]. Thiazide-induced hyperuricemia has been reported to be associated with an enhanced cardiovascular risk. In the Systematic Worksite Treatment Program which included over 7000 mild to moderately hypertensive subjects followed for 20 years, the risk of cardiovascular events was significantly increased in those who had a high serum uric acid level [177]. Similarly, in the Systolic Hypertension in the Elderly Program (SHEP) trial, the reduction in risk of coronary artery events observed with chlorthalidone was completely abolished in those subjects whose uric acid levels increased more than 1 mg/dL during treatment, despite adequate BP control [135].

The thiazide-induced increase in serum uric acid is independent of hypokalemia [175].

Thiazide diuretics may cause renal damage. Both clinical and population studies have reported that thiazide diuretics are not renoprotective, but may even accelerate

**Table 23.5** Diuretic-induced elevation in serum uric acid (low dose)

| Diuretic | Once daily dose (mg/day) |
|---|---|
| Hydrochlorothiazide | 12.5 |
| Chlorthalidone | 12.5–25 |
| Bendrofluazide | 1.25 |
| Indapamide | 1 |

the progression of renal disease in the population [175]. In several randomized clinical trials, the use of thiazides was associated with a greater decline in renal function than with other antihypertensive compounds [175]. Further, it has been postulated that thiazide use was epidemiologically associated with an increasing incidence of end-stage renal disease (ESRD) in the USA [178].

Thiazide administration to animals causes kidney damage including glomerular ischemia and medullary tubulointerstitial changes [175].

The mechanism of thiazide-associated kidney damage in animal has not been elucidated, but appears to be multifactorial [179]. Hyperuricemia appears to play an important role [108].

## 23.5 Indications for Urate-Reducing Therapy

Although there is increasing evidence for a link between hyperuricemia and risk of hypertension and cardiorenal endpoints, the role of urate-reducing therapy remains controversial.

Several drugs are known to lower serum uric acid. These include (1) uricosuric drugs, such as probenecid, which increase urinary uric acid excretion; (2) xanthine oxidase inhibitors such as allopurinol and febuxostat, which block the final step in uric acid production; and (3) rasburicase, a recombinant urate oxidase enzyme which converts uric acid to allantoin [180].

In the younger population with essential hypertension (children, adolescents, young adults), hyperuricemia is both a marker and a causal link to new onset hypertension [61, 87, 108]. Urate-reducing therapy normalizes both serum uric acid levels and BP [61]. However, urate-lowering therapy is not indicated in this age group [108]. First, there are no large clinical trials to confirm the therapeutic antihypertensive efficacy of urate-reducing therapy [108]. Second, urate-lowering therapy may be associated with serious adverse reactions. Allopurinol can cause a rare but life-threatening reaction known as allopurinol hypersensitivity syndrome, characterized by a rash, impaired renal function, hepatocellular injury, fever, eosinophilia, and leukocytosis [181, 182]. This reaction has been reported in both adolescent and adult hypertensive subjects and even in allopurinol treated gouty patients [108, 181, 182]. Further, probenecid which interferes with the renal clearance of numerous drugs can induce hyperuricemia and urate nephrolithiasis [108]. Third, the antihypertensive efficacy of traditional antihypertensive drugs is greater than that provided by urate-reducing medications [108].

In contrast, in middle-aged and elderly subjects with essential hypertension, a causal relationship between hyperuricemia and elevated BP is not obvious but appears to be minimal [123]. In this older hypertensive population, hyperuricemia represents more of a risk for cardiovascular and renal disease than a causal link with hypertension [123].

BP changes and cardiovascular outcomes, after initiation of allopurinol, were examined in elderly hypertensive subjects (>65 years) in the UK Clinical Practice Research Datalink, a large computerized database [123]. Compared to

controls, allopurinol administration induced a mild but significant fall in both systolic and diastolic BP levels (2.1/1.7 mmHg, respectively). The fall in BP was independent of baseline serum uric acid and tended to be larger with high allopurinol doses [123].

In the same study, allopurinol treatment was associated with a reduced risk of stroke by 50% and cardiac events by 39%. The reduction in cardiovascular events was greater with higher allopurinol doses [126].

Allopurinol has been reported to improve target organ involvement in patients with cardiovascular disease. In patients with ischemic heart disease, left ventricular mass was reduced with high-dose allopurinol [183]. Similarly, the progression of chronic kidney disease is slowed down by both allopurinol and febuxostat [184, 185].

The improvement in cardiorenal outcome was associated with reduction in serum uric acid and may be linked to mechanisms unrelated to reduction in serum uric acid but may be mediated by specific actions of xanthine oxidase agents [123].

Some studies also have examined the effect of urate-lowering therapy on some indices of vascular function. Allopurinol administration reduced both central blood pressure and progression of carotid intima-media thickness in patients with recent ischemic stroke or transient ischemic attacks (TIA) [186]. However, the results on endothelial function have been contradictory. Allopurinol administration normalized endothelial function in type 2 diabetes with mild hypertension [187]. In contrast, urate-reducing agents (allopurinol and probenecid) had no effect on endothelial dysfunction in normotensive overweight/obese young adults [188].

Non-pharmacologic approaches also have been recommended to reduce serum uric acid and BP. Reduction in the consumption of sugar-sweetened beverages has been associated with reduction in serum uric acid levels and BP [189]. Further, regular physical activity appears to counteract the pathogenetic mechanisms involved in the association between hyperuricemia and risk of future hypertension preventing BP elevation [190].

## Conclusion

Serum uric acid, a circulating end product of purine metabolism, is a major risk for incident hypertension, cardiovascular disease, stroke, and chronic kidney disease. It is eliminated mainly by the kidney and to a lesser extent by the gastrointestinal tract. There is a positive correlation between serum uric acid concentration and incident hypertension in children, adolescents, and younger adult hypertensive population. This relationship is lost with aging and duration of hypertension.

Hyperuricemia is a characteristic feature of new onset essential (primary) hypertension in pediatric and younger adult hypertensive patients and appears to be causally related to BP elevation. In contrast, hyperuricemia appears to act more as a risk for cardiovascular disease rather than as an etiologic determinant in older adult hypertensive patients.

In essential (primary) hypertension, elevated serum uric acid concentration is induced by increased renovascular resistance and reduced renal blood flow.

Uric acid-lowering therapy in younger hypertensive patients normalizes both serum uric acid and BP levels, while in middle-aged and elderly hypertensive subjects, it appears to be associated with reduction of cardiovascular risk and progression of chronic kidney disease.

## References


1. Ngo TC, Assimos DG (2007) Uric acid nephrolithiasis: recent progress and future directions. Rev Urol 9:17–27
2. Borghi C, Agabiti Rosei E, Bardin TH et al (2015) Serum uric acid and the risk of cardiovascular and renal disease. J Hypertens 33:1729–1741
3. Johnson RJ, Kang DH, Feig D et al (2003) Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease. Hypertension 41:1183–1190
4. Cicero AF, Salvi P, D'Addato S et al (2014) Association between serum uric acid, hypertension, vascular stiffness and subclinical atherosclerosis: data from the Brisighella Heart Study. J Hypertens 32:57–64
5. Filippatos GS, Ahmed MI, Gladden JD et al (2011) Hyperuricemia, chronic kidney disease, and outcomes in heart failure: potential mechanistic insights from epidemiological data. Eur Heart J 32:712–720
6. Erdogan D, Gullu H, Caliskan M et al (2005) Relationship of serum uric acid to measures of endothelial function and atherosclerosis in healthy adults. Int J Clin Pract 59:1276–1282
7. Culleton BF (2001) Uric acid and cardiovascular disease: a renal-cardiac relationship. Curr Opin Nephrol Hypertens 10:371–375
8. Madero M, Sarnak MJ, Wang X et al (2009) Uric acid and long-term outcomes in CKD. Am J Kidney Dis 53:796–803
9. Rosolowsky ET, Ficociello LH, Maselli NJ et al (2008) High normal serum uric acid is associated with impaired glomerular filtration rate in nonproteinuric patients with type 1 diabetes. Clin J Am Soc Nephrol 3:706–713
10. ZHU Y, Pandya BJ, Choi HK (2011) Prevalence of gout and hyperuricemia in the US general population: the national health and nutrition examination survey 2007-2008. Arthritis Rheum 63:3136–3141
11. Mohamed FA (1874) The etiology of Bright's disease and the prealbuminuric state. Med Chir Trans 39:197–228
12. Mohamed FA (1879) On chronic Bright's disease and its essential symptoms. Lancet 1:399–401
13. Haig A (1890) The connecting link between the high tensión pulse and albuminuria. Br Med J 1:65–68
14. Haig A (1892) Uric acid as a factor in the causation of disease: a contribution to the pathology of high arterial tensión, headache, epilepsy, mental depression, gout, rheumatism, diabetes, Bright's disease, and other disorders, 1st edn. J A Churchill, London
15. Davis NCL (1897) The cardiovascular and renal relations and manifestations of gout. JAMA 29:261–262
16. Desgrez A (1913) Influence de la constitution des corps puriques sure leur action vis-a-vis de la pression arterielle (in French). C R Acad Sci 156:93–94
17. Feig DI, Kang DH, Nakagawa T et al (2006) Uric acid and hypertension. Curr Hypertens Rep 8:111–115
18. Chobanian AV, Bakris GL, Black HR et al (2003) The seventh report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure: the JNC 7 report. JAMA 289:2560–2572
19. Stanton JR, Freis ED (1947) The serum uric acid concentration in essential hypertension. Proc Soc Exp Biol Med 66:193–194

20. Mazzali M, Kanbay M, Segal MS et al (2010) Uric acid and hypertension: cause or effect. Curr Rheumatol Rep 12:108–117
21. Mene P, Punzo G (2008) Uric acid: bystander or culprit in hypertension and progressive renal disease? J Hypertens 26:2085–2092
22. Ruilope LM, Garcia-Puig J (2001) Hyperuricemia and renal function. Curr Hypertens Rep 3:197–202
23. Allen DG, Milosovich G, Mattock AM (1965) Inhibition of monosodium urate crystal growth. Arthritis Rheum 8:1123–1133
24. Griebsch A, Zollner N (1974) Effect of ribomononucleotides given orally on uric acid production in man. Adv Exp Med Biol 41:443
25. Rafey MA, Lipkowitz MS, Leal-Pinto E, Abramson RG (2003) Uric acid transport. Curr Opin Nephrol Hypertens 12:511–516
26. Anton FM, Garcia Puig AJ, Ramos T et al (1986) Sex differences in uric acid metabolism in adults: evidence for a lack of influence of estradiol-17 Beta (E2) on the renal handling of urate. Metabolism 35:343
27. Wilcos WR, Khalaf A, Weinberder A et al (1972) Solubility of uric acid and monosodium urate. Mol Biol Eng 10:522–531
28. Roch-Ramel F, Diezi J (1996) Renal transport of organic ions and uric acid. In: Schrier RW, Gottschalk CW (eds) Diseases of the kidney. Little Brown, Boston, p. 231
29. Ichida K, Matsuo H, Takada T et al (2012) Decreased extra-renal urate excretion is a common cause of hyperuricemia. Nat Commun 3:764–770
30. Sorensen LB (1960) The elimination of uric acid in man. Scand J Clin Lab Invest 12(Suppl 54):1
31. Simic MG, Jovanovic SV (1989) Antioxidation mechanisms of uric acid. J Am Chem Soc 111:5778–5782
32. Squadrito GL, Cueto R, Splenser AE et al (2000) Reaction of uric acid with peroxynitrite and implications for the mechanism of neuroprotection by uric acid. Arch Biochem Biophys 376:333–337
33. Waring WS, Webb DJ, Maxwell SRJ (2000) Effect of local hyperuricemia on endothelial function in the human forearm vascular bed. Br J Clin Pharmacol 49:511
34. Rao GN, Corson MA, Berk BC (1991) Uric acid stimulates vascular smooth muscle cell proliferation by increasing platelet-derived growth factor A-chain expression. J Biol Chem 266:8604–8608
35. Corry DB, Eslami P, Yamamoto K et al (2008) Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. J Hypertens 26:269–275
36. Kang DH, Han L, Ouyang X et al (2005) Uric acid causes smooth muscle cell proliferation by entering cells via a functional urate transporter. Am J Nephrol 25:425–433
37. Feig DI, Rang DH, Johnson RJ (2008) Uric acid and cardiovascular risk. N Engl J Med 359:1811–1821
38. Mikkelsen WM, Dodge HJ, Valkenburg H (1965) The distribution of serum uric acid values in a population unselected as to gout or hyperuricemia. Tecumseh, Michigan 1959-1960. Am J Med 39:242–251
39. Rice T, Vogler GP, Perry TS et al (1990) Heterogeneity in the familial aggregation of fasting serum uric acid level in five North American populations: the Lipid Research Clinics Family Study. Am J Med Genet 36:219–225
40. Kalousdian S, Fabsitz R, Havlik R et al (1987) Heritability of clinical chemistries in an older twin cohort: the NHLBI Twin study. Genet Epidemiol 4:1–11
41. Wilk JB, Djousse L, Borecki I et al (2000) Segregation analysis of serum uric acid in the NHLBI Family Heart Study. Hum Genet 106:355–359
42. Kottgen A, Albrecht E, Teumer A et al (2013) Genome-wide association analysis identify 18 new loci associated with serum urate concentrations. Nat Genet 45:145–154
43. Parsa A, Brown E, Weir MR et al (2012) Genotype-based changes in serum uric acid affect blood pressure. Kidney Int 81:502–507

44. Merriman TR (2015) An update on the genetic architecture of hyperuricemia and gout. Arthritis Res Ther 17:98
45. Sedaghat S, Pazoki R, Uitterlinden AG et al (2014) Association of uric acid risk score with blood pressure: the Rotterdam study. Hypertension 64:1061–1066
46. Mallamaci F, Testa A, Leonardis D et al (2014) A polymorphism in the major gene regulating serum uric acid associates with clinic SBP and the White-coat effect in family based study. J Hypertens 32:1621–1628
47. Palmer TM, Nordestigaard BG, Benn M et al (2013) Association of plasma uric acid with ischemic heart disease and blood pressure: Mendelian randomisation analysis of two large cohorts. BMJ 347:f4262
48. Reginato AM, Mount DB, Yang I, Choi HY (2012) The genetics of hyperuricemia and gout. Nat Rev Rheumatol 8:610–621
49. Nath SD, Vorugant VS, Arar NH et al (2007) Genome scan for determinants of serum uric acid variability. J Am Soc Nephrol 18:3156–3163
50. Gharavi AG, Yan Y, Scolari F et al (2000) IgA nephropathy, the most common cause of glomerulonephritis is linked to 6q22-23. Nat Genet 26:354–357
51. Myllymaki J, Honkanen T, Syrjanen J et al (2005) Uric acid correlates with the severity of histopathological parameters in IgA nephropathy. Nephrol Dial Transplant 20:89–95
52. Yoo TW, Sung KC, Kim BS et al (2005) Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. Circ J 69:928–933
53. Tuomilehto J, Zimmet P, Wolf E et al (1988) Plasma uric acid level and its association with diabetes mellitus and some biologic parameters in a biracial population of Fiji. Am J Epidemiol 127:321–336
54. Johnson RJ, Segal MS, Srinivas T et al (2005) Essential hypertension, progressive renal disease and uric acid: a pathogenetic link? J Am Soc Nephrol 16:1909–1919
55. Fam AG (2002) Gout, diet and the insulin resistance syndrome. J Rheumatol 29:1350–1355
56. UK Gout Society (2014) All about gout and diet. www.ukgoutsociety.org/docs/goutsociety-allaboutgoutanddiet-0113. Accessed 28 Mar 2017
57. Zhang W, Doherty M, Bardin T et al (2006) EULAR evidence based recommendations for gout. Part II: management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 65:1312–1324
58. Khanna D, Fitzgerald JD, Khanna PP et al (2012) 2012 American College of Rheumatology guidelines for management of gout. Part I: systematic non-pharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 64:1431–1446
59. Neogi T (2011) Clinical practice. Gout. N Engl J Med 364:443–452
60. Lin KC, Lin HY, Chou P (2000) Community based epidemiological study on hyperuricemia and gout in Kin-Hu, Kinmen. J Rheumatol 27:1045–1050
61. Feig DI, Johnson RJ (2003) Hyperuricemia in childhood primary hypertension. Hypertension 42:247–252
62. Loeffler LF, Navas-Acien A, Brady TM et al (2002) Uric acid level and elevated blood pressure in US adolescents-National Health and Examination Survey, 1999-2006. Hypertension 59:811–817
63. Bardin T, Richette P (2014) Definition of hyperuricemia and gouty conditions. Curr Opin Rheumatol 26:186–191
64. Desideri G, Castaldo G, Lombardi A et al (2014) Is it time to revise the normal range of serum uric acid levels? Eur Rev Med Pharmacol Sci 18:1295–1306
65. Zalokar J, Lellouch J, Claude JR (1981) Serum urate and gout in 4663 young male workers. Sem Hop 57:664–670
66. Qiu L, Cheng XQ, Wu J et al (2013) Prevalence of hyperuricemia and its related risk factors in health adults from Northern and Northeastern Chinese provinces. BMC Public Health 13:664
67. Chou CT, Lai JS (1998) The epidemiology of hyperuricemia and gout in Taiwan aborigines. Br J Rheumatol 37:258–262

68. Mikuls TR, Farrar JT, Bilker WB et al (2005) Gout epidemiology: results from the UK general practice research database 2000-2005. Ann Rheum Dis 64:267–272
69. Desideri G, Puig TG, Richette P (2015) The management of hyperuricemia with urate deposition. Curr Med Res Opin 31(Suppl 2):27–32
70. Tremblay MS, Katzmarzyk PT, Willms JD (2002) Temporal trends in overweight and obesity in Canada, 1981-1996. Int J Obes Relat Metab Disord 26:538–543
71. Ogden CL, Carroll MD, Curtin LR et al (2006) Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 295:1549–1555
72. Nguyen ST, Choi HK, Lustig RH, Hsu C-Y (2009) Sugar sweetened beverages, serum uric acid and blood pressure in adolescents. J Pediatr 154:807–813
73. Meneses-Leon J, Denova-Gutiérrez E, Castañón-Robles S et al (2014) Sweetened beverage consumption and the risk of hyperuricemia in Mexican adults: a cross-study. BMC Public Health 14:445
74. Choi JWJ, Ford ES, Gao X, Choi HK (2008) Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid levels: the Third National Health and Nutrition Examination Survey. Arthritis Rheum 59:109–116
75. Trifiro G, Morabito P, Cavagna L et al (2013) Epidemiology of gout and hyperuricemia in Italy during the years 2005-2009: a nationwide population-based study. Ann Rheum Dis 72:694–700
76. Qazi Y (2016) Hyperuricemia. http://emedicine.medscape.com/article/241767-overview. Accessed 29 Mar 2017
77. Cannon PJ, Stason WB, Fe D et al (1966) Hyperuricemia in primary and renal hypertension. N Engl J Med 275:457–464
78. Klein R, Klein BE, Cornoni JC et al (1973) Serum uric acid: its relationship to coronary heart disease risk factors and cardiovascular disease, Evans County, Georgia. Arch Intern Med 132:401–410
79. Longo-Mbenza B, Luila EL, Mbete P, Vita EK (1999) Is hyperuricemia a risk factor of stroke and coronary heart disease among Africans? Int J Cardiol 71:17–22
80. Kim YH, Suh YD, Son SP et al (1985) Observation of the serum uric acid in essential hypertension. Korean J Med 28:56–63
81. Saggiani F, Pilati S, Targher G et al (1996) Serum uric acid and related factors in 500 hospitalized subjects. Metabolism 45:1557–1561
82. Wallace SL (1975) Gout and hypertension. Arthritis Rheum 18:721–724
83. Johnson RJ, Feig DJ, Herreira-Acosta J, Kang DH (2005) Resurrection of uric acid as a causal risk factor in essential hypertension. Hypertension 45:18–20
84. Lip GYH, Beevers M, Beevers DG (2000) Serum urate is associated with baseline renal dysfunction but not survival or deterioration in renal function in malignant phase hypertension. J Hypertens 18:97–101
85. Lee JJ, Ahn J, Hwang J et al (2015) Relationship between uric acid and blood pressure in different age groups. Clin Hypertens 21:14
86. Norwood VF (2002) Hypertension. Pediatr Rev 23:197–208
87. Viazzi F, Antolini L, Giussani M et al (2013) Serum uric acid and blood pressure in children at cardiovascular risk. Pediatrics 132:e93–e99
88. Alper AB Jr, Chen W, Yau L et al (2005) Childhood uric acid predicts adult blood pressure: the Bogalusa Heart Study. Hypertension 45:34–38
89. Grayson PC, Kim SY, LaValley M, Choi HK (2011) Hyperuricemia and incident hypertension: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 63:102–110
90. Bombelli M, Ronchi J, Volpe M et al (2014) Prognostic value of serum uric acid: new-onset in and out-of-office hypertension and long-term mortality. J Hypertens 32:1237–1244
91. Forman JP, Choi H, Curhan GC (2007) Plasma uric acid levels and risk of incident hypertension among men. J Am Soc Nephrol 18:287–292
92. Sagen N, Haram K, Nilsen ST (1984) Serum urate as a predictor of fetal outcome in severe preeclampsia. Acta Obstet Gynecol Scand 63:71–75
93. Roberts JM, Bodnar LM, Lain KY et al (2005) Uric acid is as important as proteinuria in identifying fetal risk in women with gestational hypertension. Hypertension 46:1263–1269

94. Bellomo G, Venanzi S, Saronio P et al (2011) Prognostic significance of serum uric acid in women with gestational hypertension. Hypertension 58:704–708
95. Nochy D, Birembaut P, Hinglais N et al (1980) Renal lesions in the hypertensive syndromes of pregnancy: immunomorphological and ultrastructural studies in 114 cases. Clin Nephrol 13:155–162
96. Liang J, Xue Y, Zou C et al (2009) Serum uric acid and prehypertension among Chinese adults. J Hypertens 27:1761–1765
97. Mancia G, Parati G, Hennig M et al (2001) Relation between blood pressure variability and carotid artery damage in hypertension: baseline data from the European Lacidipine Study on Atherosclerosis (ELSA). J Hypertens 19:1981–1989
98. Verdecchia P, Angeli F, Gattobigio R et al (2007) Impact of blood pressure variability on cardiac and cerebrovascular complications in hypertension. Am J Hypertens 20:154–161
99. Çağli K, Turak O, Canpolat U et al (2015) Association of serum uric acid level with blood pressure variability in newly diagnosed essential hypertension. J Clin Hypertens 17:929–935
100. Reaven GM, Lithell H, Landsberg L (1996) Hypertension and associated metabolic abnormalities—the role of insulin resistance and the sympathoadrenal system. N Engl J Med 334:374–381
101. Modan M, Halkin H, Karasik A, Lusky A (1987) Elevated serum uric acid—a facet of hyperinsulinaemia. Diabetologia 30:713–718
102. Forman JP, Choi H, Curhan GC (2009) Uric acid and insulin sensitivity and risk of incident hypertension. Arch Intern Med 169:155–162
103. Watanabe S, Kang DH, Feng L et al (2002) Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. Hypertension 40:355–360
104. Cappuccio FP, Strazzullo P, Farinaro E, Trevisan M (1993) Uric acid metabolism and tubular sodium handling. JAMA 270:354–359
105. Schachter M (2005) Uric acid and hypertension. Curr Pharm Des 11:4139–4143
106. Mazzali M, Hughes J, Kim YG et al (2001) Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension 38:1101–1106
107. Mazzali M, Kanellis J, Han C et al (2002) Hyperuricemia induces a primary renal arteriolopathy in rats by a blood-independent mechanism. Am J Physiol Renal Physiol 282:F991–F997
108. Yanik M, Feig DI (2013) Serum urate: a biomarker or treatment target in pediatric hypertension. Curr Opin Cardiol 28:433–438
109. Kanellis J, Watanabe S, Li JH et al (2003) Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. Hypertension 41:1287–1293
110. Price K, Sautin Y, Long D et al (2006) Human vascular muscle cells express a urate transporter. J Am Soc Nephrol 17:1791–1795
111. Török E, Gyárfás I, Csukás M (1985) Factors associated with stable high blood pressure in adolescents. J Hypertens Suppl 3:S389–S390
112. Gruskin AB (1985) The adolescent with essential hypertension. Am J Kidney Dis 6:86–90
113. Krishnan E, Kwoh CK, Schumacher HR, Kuller L (2007) Hyperuricemia and incidence of hypertension among men without metabolic syndrome. Hypertension 49:298–303
114. Feig DI, Soletsky B, Johnson RJ (2008) Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension. A randomized trial. JAMA 300:924–932
115. Soletsky B, Feig DI (2012) Uric acid reduction rectifies prehypertension in obese adolescents. Hypertension 60:1148–1156
116. Messerli FH, Frohlich ED, Dreslinski GR et al (1980) Serum uric acid in essential hypertension: an indicator of renal vascular involvement. Ann Intern Med 93:817–821
117. Ferris TF, Gorden P (1968) Effect of angiotensin and norepinephrine upon urate clearance in man. Am J Med 44:359–365
118. Scheepers LE, Boonen A, Pijnenburg W et al (2017) Associations of plasma uric acid and purine metabolites with blood pressure in children: the KOALA Birth Cohort Study. J Hypertens 35:982–993

119. Scheepers LE, Wei FF, Stolarz-Zkrzypek K et al (2016) Xanthine oxidase-gene variants and their association with blood pressure and incident hypertension: a population study. J Hypertens 34:2147–2154
120. Li Y, Wei FF, Wang S et al (2014) Cardiovascular risks associated with diastolic blood pressure and isolated diastolic hypertension. Curr Hypertens Rep 16:489
121. Dawson J, Jeemon P, Hetherington L et al (2013) Serum uric acid level, longitudinal blood pressure, renal function and long-term mortality in treated hypertensive patients. Hypertension 62:105–111
122. Agarwal V, Hans N, Messerli FH (2013) Effect of allopurinol on blood pressure: a systematic review and meta-analysis. J Clin Hypertens 15:435–442
123. Beattie CJ, Fulton RL, Higgins P et al (2014) Allopurinol initiation and change in blood pressure in older adults with hypertension. Hypertension 64:1102–1107
124. Cai H, Harrison DG (2000) Endothelial dysfunction in cardiovascular disease: the role of oxidant stress. Circ Res 87:840–844
125. Khosla UM, Zharikov S, Finch JL et al (2005) Hyperuricemia induces endothelial dysfunction. Kidney Int 67:1739–1742
126. MacIsaac RL, Salatzki J, Higgins P et al (2016) Allopurinol and cardiovascular outcomes in adults with hypertension. Hypertension 67:535–540
127. Kang DH, Finch J, Nakagawa T et al (2004) Uric acid, endothelial dysfunction and preeclampsia: searching for a pathogenetic link. J Hypertens 22:229–235
128. Latif W, Karaboyas A, Tong L et al (2011) Uric acid levels and all-cause and cardiovascular mortality in the hemodialysis population. Clin J Am Soc Nephrol 6:2470–2477
129. Rodriguez-Arias JJ, Coll-de-Tuero G (2015) Could uric acid be considered a cardiovascular risk factor? J Clin Hypertens 17:936–937
130. Zhao G, Huang L, Song M, Song Y (2013) Baseline serum uric acid level as a predictor of cardiovascular disease related mortality and all-cause mortality: a meta-analysis of prospective studies. Atherosclerosis 231:61–68
131. Kim SY, Guevara JP, Kim KM et al (2009) Hyperuricemia and risk of stroke: a systematic review and meta-analysis. Arthritis Rheum 61:885–892
132. Niskanen LK, Laaksonen DE, Nyyssonen K et al (2004) Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. Arch Intern Med 164:1546–1551
133. Culleton BF, Larson MG, Kannel WB, Levy D (1999) Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med 131:7–13
134. Weiner DE, Tighiouart H, Elsayed EF et al (2008) Uric acid and incident kidney disease in the community. J Am Soc Nephrol 19:1204–1211
135. Franse LV, Pahor M, Di Bari M et al (2000) Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). J Hypertens 18:1149–1154
136. Stack AG, Hanley A, Casserly LF et al (2013) Independent and conjoint associations of gout and hyperuricaemia with total and cardiovascular mortality. QJM 106:647–658
137. Hoieggen A, Alderman MH, Kjeldsen SE et al (2004) The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int 65:1041–1049
138. Hooper DC, Spitsin S, Kean RB et al (1998) Uric acid, a natural scavenger of peroxynitrite, in experimental allergic encephalomyelitis and multiple sclerosis. Proc Natl Acad Sci U S A 95:675–680
139. Ascherio A, LeWitt PA, Xu K et al (2009) Urate as a predictor of the rate of clinical decline in Parkinson disease. Arch Neurol 66:1460–1468
140. Spitsin S, Koprowski H (2010) Role of uric acid in Alzheimer's disease. J Alzheimers Dis 19:1337–1338
141. Hershfield MS, Roberts LJ II, Ganson NJ et al (2010) Treating gout with pegloticase, a PEGylated urate oxidase, provides insight into the importance of uric acid as an oxidant in vivo. Proc Natl Acad Sci U S A 107:14351–14356
142. Viazzi F, Parodi D, Leoncini G et al (2005) Serum uric acid and target organ damage in primary hypertension. Hypertension 45:991–995

143. Chonchol M, Shlipak MG, Katz R et al (2007) Relationship of uric acid with progression of kidney disease. Am J Kidney Dis 50:239–247
144. Iseki K, Oshiro S, Tozawa M et al (2001) Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. Hypertens Res 24:691–697
145. Syrjanen J, Mustonen J, Pastemack A (2000) Hypertriglyceridemia and hyperuricemia are risk factors for progression of IgA nephropathy. Nephrol Dial Transplant 15:34–42
146. Obermayr RP, Temmi C, Gutjahr G et al (2008) Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol 19:2407–2413
147. Siu YP, Leung KT, Tong MKH, Kwan TH (2006) Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis 47:51–59
148. Moe OW (2010) Posing the question again: does chronic uric acid nephropathy exist? J Am Soc Nephrol 21:395–397
149. Zhu Y, Pandya BJ, Choi HK (2012) Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. Am J Med 125:679–687
150. Chonko AM, Richardson WP (1994) Urate and uric acid nephropathy, cystinosis, and oxalosis. In: Tisher CC, Brenner BM (eds) Renal pathology with clinical and functional correlations. JP Lippincott, Philadelphia, pp 1413–1441
151. Ejaz AA, Mu W, Kang DH et al (2007) Could uric acid have a role in acute renal failure? Clin J Am Soc Nephrol 2:16–21
152. Shimada M, Johnson RJ, May WS Jr et al (2009) A novel role for uric acid in acute kidney injury associated with tumour lysis syndrome. Nephrol Dial Transplant 24:2960–2964
153. Ronco C, Inguaggiato P, Bordoni V et al (2005) Rasburicase therapy in acute hyperuricemia and renal dysfunction. Contrib Nephrol 147:115–123
154. Ejaz AA, Beaver TM, Shimada M et al (2009) Uric acid: a novel risk factor for acute kidney injury in high-risk cardiac surgery patients? Am J Nephrol 30:425–429
155. Mehta RL, Pascual MT, Soroco S, Chertow GM (2002) Diuretics, mortality and nonrecovery of renal function in acute renal failure. JAMA 288:2547–2553
156. Wallace KL, Riedel AA, Joseph-Ridge N, Wortmann R (2004) Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population. J Rheumatol 31:1582–1587
157. So A, Thorens B (2010) Uric acid transport and disease. J Clin Invest 120:1791–1799
158. Sui X, Church TS, Meriwether RA et al (2008) Uric acid and the development of metabolic syndrome in women and men. Metabolism 57:845–852
159. Bomback AS, Derebail VK, Shoham DA et al (2010) Sugar-sweetened soda consumption, hyperuricemia and kidney disease. Kidney Int 77:609–616
160. Welsh JA, Sharma A, Abramson JL et al (2010) Caloric sweetener consumption and dyslipidemia among US adults. JAMA 303:1490–1497
161. Fox IH, Kelley WN (1972) Studies of the mechanism of fructose-induced hyperuricemia in man. Metabolism 21:713–721
162. Johnson RJ, Sanchez-Lozada LG, Nakagawa T (2010) The effect of fructose on renal biology and disease. J Am Soc Nephrol 21:2036–2039
163. DiNicolantonio JJ, Lucan SC (2014) The wrong white crystals: not salt but sugar as aetiological in hypertension and cardiometabolic disease. Open Heart 1:e000167
164. Bunag RD, Tomita T, Sasaki S (1983) Chronic sucrose ingestion induces mild hypertension and tachycardia in rats. Hypertension 5:218–225
165. Hwang IS, Ho H, Hoffman BB, Reaven GM (1987) Fructose-induced insulin resistance and hypertension in rats. Hypertension 10:512–516
166. Jalal DI, Smits G, Johnson RJ, Chonchol M (2010) Increased fructose associates with elevated blood pressure. J Am Soc Nephrol 21:1543–1549
167. Souza Bda S, Cunha DB, Pereira RA, Sichieri R (2016) Soft drink consumption, mainly diet ones, is associated with increased blood pressure in adolescents. J Hypertens 34:221–225
168. Perez-Pozo SE, Schold J, Nakagawa T et al (2010) Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response. Int J Obes 34:454–461

169. Forman JP, Choi H, Curhan GC (2009) Fructose and vitamin C intake do not influence risk for developing hypertension. J Am Soc Nephrol 20:863–871
170. Cohen L, Curhan G, Forman J (2012) Association of sweetened beverage intake with incident hypertension. J Gen Intern Med 27:1127–1134
171. Shoham DA, Durazo-Arvizu R, Kramer H et al (2008) Sugary soda consumption and albuminuria: results from the National Health and Nutrition Examination Survey, 1999-2004. PLoS One 3:e3431
172. Hollander W, Wilkins RW (1957) Chlorothiazide: a new type of drug for the treatment of arterial hypertension. BMQ 8:69–75
173. Psaty BM, Smith NL, Siscovick DS et al (1997) Health outcomes associated with antihypertensive therapies used as first-line agents. A systemic review and meta-analysis. JAMA 277:739–745
174. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group (2002) Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipi-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 288:2981–2997
175. Reungjui S, Pratipanawatr T, Johnson RJ, Nakagawa T (2008) Do thiazides worsen metabolic syndrome and renal disease? The pivotal roles for hyperuricemia and hypokalemia. Curr Opin Nephrol Hypertens 17:470–476
176. Reyes AJ (2002) Diuretics in the therapy of hypertension. J Hum Hypertens 16(Suppl 1):S78–S83
177. Alderman MH, Cohen H, Madhavan S, Kivlighn S (1999) Serum uric acid and cardiovascular events in successfully treated hypertensive patients. Hypertension 34:144–150
178. Hawkins RG, Houston MC (2005) Is population-wide diuretic use directly associated with the incidence of end-stage renal disease in the Unites States? A hypothesis. Am J Hypertens 18:744–749
179. Reungjui S, Hu H, Mu W et al (2007) Thiazide-induced subtle renal injury not observed in states of equivalent hypokalemia. Kidney Int 72:1483–1492
180. Dawson J, Walters M (2006) Uric acid xanthine oxidase: future targets in the prevention of cardiovascular disease? Br J Clin Pharmacol 62:633–644
181. Elasy T, Kaminsky D, Tracy M, Mehler PS (1995) Allopurinol hypersensitivity syndrome revisited. West J Med 162:360–361
182. Singer JZ, Wallace SL (1986) The allopurinol hypersensitivity syndrome. Unnecessary morbidity and mortality. Arthritis Rheum 29:82–87
183. Rekhraj S, Gandy SJ, Szwejkowski BR et al (2013) High-dose allopurinol reduces left ventricular mass in patients with ischemic heart disease. J Am Coll Cardiol 61:926–932
184. Sezer S, Karakan S, Atesagaoglu B, Acar FN (2014) Allopurinol reduces cardiovascular risks and improves renal function in pre-dialysis chronic kidney disease patients with hyperuricemia. Saudi J Kidney Dis Transpl 25:316–320
185. Sircar D, Chatterjee S, Waikhom R et al (2015) Efficacy of febuxostat for slowing the GFR decline in patients with CKD and asymptomatic hyperuricemia: a 6-month double-blind, randomized, placebo-controlled trial. Am J Kidney Dis 66:945–950
186. Higgins P, Walters MR, Murray HM et al (2014) Allopurinol reduces brachial and central blood pressure and carotid intima media thickness progression after ischaemic stroke and transient ischaemic attack: a randomized controlled trial. Heart 100:1085–1092
187. Butler R, Morris AD, Belch JJ et al (2000) Allopurinol normalizes endothelial dysfunction in type 2 diabetics with mild hypertension. Hypertension 35:746–751
188. Borgi L, McMullan C, Wohlhueter A et al (2017) Effect of uric acid lowering agents on endothelial function: a randomized, double-blind, placebo-controlled trial. Hypertension 69:243–248
189. Chen L, Caballero B, Mitchell DC et al (2010) Reducing consumption of sugar sweetened beverages is associated with reduced blood pressure: a prospective study among United States adults. Circulation 121:2398–2406
190. Saladini F, Mos L, Fania C et al (2017) Regular physical activity prevents development of hypertension in young people with hyperuricemia. J Hypertens 35:994–1001

# Hypertension in Dialysis Patients: Clinical Epidemiology, Pathogenesis, Diagnosis, and Treatment

# 24

Pantelis A. Sarafidis, Panagiotis Georgianos, and Carmine Zoccali

## 24.1 Introduction

Among end-stage renal disease (ESRD) patients receiving maintenance hemodialysis or peritoneal dialysis, hypertension is very common, difficult to diagnose and often poorly controlled [1]. Elevated blood pressure (BP), especially recorded outside of the hemodialysis unit with home or ambulatory BP monitoring, is associated with shorter survival [2–4]. Sodium and volume overload is the most important cause of hypertension in dialysis patients; accordingly, non-pharmacologic strategies such as dietary sodium restriction, individualized dialysate sodium prescription, and gradual dry-weight reduction should be the initial therapeutic approaches to achieve BP control [1, 5]. However, this approach still remains inadequately implemented [6, 7]. Even following proper management of sodium and volume excess, hypertension remains poorly controlled in a substantial proportion of dialysis patients; in these patients, pharmacologic therapy is obviously necessary to control BP [1, 5].

In this chapter, we discuss the epidemiology, pathogenesis, diagnosis, and treatment of hypertension among patients on dialysis in the light of currently available

P.A. Sarafidis, M.D., M.Sc., Ph.D.
Department of Nephrology, Hippokration Hospital,
Aristotle University of Thessaloniki, Thessaloniki, Greece

P. Georgianos, M.D., Ph.D.
Section of Nephrology and Hypertension, First Department of Medicine,
AHEPA Hospital, Thessaloniki, Greece

C. Zoccali, M.D., Ph.D. (✉)
CNR-IFC, Clinical Epidemiology and Pathophysiology of Hypertension and Renal Diseases,
Ospedali Riuniti, 89124 Reggio Calabria, Italy
e-mail: carmine.zoccali@tin.it



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_24

evidence derived from observational and randomized controlled studies; non-pharmacological and pharmacological strategies to manage hypertension in dialysis are both included in our discussion. We discuss data from the fewer relevant studies in peritoneal dialysis patients, summarizing clinical evidence that may be useful for the management of hypertension in these individuals.

## 24.2 Diagnosis

In the 2004 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guideline document [8], the diagnosis of hypertension among patients on hemodialysis was based on BP measurements obtained shortly before or after dialysis, i.e., when predialysis BP is >140/90 mmHg or when postdialysis BP is >130/80 mmHg, respectively [8]. Whether using conventional peridialytic BP recordings is efficient to diagnose and guide the management of hypertension in the hemodialysis population is a matter of debate for several reasons. Pre- and postdialysis BP is typically recorded by the dialysis unit staff and without the necessary attention to the technique of BP measurement and the prerequisites for objective office BP recordings [9]. The high variability of BP from pre- to postdialysis and from one day to the next in response to the shifts and fluctuations in volume status and other parameters during the intra- and interdialytic period is another important issue that imposes particular difficulties in the accurate detection of hypertension [10]. The typical pattern of hemodynamic response to ultrafiltration is a BP decrease from pre- to postdialysis; the magnitude of intradialytic BP reduction is at least partially related to the magnitude and the rate of volume withdrawal during dialysis. The exact opposite phenomenon occurs during the out-of-dialysis interval [11], with several studies showing that interdialytic weight gain is closely associated with higher predialysis BP [12]. It is therefore not uncommon that predialysis BP levels are within the hypertensive range, whereas postdialysis BP measurements in the same patient are in the normotensive range. The poor diagnostic accuracy of peridialytic BP recordings is supported by a meta-analysis of clinical studies showing that both pre- and postdialysis BP provide imprecise estimates of the mean interdialytic BP recorded with 44-h ambulatory BP monitoring [13]. Furthermore, peridialytic BP recordings have little or no prognostic relations with mortality in hemodialysis patients [2, 3].

The rate of hypertension misdiagnosis when using peridialytic BP measurements is unacceptably high [14]. Using BP measurements obtained during the dialysis session in combination with the pre- and postdialysis BP may be an alternative approach to improve the reproducibility, precision, and accuracy of hypertension diagnosis among hemodialysis patients [15]. Intradialytic BP is usually recorded every 30 min with the use of an oscillometric devices, sometimes attached to the dialysis machine. In a diagnostic test study using 44-h interdialytic ambulatory BP as the reference standard, the average intradialytic BP in combination with peridialytic BP was shown to have greater diagnostic value compared with peridialytic BP recordings alone [16]. A median intradialytic cutoff BP of 140/90 mmHg during a midweek

dialysis session provided greater sensitivity and specificity in detecting interdialytic hypertension as compared with pre- and postdialysis BP measurements [16]. Despite the fact that the diagnostic accuracy is improved when peridialytic BP recordings are considered together with intradialytic BP, this approach should remain a method of last resort, as BP measurements obtained outside of the dialysis unit appear better methods for the diagnosis of hypertension in these patients [14].

Home BP monitoring is a widely applied and recommended international guideline method to diagnose and manage hypertension in the general population [17, 18]. Among patients on dialysis, home BP monitoring is reported to have several advantages over conventional peridialytic BP recordings [19]. Compared with BP recordings obtained pre- or postdialysis, home BP exhibits stronger associations with mean 44-h ambulatory BP [20, 21]. In the Dry-Weight Reduction in Hemodialysis Patients (DRIP) trial, changes in home BP after 4 and 8 weeks of dry-weight probing were closely associated with the relevant changes in 44-h ambulatory BP; in contrast, predialysis and postdialysis BP recordings were unable to detect the changes in ambulatory BP caused in response to dry-weight reduction [22]. Contrary to the high variability and poor reproducibility of conventional peridialytic BP recordings, home BP was shown to have high short-term reproducibility from 1 week to the next [21]. Compared with the BP measurements obtained within the dialysis unit, home BP exhibits stronger associations with indices of target-organ damage [23–25] and represents a more powerful predictor of future cardiovascular events or all-cause mortality [2, 3].

The notion that home BP may be a useful tool to guide the management of hypertension among dialysis patients is supported by a pilot study which randomized 65 hypertensive hemodialysis patients to have their antihypertensive drug therapy adjusted either on the basis of routine predialysis BP recording or with the use of home BP monitoring [26]. Over a mean follow-up period of 6 months, a significant reduction in interdialytic ambulatory BP of 9/7 mmHg was noted in the home BP-guided group, but not in the predialysis BP-guided group [26]. Another study randomized 34 hemodialysis patients to home BP-guided management plus usual care or usual care alone for management of hypertension. After 12 weeks of follow-up, the use of home BP recordings in decision making resulted also in significant reduction of the average weekly systolic BP as compared with the usual care alone [27].

Ambulatory BP monitoring is considered the “gold standard” method for diagnosing hypertension among patients receiving dialysis [1, 18, 28]. The superiority of this technique over the conventional peridialytic BP measurements is strongly supported by comparative studies showing that mean 44-h interdialytic BP can better predict the presence of target-organ damage (such as echocardiographic LV hypertrophy) [23] and is more closely associated with all-cause and cardiovascular mortality [2, 4]. The use of ambulatory BP monitoring has also the advantage of recording BP during nighttime, providing additional information with respect to the circadian variation of BP; the presence of a non-dipping nocturnal BP pattern is very common among dialysis patients and has been associated with LVH [29] and increased risk of all-cause and cardiovascular mortality [30]. It is important noting that the superiority of ambulatory BP monitoring over peridialytic BP recordings

can only partially be explained by the higher number of BP measurements, as interdialytic BP recordings retain their strong prognostic association with cardiovascular outcomes even when a small number of randomly selected measurements are used to assess the interdialytic BP burden [31]; the latter suggests that the location and time frame covered and not the quantity of BP recordings are the major factor determining the strong prognostic significance of interdialytic ambulatory BP. Despite the above advantages, ambulatory BP monitoring is still perceived as a technique with limited applicability in dialysis patients in a reservation arising partly from the fact that many studies on ambulatory BP monitoring in this population dialysis patients were performed in a single American academic hemodialysis unit [2, 11, 23]. The high prevalence of non-dipping and nocturnal hypertension among dialysis patients [32] suggests that the application of ABPM for the diagnosis and the treatment of hypertension is more compelling than in the general population, where ABPM has already been firmly recommended by different guidelines [33, 34]. Additional research efforts are needed in order to fully elucidate the particular indications, tolerability, and cost-effectiveness of ABPM. Until such studies are completed, the wide application of home BP monitoring should be encouraged as a simple and efficient approach to measure BP and make therapeutic decisions among patients on dialysis [14]. Figure 24.1 summarizes the thresholds to define hypertension using home and ambulatory BP monitoring proposed in a recent document of the EURECA-m working group of ERA-EDTA [18].

Contrary to the typical decline in BP during dialysis, in approximately 10–15% of dialysis patients, BP exhibits a "paradoxical" intradialytic elevation [35, 36]. Despite the fact that this abnormal pattern of intradialytic hemodynamic response has been for long recognized, there is no universally agreed definition of intradialysis hypertension. For example, in some studies, intradialysis hypertension was defined as a rise of at least 10 mmHg in systolic BP during dialysis or immediately postdialysis in a certain number of dialysis treatments [35, 36]. In other studies, patients were considered as suffering from intradialysis hypertension when their BP

| Definition |
|---|
| Hypertension in CKD and in dialysis patients should be defined on the basis of home (HBPM) or 24-h ambulatory BP monitoring (ABPM) during a mid-week dialysis interval. Thresholds proposed by the ESH and the ESC can be adopted for CKD patients,[9] and those by the ASH,[5] for hemodialysis patients, as below |
| Home BP measurements: ≥135/85 mmHg both for CKD patients and for hemodialysis patients. |
| Twenty-four- hour ambulatory BP ≥130/80 mmHg for CKD patients and ≥135/85 mmHg for hemodialysis patients. In hemodialysis patients, ABPM should be performed during a mid-week dialysis interval and, whenever feasible, extended to 44 h. |
| For hemodialysis patients, no recommendation can be made on the basis of predialysis or postdialysis BP. When neither ABPM nor home BP measurements are applicable in dialysis patients, the diagnosis and the management of hypertension can be made on the basis of conventional BP (CBP) measurements taken during the dialysis interval. At variance with predialysis BP which has an U-shaped relationship with risk of death, in the same patients, the average of 3 office measurements (obtained in the sitting position after at least 5 min of quiet rest by trained personnel) is almost linearly related to the risk of the same outcome.[21] The threshold of office BP (140/90 mmHg) recommended by current guidelines for the definition of hypertension in CKD patients[9] can be extended also to hemodialysis patients. |
| **Drug therapy goals** |
| Particularly for hemodialysis patients, arterial pressure goals should be established individually, taking into account age, comorbid conditions, cardiac function, and neurological status |

ASH indicates American Society of Hypertension; ASN, American Society of Nephrology; BP, blood pressure; CKD, chronic kidney disease; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ESRD, end-stage renal disease.

**Fig. 24.1** Definition of hypertension in CKD and in ESRD patients (reprinted with permission from Parati et al. [18])

showed a change of >0 mmHg from pre- to postdialysis; another definition was the regression of all intradialytic BP measurements over time with a slope greater than zero [37]. Of note, intradialysis hypertension is not solely related to mechanistic changes exerted during the dialysis session but also related to the BP burden during the interdialytic period. In a case-control study comparing the interdialytic BP profile of 25 patients with intradialysis hypertension (increase in systolic BP >10 mmHg from pre- to postdialysis in four out of six consecutive dialysis treatments) with that of 25 age- and sex-matched controls with normal intradialytic hemodynamic response, Van Buren et al. [38] made the important observation that intradialysis hypertension is a phenomenon superimposed to systemic background hypertension. Patients with intradialysis hypertension had higher 44-h interdialytic BP than controls, as well as a gradual BP decline during the first 24 h after dialysis, which contrasted with the (typical) gradual increase from postdialysis onward in patients without intradialytic hypertension [38].

## 24.3 Epidemiology

The estimates of the prevalence, treatment, and control of hypertension among patients on chronic dialysis are highly variable, depending on the definitions used to diagnose hypertension as well as on the setting of BP measurement (i.e., routine peridialytic BP recordings or interdialytic ambulatory BP monitoring) [39–43].

### 24.3.1 Epidemiology Based on Peridialytic BP Recordings

Hypertension is highly prevalent among patients with chronic kidney disease (CKD) not yet on dialysis. In a cross-sectional analysis of 10,813 CKD patients participating in the Kidney Early Evaluation Program (KEEP) in the USA, hypertension (defined as BP ≥130/80 mmHg or use of antihypertensives) was detected in 86.2% of the overall study cohort; prevalence of hypertension exhibited a stepwise increase with advancing stage of CKD, increasing from 79.1% in participants with stage 1 CKD to approximately 95%% (or 91% with the use of 140/90 threshold) in participants with stage 4 and 5 CKD [44]. An analysis of 238 patients with predialysis CKD followed in a low clearance clinic in the UK confirmed that the prevalence of hypertension is at 95% (Fig. 24.2) [45]; the mean estimated glomerular filtration rate (eGFR) in this cohort was 14.5 mL/min/1.73 $m^2$, suggesting that nearly all CKD patients just before the initiation of renal replacement therapy are already hypertensives.

Initiation of dialysis per se may have a substantial impact on management of hypertension, given the severely impaired ability of patients with advanced CKD for sodium excretion and the fact that dialysis represents a potent therapeutic tool to remove the sodium excess [1]. Achievement of sodium and volume control via dialysis often decreases the need for antihypertensive drug therapy in incident dialysis patients. It is therefore unsurprising that the rates of hypertension prevalence may

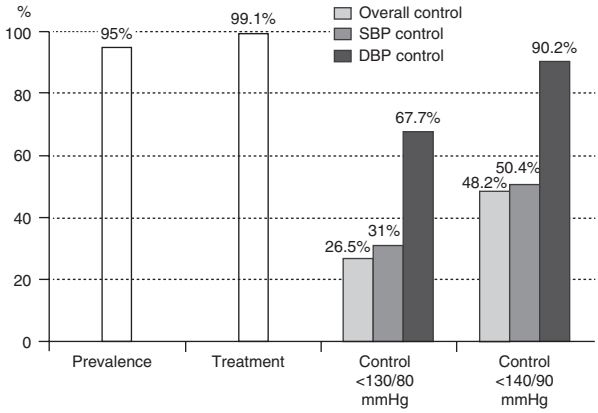



**Fig. 24.2** Prevalence (at the 130/80 threshold for office BP), treatment, and control of hypertension in predialysis patients followed in a low clearance clinic with average eGFR 14.5 mL/min/1.73 $m^2$ (reprinted with permission from Sarafidis et al. [45])

be higher among predialysis CKD patients than among ESRD patients receiving renal replacement therapy, as discussed below. Moreover, hypertension prevalence after initiation of dialysis depends on the clinical policies adopted in the renal units where the patients are being treated. In some renal units which apply long dialysis and strict control of salt intake, hypertension has a lower prevalence than in those which don't apply such a clinical policy [46].

Using the definition of predialysis mean arterial pressure ≥114 mmHg, Salem et al. [42] reported that the prevalence of hypertension among 649 hemodialysis patients from ten dialysis units in Mississippi was 72%. Eighty percent of hypertensive patients had combined systolic and diastolic hypertension and 20% isolated systolic hypertension. Race, dialysis vintage, primary cause of ESRD, or adequacy of dialysis had no association with the hypertension status in this study [42]. In 5369 patients participating in the Dialysis Morbidity and Mortality Study Wave 1 [40], the prevalence of hypertension was 63% using the JNC 6 classification to define hypertension. A hypertension prevalence rate of 70% was reported in a cross-sectional analysis of the baseline characteristics of 1238 chronic hemodialysis patients enrolled in the HEMO study [41]. A more detailed evaluation of prevalence, treatment, and control of hypertension was provided by a cross-sectional analysis of 2535 clinically stable, hemodialysis patients participating in a multicenter trial of the safety and tolerability of an intravenous iron preparation [39]. In this survey, hypertension was defined as a 1-week average predialysis systolic BP >150 mmHg or diastolic BP >85 mmHg or the use of antihypertensive drugs with prevalence at 86%, and despite the fact that 88% of hypertensives were treated, only 30% of them had their BP adequately controlled [39]. Information on hypertension prevalence in countries other than the USA is limited. In surveys made within the frame of the DOPPS [47], the prevalence of hypertension was very high and rising over time in all countries. In the last of these surveys [48], hypertension prevalence ranged from 78% in Japan to 95.9% in Germany. All the above estimates should be interpreted within the context of the unavoidable limitation of the use of routine peridialytic BP recordings to assess the hypertension status of study participants.

### 24.3.2 Epidemiology Based on Interdialytic Ambulatory BP Monitoring

A more valid estimation of hypertension prevalence and control among dialysis patients was provided by a recent study using the "gold standard" method of 44-h interdialytic ambulatory BP monitoring and defining hypertension as average systolic BP values ≥135 mmHg and/or diastolic BP ≥85 mmHg or the use of antihypertensive medications in a population of 369 predominantly African-American patients who received hemodialysis treatment in units affiliated with the Indiana University in Indianapolis. The prevalence of hypertension was 82% [43], and although 89% of hypertensives were treated with antihypertensive drugs, the rate of adequate 44-h BP control was as low as 38% [43]. Poor hypertension control in this study was associated with excessive antihypertensive drug use and volume expansion as measured by the inferior vena cava diameter in expiration [49]. Of note, other studies suggest that the higher the number of antihypertensive agents prescribed, the greater the likelihood a dialysis patient to be on a volume-expanded state [43]. Apart from this study in African-Americans, no large surveys reporting hypertension prevalence based on ABPM have been made in other ethnicities and in other countries.

### 24.3.3 The Association of BP with All-Cause and Cardiovascular Mortality

The relationship of BP with all-cause and cause-specific mortality among patients on dialysis is an issue surrounded by substantial controversy, due to the diverse patterns of association between BP and mortality according to timing (i.e., predialysis, postdialysis, or intradialysis) or the technique of BP measurement (i.e., peridialytic BP recordings vs. interdialytic BP recording either with home or ambulatory BP monitoring). Several studies have shown a U-shaped association of the BP recorded either predialysis or postdialysis with all-cause and cardiovascular mortality [50–52], a phenomenon described as "reverse epidemiology of hypertension" in the dialysis population. This observation has raised substantial concerns on whether BP lowering is a strategy associated with benefits for ESRD patients receiving hemodialysis [53]. However, this U-shaped association seems to be due to the incapacity of peridialytic BP recordings per se to describe the true BP load, rather than reflect a true U-shaped relation of BP with cardiovascular morbidity and mortality.

Contrary to the unclear association of peridialytic BP recordings with all-cause and cardiovascular mortality, prospective cohort studies have shown that interdialytic BP recorded either with home or with ambulatory BP monitoring associates directly with mortality and cardiovascular events relevant to what happens in non-dialysis populations. In a cohort of 57 treated hypertensive hemodialysis patients prospectively followed for a mean period of 34.4±20.4 months, Amar et al. [4] showed elevated 24-h ambulatory pulse pressure (PP) [relative risk (RR), 1.85 for

each 10 mmHg increase in PP; 95% confidence intervals (CIs), 1.28–2.65] as well as elevated nocturnal systolic BP (RR, 1.41 for each 10 mmHg increase in nocturnal systolic BP; 95% CIs, 1.08–1.84) to be independently associated with increased risk of cardiovascular mortality [4]. In larger study by Tripepi et al., in 168 nondiabetic hemodialysis patients, nocturnal BP burden (as estimated by the night/day ratio) was a direct predictor of death and cardiovascular events as well as of LVH [30]. In a subsequent cohort study of 150 hemodialysis patients, Alborzi et al. [3] showed that increasing interdialytic BP measured with home and ambulatory BP monitoring was directly associated with heightened risk of mortality over a mean follow-up period of 24 months. No such relationship was detectable using BP measurements obtained before or after dialysis (Fig. 24.3) [3]. In a larger cohort of hemodialysis patients followed for 32 months, Agarwal et al. confirmed that the higher quartiles of home and 44-h ambulatory systolic BP were independently associated with increased risk of mortality [2]. Once again, BP recorded outside of the dialysis unit was of stronger prognostic significance as compared with BP recorded before or after dialysis.

Additional support to the notion that out-of-dialysis BP recordings have closer association with outcomes is provided by a recent prospective analysis of 326 patients participating in the Chronic Renal Insufficiency Cohort (CRIC) study [54]. The prognostic association of systolic BP with all-cause mortality was assessed in

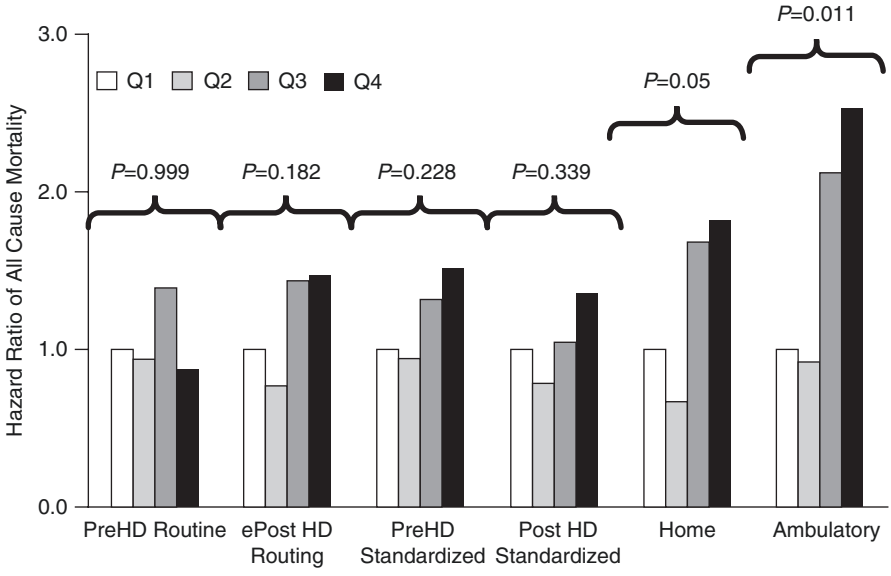



**Fig. 24.3** Hazard ratios for all-cause mortality for quartiles of predialysis, postdialysis, and home and ambulatory systolic blood pressure (BP). Higher levels of home BP and ambulatory BP were significantly associated with mortality, whereas pre- and postdialysis BP was not. *P* values are those reported for linear trend. HD indicates hemodialysis and Q quartile (reproduced with permission from Alborzi et al. [3])

three different time points of this prospective cohort: (1) when participants had stage 4 CKD (eGFR <30 mL/min/1.73 $m^2$), (2) when participants initiated hemodialysis and dialysis unit BP measurements were available, and (3) when incident hemodialysis patients had an out-of-dialysis BP measurement obtained during a prespecified follow-up visit at home [54]. Systolic BP had no association with mortality among participants not yet on dialysis. In accordance with earlier reports from other cohorts of hemodialysis patients, dialysis unit systolic BP provided a U-shaped association with mortality. In contrast, a direct linear association between systolic BP and all-cause mortality was evident when BP measurements were obtained outside of the unit (HR, 1.26 for each 10 mmHg higher systolic BP; 95% CIs, 1.14–1.40) [54].

The pattern of intradialytic hemodynamic response (i.e., the change in BP from pre- to postdialysis) has been also associated with increased risk of all-cause and cardiovascular mortality [54, 55]. In this regard, Park et al. [56] revealed a U-shaped association between intradialytic change in systolic BP and mortality. In a huge cohort study of 113,215 US hemodialysis patients retrospectively followed over a median period of 5 years, it was shown that drops in systolic BP from pre- to postdialysis between 30 and 0 mmHg were associated with better survival, but large declines in systolic BP (>30 mmHg) and intradialytic rise in systolic BP of any degree were both linked with increased risk of mortality [56].

### 24.3.4 Epidemiology of Hypertension Among Patients Receiving Peritoneal Dialysis

The prevalence of hypertension among patients on peritoneal dialysis was evaluated in a cross-sectional study conducted in 504 patients in 27 peritoneal dialysis centers belonging to the Italian Co-operative Peritoneal Dialysis Study Group [57]. Valid ambulatory BP measurements were obtained in 414 patients (82%) using the WHO/ISH and the JNC 7 report criteria; Cocchi et al. reported that the prevalence of hypertension was 88.1%. Applying the definition of a BP load >30% over a 24-h ambulatory BP monitoring, the estimated prevalence of hypertension was lower (69%). The average 24-h blood pressure in this study was 139±19/81±11 mmHg, clearly indicating that the prevalence of hypertension as defined by the joint document of the American Society of Nephrology and the American Society of Hypertension (SBP ≥135 and/or DBP ≥85 mmHg) [1] exceeds 50–60% in the peritoneal dialysis population [57]. Of note, as much as 53% of patients in this study were non-dippers and an additional 9% had an inverted day/night BP profile. Small studies comparing the ambulatory BP profile between patients treated with automated peritoneal dialysis vs. continuous ambulatory peritoneal dialysis showed that the average 24-h BP, diurnal BP variation, and BP control rates were no different between these two modalities [58, 59]. Other studies have described an association between BP and peritoneal transport status. Patients with high peritoneal transport (reflecting poor peritoneal ultrafiltration) have higher BP levels during both daytime and nighttime periods as well as higher LVMI as compared to "low transporters," and this difference most likely reflects volume overload triggered by high peritoneal

transport in the first group. Volume expansion is more marked in peritoneal than in hemodialysis patients [60], and these patients more frequently require antihypertensive drugs (65%) than hemodialysis patients (38%, $P<0.001$). The detrimental role of volume expansion in patients maintained on peritoneal dialysis is notorious [61].

Given the more continuous nature of renal replacement therapy and the absence of cyclic variations in volume status and in several other metabolic parameters in patients receiving peritoneal dialysis, it is long hypothesized that BP control and diurnal variation of BP may be substantially different between patients treated with peritoneal dialysis and those receiving thrice-weekly hemodialysis. However, only two small studies have so far tested this hypothesis. Tonbul et al. [62] compared the 44-h ambulatory BP profile of 22 hemodialysis patients with that of 24 patients treated with continuous ambulatory peritoneal dialysis. Mean 44-h systolic and diastolic BP was no different between the two dialytic modalities; however, in hemodialysis nighttime BP recorded on the dialysis-off day was significantly higher, and daytime BP recorded on the dialysis-on day was significantly lower than the relevant BP recordings obtained in the same time periods in patients treated with continuous ambulatory peritoneal dialysis [62]. Another comparative study including 33 hemodialysis and 27 peritoneal dialysis patients showed that diurnal BP pattern (i.e., dipping status) did not differ between the two dialytic modalities over a 48-h ambulatory BP recording, but average ambulatory systolic BP (142.1±16.3 vs. 130.4±17.1 mmHg, $P<0.01$) and systolic loads (54±29% vs. 30±31%, $P<0.01$) were higher in those receiving hemodialysis [63]. It has to be noted, however, that methodologically rigorous randomized comparisons between hemodialysis and peritoneal dialysis are missing, and the studies performed so far are small and largely inconclusive.

## 24.4 Pathogenesis

Increase in cardiac output or in peripheral vascular resistance or in both these hemodynamic parameters may result in sustained BP elevation among patients on dialysis. Undoubtedly, sodium and volume expansions are considered the prominent pathogenic mechanisms of hypertension in these individuals. A number of non-volume-mediated pathways, such as activation of the renin-angiotensin-aldosterone and sympathetic nervous systems, structural arterial wall alterations related to the long-term arteriosclerotic process, endothelial dysfunction, sleep apnea, and the use of particular medications like erythropoietin-stimulating-agents (ESAs), are also reported to play an important role in the complex mechanistic background of hypertension in dialysis patients.

### 24.4.1 Volume Overload

In patients with ESRD, even when residual renal function is preserved, the sodium and fluid excretory capacity is substantially impaired; subsequently, the presence of

sodium and volume expansion is very common and often not easily identifiable in dialysis patients. Moreover, patients with ESRD are those with the highest sodium sensitivity of BP [64, 65]. In addition, it is now well documented that in addition to classical osmotic volume expansion, sodium retention may occur in the form of osmotically inactive sodium in the connective tissue and the skin where sodium accumulates linked to glycosaminoglycans [66]. Such a non-osmotic sodium retention triggers local macrophage recruitment, lympho-angiogenesis, and hypertensive mechanisms independent of those traditionally ascribed to isoosmotic volume retention. In hemodialysis patients, sodium and water in skin and muscle are increased and vascular endothelial growth factor is reduced as compared to age-matched healthy individuals, and these phenomena may also contribute to hypertension [67]. Fluid and sodium accumulation between subsequent dialysis treatments exerts a substantial impact on the patterns and rhythms of interdialytic BP, which is superimposed on the circadian variation of BP. Among hemodialysis patients, BP steadily increases during the interdialytic interval and the rate of BP increment is directly proportional to the interdialytic weight gain [68]. Studies including 48-h ambulatory monitoring of central hemodynamic indices in hemodialysis patients showed a gradual increase in peripheral and central aortic BP between the intra- and interdialytic periods [69]. Excess volume accumulation over the long interdialytic interval in patients receiving thrice-weekly hemodialysis imposes an additional BP load during the third interdialytic day (Fig. 24.4). In a study of 55 hemodialysis patients having a 72-h ambulatory aortic BP monitoring, a significant increase of 5/3.5 mmHg in aortic BP was noted between the third and the second day of the long interdialytic intervals; nighttime BP and the proportion of patients with a non-dipping circadian BP pattern were also higher during the third interdialytic day [70]. Unless extracellular fluid and sodium overload is removed with ultrafiltration, a rise in vascular resistance would sustain hypertension in these individuals. In this context, strict volume and sodium control emerges as the principal target of therapy in hypertensive patients with ESRD.

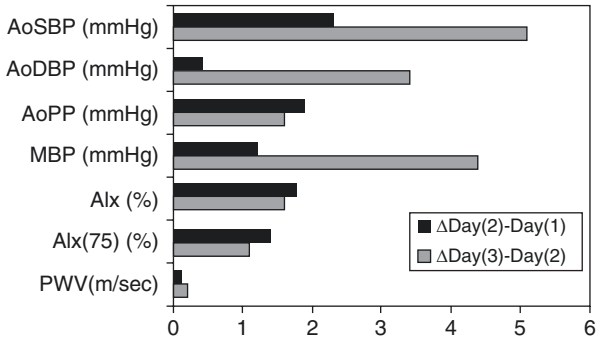



**Fig. 24.4** Changes in aortic blood pressures, wave reflections, and arterial stiffness parameters between the first and the second interdialytic day Δ[day(2)–day(1)], in comparison with relevant changes between the second and the third interdialytic day Δ[day(3)–day(2)] (reprinted with permission from Koutroumpas et al. [70])

### 24.4.2 Renin-Angiotensin-Aldosterone System

Activation of the renin-angiotensin-aldosterone system (RAAS) even in patients with ESRD under renal replacement therapy is long known [71, 72]. Plasma renin activity (PRA) is maintained within the normal range in the majority of dialysis patients; however, PRA may be inappropriately elevated in relation to the total exchangeable sodium and may contribute to the sustained BP elevation [73]. This notion is supported by clinical studies showing a significant increase in PRA and plasma aldosterone levels from pre- to postdialysis, suggesting that residual functioning nephrons in the failing kidneys of ESRD patients retain their ability to sense acute changes in sodium and intravascular volume status that occur in response to ultrafiltration [71, 73]. Additional support to the fact that BP elevation in a subset of dialysis patients may be in part renin mediated is provided by earlier studies showing a sustained BP reduction in hypertensive dialysis patients after the administration of the angiotensin II antagonist saralasin; removal of the native kidneys from the BP responders was associated with long-term normalization of their BP levels [74]. More recent studies have shown a dose-dependent elevation in pre- and postdialysis PRA levels along with a parallel fall in 44-h [75] interdialytic ambulatory BP in response to the supervised administration of the angiotensin-converting enzyme inhibitor (ACEI) lisinopril [75]. In addition to the above, the relationship between PRA, aldosterone, and major clinical outcomes in dialysis patients is complex and much influenced by malnutrition and inflammation. Indeed, independently of predialysis BP, aldosterone is an inverse predictor of mortality and CV events in this population, and this seemingly paradoxical relationship is abolished by adjustment for inflammation, protein energy malnutrition, and volume expansion biomarkers indicating that it is the mere expression of the confounding effect of these factors [76].

### 24.4.3 Sympathetic Nervous System

Seminal microneurography studies assessing efferent sympathetic nerve activity have provided evidence that sympathetic overactivity is an important cause of hypertension among patients on dialysis. These clinical studies showed a doubling in the rate of sympathetic discharge in hemodialysis patients with intact native kidneys; in contrast, sympathetic nerve activity in bilaterally nephrectomized hemodialysis patients was similar to that of healthy individuals [77]. Bilateral nephrectomy of native failing kidneys was shown to be associated with sustained reduction in peripheral vascular resistance as well as with dramatic drop in BP levels [78]. The notion that sympathetic overactivity is implicated in the causal pathway of hypertension in dialysis patients is also supported by recent reports in small groups of patients suggesting that renal denervation exerts a significant BP-lowering effect and improves sympathetic nerve discharge among dialysis patients with hypertension that remains unresponsive to multidrug antihypertensive therapy and ultrafiltration intensification [79, 80]. In a proof-of-concept study, Schlaich et al. [81] performed

renal nerve ablation in 12 hemodialysis patients with uncontrolled hypertension (office BP>140/90 mmHg) despite the current use of ≥3 antihypertensive drugs. The procedure of renal denervation was feasible in nine out of 12 study participants; among these patients, a significant drop of 28/10 mmHg in office BP was noted over a mean 12-month-long follow-up period [81].

Renalase, an enzyme that metabolizes catecholamines and catecholamine-like substances, may contribute to the excessive sympathetic overactivity and hypertension in CKD [82]. Renalase is a flavin adenine dinucleotide-dependent amine oxidase which is secreted in the blood by the kidney [82]. Infusion of recombinant renalase in rats produces a significant reduction in BP and heart rate, an effect predominantly mediated through reduced peripheral vascular tone and cardiac output [83]. The plasma concentration of renalase was shown to be markedly decreased in hemodialysis patients as compared to age- and sex-matched controls with normal renal function [84].

### 24.4.4 Arterial Stiffness

Patients with ESRD display a distinct form of early increase in arterial stiffness, due to a combination of factors, mostly relevant to inappropriate calcium-phosphate homeostasis [85]. Among dialysis patients, arterial stiffness, as assessed by aortic pulse wave velocity (PWV), is a relevant determinant of the patterns and rhythms of BP recorded over the entire interdialytic period [85–87]. Analyzing 11,833 interdialytic BP measurements obtained from 125 hemodialysis patients with the use of a generalized cosinor model, Agarwal et al. [86] showed that each one log increase in aortic PWV was associated with a rise of 18.8/7.08 mmHg in the intercept of systolic/diastolic BP and with elevation of 11.7 mmHg in the intercept of PP. Increasing aortic PWV tended also to blunt the circadian amplitude of systolic BP and PP [86]. Subsequently, in a post hoc analysis of the HDPAL trial, it was shown that increasing aortic PWV at baseline was an independent determinant of 44-h ambulatory systolic BP and PP. After adjustment for several confounding factors, each 1-m/s higher baseline aortic PWV was associated with 1.34-mmHg higher baseline systolic BP and 1.02-mmHg higher PP [87]. However, aortic PWV at baseline was unable to predict the treatment-induced reduction in 44-h ambulatory systolic and diastolic BP at 3, 6, and 12 months of follow-up [87]; the latter suggests that among dialysis patients, arterial stiffness does not make hypertension more resistant to the BP-lowering therapy. Studies evaluating acute changes in arterial stiffness indexes during the interdialytic periods showed that augmentation index (AIx) and central aortic PP are increased during both 3-day and 2-day interdialytic intervals; aortic and brachial PWV was unchanged in this short time frame [88]. This increase in wave reflection indices was by 30% higher during the 3-day as compared to the 2-day interdialytic interval and was linearly associated with interdialytic weight gain [88]. This observation was confirmed in subsequent studies showing a gradual interdialytic increase in wave reflection indices and central aortic BP with the use of ambulatory BP monitoring [69, 70].

### 24.4.5 Endothelial Dysfunction

An imbalance between endothelium-derived vasoconstrictors and vasodilators in favor of the former may be another mechanistic pathway of hypertension among patients on dialysis [89]. This is supported by animal studies showing downregulation of the endothelial and inducible nitric oxide synthase activity in 5/6 nephrectomized rats, an alteration that resulted in sustained BP elevation [90]. Endothelial dysfunction results from several mechanisms including high circulating levels of asymmetric dimethylarginine (ADMA) [91, 92]; an endogenous nitric oxide synthase inhibitor and its accumulation result in reduced generation of nitric oxide [93]. The higher levels of ADMA in ESRD result from both a diminished intracellular degradation by desamino-D-argininehydrolase and diminished renal clearance of ADMA, since this molecule is mainly excreted by the kidney [93]. Among ESRD patients, ADMA is associated with increased LV relative wall thickness and reduced ejection fraction. Importantly, prospective cohort studies have associated increased ADMA levels with excessive risk of cardiovascular morbidity and mortality in hemodialysis patients [91, 93].

### 24.4.6 Sleep Apnea

Sleep apnea is highly prevalent among dialysis patients and volume expansion may be a major player in this alteration [94]. In the recumbent position, volume overload may promote sleep-disordered breathing and nocturnal hypoxemia through an overnight fluid shift from the legs to the neck soft tissues that increases peripharyngeal and upper airway resistance [95]. Nocturnal hypoxemia in sleep apnea has been associated with a reversed circadian BP pattern, triggering in this way nocturnal hypertension. This notion is supported by a study of 32 hemodialysis patients showing that those patients experiencing sleep apnea had higher nocturnal systolic BP and higher LV relative wall thickness than those without sleep apnea; an inverse relationship was noted between the average nocturnal arterial oxygen saturation and LV relative wall thickness [29]. In another study, Abdel-Kader et al. [96] showed that ESRD patients with sleep apnea had 7.1 times higher risk of developing resistant hypertension (defined as office BP >140/90 mmHg despite the use of >3 different antihypertensive agents); in contrast, no such association between sleep apnea and resistant hypertension was noted among patients with non-dialysis-requiring CKD [96]. Whether strict management of volume status improves sleep apnea symptoms and restores the blunted nocturnal BP fall in dialysis patients still remains elusive.

### 24.4.7 Erythropoietin-Stimulating Agents

Hypertension is a common but frequently overlooked complication of erythropoietin therapy [97]. New-onset hypertension or worsening of pre-existing hypertension can be easily missed due to the high variability of BP in dialysis patients [10]

particularly in the absence of properly performed home or ambulatory BP measurements. Studies that did not detect BP elevation in response to erythropoietin therapy may have managed hypertension more aggressively through intensification of antihypertensive drug therapy and closer monitoring of volume status [97]. Existing studies have associated erythropoietin-induced hypertension with increased circulating endothelin-1 concentration or enhanced vasoconstrictive response to endothelin-1 [98, 99], increased sensitivity to the pressor effect of angiotensin II [100], and increased vascular reactivity to norepinephrine [101].

## 24.5 Treatment

### 24.5.1 Non-pharmacological Management of Hypertension

Once an accurate diagnosis of hypertension is made (see above), the management of hypertension in dialysis patients should start with non-pharmacological therapeutic measures aiming to control sodium and volume excess. This includes (1) dietary sodium restriction [102, 103], (2) individualized prescription of the sodium concentration in the dialysate to avoid intradialytic sodium loading, (3) proper adjustment of dry weight, and (4) avoiding shorter dialysis. Outside the realm of hypertensive urgencies and emergencies [6], and the fact that common antihypertensive agents may be needed for other indications (i.e., β-blockers for angina symptoms, heart failure, or rate control, RAS blockers for heart failure, etc.), administration of antihypertensive drug therapy in dialysis patients considered to be volume overloaded should follow the attainment of dry weight.

#### 24.5.1.1 Restricting Dietary Sodium Intake

Among dialysis patients, restricting dietary sodium is proposed as a simple and effective maneuver to limit the sense of thirst, reduce interdialytic weight gain, and facilitate the achievement of dry weight [102]. Instead of dietary sodium restriction, patients on dialysis are often instructed to avoid excess fluid accumulation during the interdialytic interval. With the exception of treating hyponatremia, there is no specific indication to prescribe fluid-restrictive diets in chronic dialysis patients [104]. Currently available recommendations suggest that among dialysis patients, dietary sodium intake should not exceed 1.5 g (or approximately 65 mmol) sodium per day [103].

#### 24.5.1.2 Individualizing the Dialysate Sodium Prescription

To ensure hemodynamic stability during dialysis and limit the risk of intradialytic symptoms (i.e., disequilibrium, nausea, vomiting, muscle cramps, etc.), prescription of a high dialysate sodium concentration was initially the most preferable therapeutic choice for patients receiving long-term dialysis [105, 106]. Earlier studies supported the notion that high dialysate sodium minimizes the intradialytic hypotensive episodes without worsening interdialytic hypertension [107, 108]. However, more recent works challenged the conclusions of those studies and emphasized that a high

dialysate sodium concentration may increase thirst and, therefore, interdialytic weight gain leading to the need for higher ultrafiltration during the next dialysis session [105, 106]. Indeed, in a study in 1084 hemodialysis patients, Munoz Mendoza et al. [109] found that dialysate sodium prescriptions ranging from 136 to 149 (median, 140) mEq/L, with most patients being dialyzed against a positive sodium gradient, resulted in over 90% of patients having a rise in serum sodium across dialysis and thus higher postdialysis thirst and interdialysis weight gain. A consensus document by the chief medical officers of US dialysis providers warns against the use of dialysate with a sodium concentration exceeding predialysis serum sodium [105, 106]. This increase in interdialytic weight gain leads to the need for higher ultrafiltration during the next dialysis session, which may act as a triggering factor for more frequent episodes of intradialytic hypotension and prescription of even a higher dialysate sodium concentration, precipitating in this way a vicious cycle [105, 106].

A positive intradialytic sodium balance may also arise in patients receiving sodium-profiling dialysis. A randomized crossover study of 11 dialysis patients compared the effect of performing sodium-profiling dialysis with a time-averaged concentration (TAC) of dialysate sodium of 140 mmol/L [TAC(140)] vs. sodium-profiling dialysis with a TAC of 147 mmol/L [TAC(147)] vs. conventional dialysis with a dialysate sodium of 138 mmol/L [110]. An increase in mean 24-h interdialytic BP, in interdialytic weight gain, as well as in interdialytic discomfort symptoms was evident during the period of TAC(147) sodium-profiling dialysis as compared with the periods of TAC(140) and TAC(138). Increase in interdialytic weight gain and interdialytic systolic BP was directly proportional to the TAC of the dialysate sodium [110].

The vicious cycle of intradialytic sodium loading can be interrupted by individualizing the prescription of the sodium concentration in the dialysate. A single-blind, randomized, crossover study compared the effect of individualized prescription of the dialysate sodium concentration (the dialysate sodium set to match predialysis sodium during standard dialysis applying a 138 mEq/L sodium concentration multiplied by 0.95 to allow for the Gibbs-Donnan effect) with that of a standard dialysate sodium concentration set to 138 mEq/L in nondiabetic, non-hypotension-prone dialysis patients. Compared with the period of standard dialysate sodium, a significant reduction in interdialytic weight gain (2.91±0.87 vs. 2.29±0.65 kg, $P<0.001$), interdialytic thirst score, and episodes of intradialytic hypotension was evident during the period of individualized dialysate sodium prescription [111]. A pilot study using a biofeedback software system to progressively reduce postdialysis plasma conductivity from 14.0 to 13.5 mS/cm [112] showed that this maneuver resulted in significant reduction of postdialysis plasma sodium from 137.8 to 135.6 mmol/L. Diffusive sodium removal in addition to convective losses induced a nearly 100 mmol/L higher net intradialytic sodium loss resulting in reduction in the extracellular body water compartment, lower interdialytic weight gain, and drop in predialysis BP [112]. In a subsequent single-blind, crossover study of 15 patients receiving thrice-weekly in-center, nocturnal dialysis, lowering the dialysate sodium concentration from 140 to 136 or 134 mEq/L for a 12-week treatment

period decreased interdialytic weight gain by 0.6±0.6 kg and predialysis systolic BP by 8.3±14.9 mmHg without increasing intradialytic hypotensive episodes [113]. In a 3-week, two-arm, randomized, crossover trial of 16 dialysis patients with intradialysis hypertension, Inrig et al. [114] compared the effect of a high (5 mEq/L above serum sodium) vs. a low dialysate sodium concentration (5 mEq/L below serum sodium) on intradialytic BP and endothelium-derived vasoregulators. The weekly averaged predialysis systolic BP was lower during the period of low dialysate sodium concentration compared with dialysis treatments with high dialysate sodium (parameter estimate, −9.9 mmHg; 95% CI, −13.3 to −6.4 mmHg; $P<0.001$) [114]. Overall these studies suggest that a single dialysate sodium prescription may not fit all patients. Individualizing the dialysate sodium prescription may facilitate the achievement of euvolemia without aggravating the risk of intradialytic hemodynamic instability.

Similarly to the low dialysate sodium in hemodialysis patients, increasing the diffusive component of sodium removal with the use of low-sodium peritoneal dialysis fluids is suggested to be an effective maneuver to improve BP control among patients receiving peritoneal dialysis. In a nonrandomized interventional study comparing a standard vs. a low-sodium peritoneal dialysis solution substituted for one 3- to 5-h exchange over a mean follow-up period of 2 months, low-sodium concentration in the dialysate resulted in a significant increase of 30–50 mmol/dwell diffusive peritoneal sodium removal [115]. Associated benefits of this intervention were significant reductions in the sense of thirst and total body water assessed by bioelectrical impendence analysis, together with a significant fall of 8 mmHg in nighttime systolic BP [115]. Prescribing low-sodium dialysate solutions and achieving adequate volume control through icodextrin solutions may have additive benefits in patients being on a volume-expanded state. A small, open-label randomized study lasting 12 months showed that compared with standard glucose peritoneal dialysis solutions, the use of icodextrin as an osmotic agent is associated with better extracellular volume control and greater reduction in systolic and diastolic 24-h ambulatory BP [116].

#### 24.5.1.3 Probing of Dry Weight

The adequate management of dry weight among dialysis patients is challenging [117]. The most important issue is the absence of a widely accepted definition of dry weight. Sinha and Agarwal [118] defined dry weight as the lowest tolerated postdialysis weight achieved through gentle and gradual reduction in postdialysis weight at which patients experience minimal signs or symptoms of either hypovolemia or hypervolemia [118].

Another challenge in the management of volume status among dialysis patients is the absence of a single clinical test to reliably adjudicate whether a patient has reached the “ideal” dry weight or whether the patient remains volume overloaded. The presence of pedal edema is frequently used in daily clinical practice as a simple physical sign to assess dry-weight achievement. The reliability of pedal edema as a sign of volume excess was investigated in a cross-sectional analysis of 146 asymptomatic dialysis patients, in which echocardiographic parameters, blood volume

monitoring, plasma volume markers, and inflammatory markers were measured as exposure variables, whereas pedal edema was assessed as an outcome variable [119]. This study showed that pedal edema exhibited significant associations with several cardiovascular risk factors such as age, body mass index, and LV mass index. However, indices reflecting intravascular volume, such as inferior vena cava diameter, blood volume monitoring, and plasma volume biomarkers, were not independent determinants of the presence of pedal edema [119].

Achievement of dry weight is a long-term process, in which the interaction between the doctor and the patient plays a prominent role. Dry-weight reduction is often accompanied by uncomfortable intradialytic symptoms such as hypotension, dizziness, cramps, nausea, and vomiting. Physicians often respond falsely to these symptoms with therapeutic interventions such as cessation of ultrafiltration, intravenous saline infusion, premature termination of dialysis, increasing the dialysate sodium concentration or finally raising the dry weight, and subsequently increasing the number of prescribed antihypertensive medications, which all finally act as barriers to the dry-weight achievement [1, 106]. The strongest evidence that probing of dry weight is an effective intervention in order to improve BP control among patients on dialysis is provided by the DRIP trial [120]. In this trial, 100 long-term hypertensive dialysis patients were randomly assigned to an intensive ultrafiltration group, in which the dry weight was probed without increasing the frequency or duration of dialysis; another 50 patients were randomly assigned to a control group, in which patients had only physician visits without any modification in their volume status [120]. The primary trial end point was the difference between the ultrafiltration and control groups in the change of 44-h interdialytic ambulatory BP during follow-up. Postdialysis weight was reduced by 0.9 kg at 4 weeks and resulted in a significant reduction of 6.9 mmHg (95% CI, −12.4 to −1.3 mmHg) in systolic BP; diastolic BP exhibited also a significant drop of 3.1 mmHg (95% CI, −6.2 to −0.02 mmHg). The overall dry-weight reduction achieved at study completion (8 weeks) was 1 kg; the associated BP-lowering benefit was a reduction of 6.6/3.3 mmHg in 44-h interdialytic ambulatory BP at 8 weeks of dry-weight probing (Fig. 24.5) [120]. The DRIP trial provided the net BP-lowering efficacy of dry-weight reduction, since background antihypertensive treatment of study participants remained unchanged throughout the trial. Of importance, this benefit was seen without any deterioration in parameters of health-related quality of life [120] and with a reduction in LV chamber volume [121]. The findings of the DRIP trial are in general agreement with previous uncontrolled observations in small series of patients [122–124].

In contrast to the above, benefits on BP control of intensification of ultrafiltration without prolonging dialysis time may be counterbalanced by a higher risk of hospitalizations for cardiovascular complications and arteriovenous fistula clotting [125]. High ultrafiltration rates increase the risk of dialysis hypotension, and in one observational study, ultrafiltration rates greater than 12.4 mL/kg per hour were associated with increased mortality [126]. Overall, dry-weight reduction may be more easily and safely achieved in multiple sessions or by prolonging the dialysis time to achieve a slower ultrafiltration rate, as discussed below.

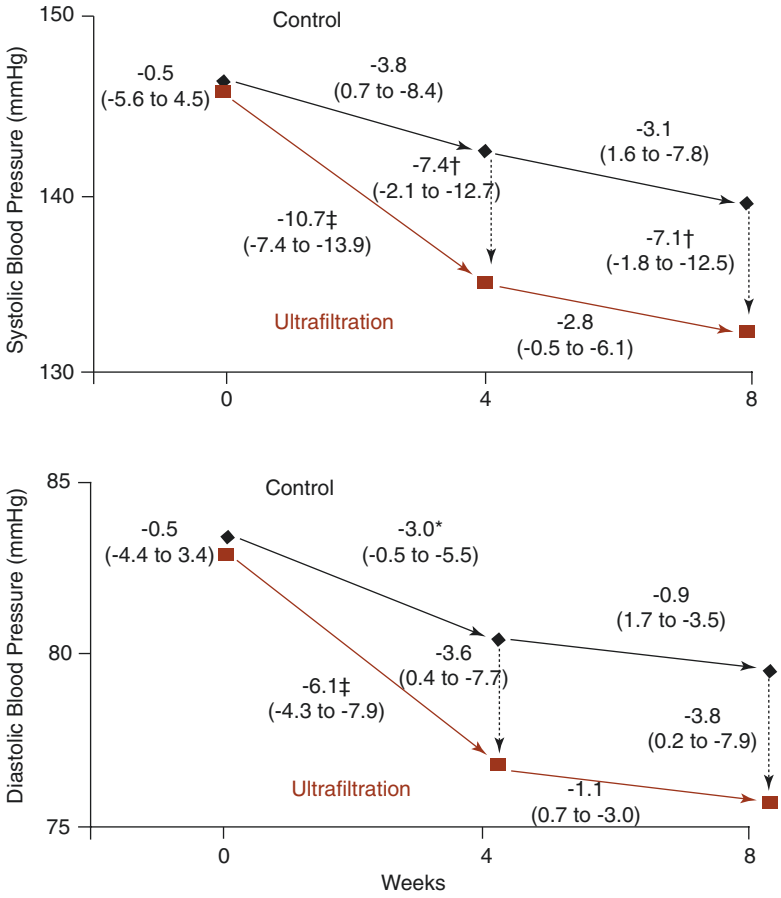



**Fig. 24.5** The effect of dry-weight reduction on changes in interdialytic (44-h) ambulatory systolic and diastolic BP over 4 and 8 weeks in hypertensive hemodialysis patients (reprinted with permission from Agarwal et al. [120])

### 24.5.1.4 Avoiding Shorter Delivered Dialysis

Current best practice guidelines recommend that patients with ESRD should receive renal replacement therapy with at least three dialysis sessions weekly, and the total duration of dialysis time should be at least 12 h per week [127]. Exception to this recommendation is proposed to be incident dialysis patients with substantial residual renal function or patients who started earlier dialysis; these specific subgroups of dialysis patients may be able to maintain the homeostasis of volume and metabolic parameters over a longer dialysis-free interval [127–129]. In contrast to guidelines, real-world data derived from the ESRD Clinical Performance Measures Project in the USA suggest that one quarter of the 32,065 patients participating in

this program were receiving less than 3 h and 15 min of dialysis/session and only one quarter of patients were receiving an extended-time (>4 h/session) dialysis regimen [130].

Among several other potential hazards, shorter delivered dialysis is reported to be an important barrier to the achievement of adequate BP control. This notion is supported by a post hoc analysis of the DRIP trial [131], in which median intradialytic systolic BP at baseline and its change over time were modeled against the duration of delivered dialysis. At baseline, median intradialytic systolic BP was higher with fewer hours of delivered dialysis. Among patients who did not have their dry weight probed (control group), median intradialytic systolic BP followed an increasing trend over the course of the trial. Dry-weight reduction in the ultrafiltration group induced a significant drop in median intradialytic systolic BP regardless of the duration of delivered dialysis [131]. However, patients with longer delivered dialysis required fewer dialysis sessions in order to gain the BP-lowering benefit of dry-weight reduction. A similar relationship was evident between the duration of delivered dialysis and the magnitude of change in 44-h interdialytic ambulatory systolic BP over time [131].

Increasing the duration or the frequency of the delivered dialysis may represent an alternative approach to control BP among dialysis patients who either experience frequent episodes of intradialytic hemodynamic instability or remain hypertensive despite the intensification of volume withdrawal that can be achieved within the conventional thrice-weekly 12-h dialysis regimen [132]. For example, in a crossover study of 38 dialysis patients comparing the frequency of intradialytic symptoms during 5-h vs. 4-h duration dialysis sessions, the incidence of intradialytic hypotension and postdialysis orthostatic hypotension was shown to be less common during the period of extended-time dialysis [133]. This notion is also supported by several other randomized and nonrandomized observations showing that patients assigned to longer or more frequent dialysis regimens achieve adequate BP control with minimal requirements for antihypertensive medications, a benefit that is possibly mediated through better achievement of postdialysis dry weight [132, 134–136].

### 24.5.2 Pharmacological Management of Hypertension

Two meta-analyses of randomized controlled trials have provided evidence that BP lowering with the use of antihypertensive drugs is associated with reduced cardiovascular morbidity and mortality in dialysis patients [137, 138]. The first meta-analysis included eight randomized controlled trials incorporating data from 1697 ESRD patients and 495 cardiovascular events [138]. The weighted mean difference in the change of BP between the active treatment and control groups was −4.5 mmHg for systolic and −2.3 mmHg for diastolic BP. This BP-lowering effect of antihypertensive drug treatment was associated with 29% reduction in the risk of all-cause mortality (pooled RR, 0.71; 95% CIs, 0.55–0.92) and 29% reduction in the risk of cardiovascular mortality (pooled RR, 0.71; 95% CIs, 0.50–0.99) [138]. The second meta-analysis [137] included five randomized trials with 1202 study participants.

Compared with placebo or control therapy, the overall cardiovascular benefit of BP lowering with antihypertensive therapy was a 31% reduction in the risk of future cardiovascular events (pooled HR, 0.69; 95% CIs, 0.56–0.84) [137]. In a subanalysis according to the hypertension status of patients participating in the individual studies, it was shown that cardiovascular protection provided by BP lowering was lesser when normotensive patients were included in the analysis (pooled HR, 0.86; 95% CIs, 0.67–1.12) [137]. These meta-analyses indicate that the use of antihypertensive drugs in dialysis patients may afford cardiovascular protection both in hypertensive patients and in normotensive patients with LV systolic dysfunction [137]; the cardiovascular benefit seems to be greater for hypertensives [137].

All major antihypertensive drug classes are useful for pharmacological treatment of hypertension [1, 139, 140]. Exception may be diuretic compounds, which are generally ineffective for BP control in patients with ESRD [1, 139, 140]. Echocardiographic studies conducted in anuric hemodialysis patients showed that intravenous administration of loop diuretics, even at high doses, exerts only minimal alterations in central hemodynamic indices [141]. Given the high risk of ototoxicity, the use of loop diuretics in anuric dialysis patients should be avoided. It remains to be elucidated whether these compounds have a beneficial role in those patients with preserved residual diuresis as a therapeutic intervention targeting to enhance urine output and limit fluid accumulation between subsequent dialysis treatments [142].

#### 24.5.2.1 Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Inhibition of the RAAS is often recommended as first-line BP-lowering therapy for dialysis patients, by extrapolation of the cardiovascular benefits of RAAS-blockers in the general population. However, whether RAAS-blockade affords the same benefits in hypertensive dialysis patients with hypertensive patients in the general population still remains unclear. In the Fosinopril in Dialysis (FOSIDIAL) trial [143] (Table 24.1), 397 hemodialysis patients were randomized to receive the ACEI fosinopril (titrated up to 20 mg/day) or placebo for a mean follow-up period of 48 months. Patients participating in the FOSIDIAL trial had by protocol LV hypertrophy, but were not necessarily hypertensives. Although therapy with fosinopril resulted in a significant reduction of predialysis BP vs. placebo in the subgroup of hypertensive participants, occurrence of fatal and nonfatal cardiovascular events during the follow-up did not significantly differ between the active treatment and placebo arms (RR, 0.93; 95% CIs, 0.68–1.26) [143].

Three trials (Table 24.1) [144–146] all performed in Japan compared angiotensin II receptor blockers (ARBs) to placebo or active therapy. The first enrolled 80 hemodialysis patients without overt cardiovascular disease and showed candesartan was superior to placebo in improving cardiovascular event-free survival [144]. In the second, 360 hypertensive hemodialysis patients were randomly assigned to receive ARB therapy (valsartan, candesartan, or losartan) or control therapy not including ACEIs or ARBs [145]. Over a mean follow-up period of 36 months, ARB therapy was associated with a 49% reduction in the risk of cardiovascular death, nonfatal myocardial infarction (MI), stroke, coronary revascularization, and

**Table 24.1** Randomized studies evaluating the effect of antihypertensive agents on cardiovascular outcomes among patients on dialysis

| Author | Year | BP medication | Design | Follow-up | Patient characteristics | N | BP assessment | Baseline BP (mmHg) | Final BP (mmHg) | Main finding |
|---|---|---|---|---|---|---|---|---|---|---|
| Matsumoto et al. [160] | 2014 | Spironolactone vs. nothing | Open-label, randomized | 36 months | Oligoanuric HD patients | 157 vs. 152 | Predialysis BP | 152.8/77.8 vs. 148.8/76.2 | 152.7/77.9 vs. n/a | Spironolactone reduced the risk of death or hospitalization for CV event (HR, 0.38; 95% CI, 0.17–0.83) |
| Lin et al. [161] | 2015 | Spironolactone vs. placebo | Open-label RCT | 24 months | HD or PD patients without CHF | 125 vs. 128 | Predialysis BP | 144.7/76.9 vs. 141.9/77.4 | n/a n/a | Spironolactone reduced the risk of CV death, sudden death, or aborted cardiac arrest (HR, 0.42; 95% CI, 0.26–0.78) |
| Agarwal et al. [150] | 2014 | Lisinopril vs. atenolol | Open-label RCT | 12 months | Hypertensive HD patients with LVH | 100 vs. 100 | Interdialytic ABPM | 151.5/87.1 vs. 151.5/87.1 | 133.6/77.5 vs. 130.1/74.5 | Incidence of MI, stroke, CHF, and cardiovascular death was higher in the lisinopril group (IRR, 2.36; 95% CI, 1.36–4.23) |
| Iseki et al. [146] | 2013 | Olmesartan vs. nothing vs. placebo | Open-label RCT | 42 months | Hypertensive HD patients | 235 vs. 234 vs. 167 | Predialysis BP | 159/80 vs. 160/81 vs. n/a | 151.7/77.7 vs. 152.6/77.7 vs. unchanged | Occurrence of CV death, nonfatal MI, stroke, and coronary revascularization was identical in the olmesartan and control groups (HR, 1.00; 95% CI, 0.71–1.40) |
| Suzuki et al. [145] | 2008 | ARB vs. nothing | Open-label, randomized | 36 months | Hypertensive HD patients | 180 vs. 180 | Predialysis BP | 154/81 vs. 156/82 | 140/80 vs. 140/78 | ARB treatment reduced the occurrence of fatal and nonfatal CV events (HR, 0.51; 95% CI, 0.33–0.79) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Zannad et al. [143] | 2006 | Fosinopril vs. placebo | Double-blind RCT | 24 months | HD patients (not all hypertensive) with LVH | 196 vs. 201 | Predialysis BP | 146/77 vs. 145/77 | 139/76 vs. 143/74 | Incidence of fatal and nonfatal CV events was not different between the fosinopril and placebo groups (RR, 0.93; 95% CI, 0.68–1.26) |
| Takahashi et al. [144] | 2006 | Candesartan vs. nothing | Open-label, randomized | 36 months | HD patients without overt cardiovascular disease | 43 vs. 37 | Predialysis BP | 153/82 vs. 152/85 | 149/80 vs. 153/83 | Candesartan therapy improved CV event-free survival (OR, 0.23; 95% CI, 0.08–0.67) |
| Tepel et al. [157] | 2008 | Amlodipine vs. placebo | Double-blind RCT | 19 months | Hypertensive HD patients | 123 vs. 128 | Predialysis BP | 140/80 vs. 141/80 | 130/80 vs. 140/80 | Amlodipine reduced the risk of all-cause mortality and future CV event relative to placebo (HR, 0.53; 95% CI, 0.31–0.93) |
| Cice et al. [149] | 2003 | Carvedilol vs. placebo | Double-blind RCT for 12 months | 24 months | HD patients with dilated cardiomyopathy | 58 vs. 56 | Predialysis BP | 134/75 vs. 135/75 | 120/70 vs. 135/76 | Carvedilol reduced all-cause (HR, 0.51; 95% CI, 0.32–0.82) and CV mortality (HR, 0.32; 95% CI, 0.18–0.57) |

*ACEIs* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blocker, *BP* blood pressure, *ABPM* ambulatory BP monitoring, *CV* cardiovascular, *CHF* congestive heart failure, *CI* confidence intervals, *HD* hemodialysis, *HR* hazard ratio, *LVH* left ventricular hypertrophy, *PD* peritoneal dialysis, *RR* relative risk, *SCD* sudden cardiac death, *TIW* thrice in week, *n/a* not applicable

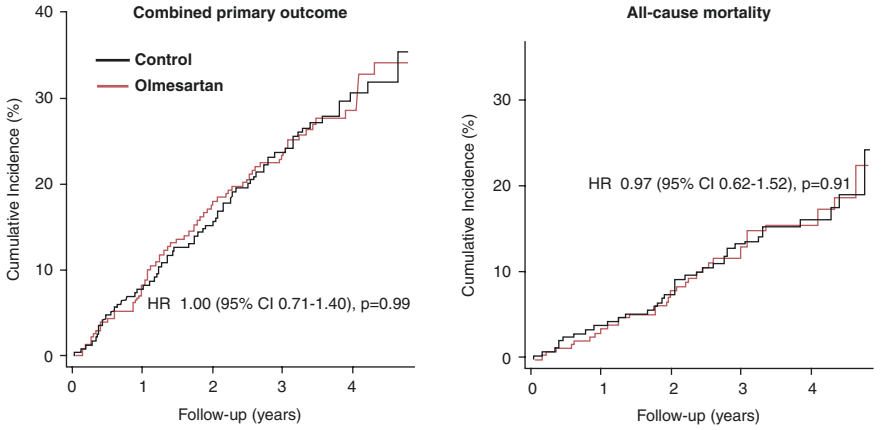



**Fig. 24.6** Effects of olmesartan vs. other antihypertensive treatments on primary outcome (death, nonfatal stroke, myocardial infarction, and coronary revascularization) and all-cause mortality in hemodialysis patients in the OCTOPUS trial (reprinted with permission from Iseki et al. [146])

hospitalized congestive heart failure (CHF) as compared with control therapy not including RAAS inhibitors (HR, 0.51; 95% CI, 0.33–0.79) [145]. In the subsequent Olmesartan Clinical Trial in Okinawan Patients Under Okinawa Dialysis Study (OCTOPUS) trial [146], 469 hypertensive hemodialysis patients were randomized to the ARB olmesartan (10–40 mg/day) or control therapy not including ACEIs or ARBs. Over a mean follow-up of 3.5 years, incidence of all-cause death, nonfatal stroke, MI, and coronary revascularization was similar in the olmesartan and control groups (HR, 1.00; 95% CI, 0.71–1.40); mortality was also not different (Fig. 24.6) [146]. A meta-analytical estimate of the risk reduction by ARBs in these trials (which included around 900 patients and 175 deaths) showed a nonsignificant ($P = 0.10$) 42% risk reduction [147]. Overall, a superiority of ACEIs and ARBs over other antihypertensive drugs seems unlikely in dialysis patients, and antihypertensive treatment per se and not the use of a RAAS blocker is rather the factor reducing cardiovascular risk. It should be also noted that there are important differences between ACEIs and ARBs in renal clearance and removal during dialysis [5]; most ARBs are not dialyzed during conventional dialysis and may be therefore preferred in these patients for BP reduction.

#### 24.5.2.2 β-Blockers

Sympathetic overactivity as measured by plasma norepinephrine is a powerful predictor of death and cardiovascular events in dialysis patients [148]. Susceptibility of dialysis patients to serious arrhythmias and sudden death along with the excessive activation of the sympathetic nervous system makes β-blockers an attractive therapeutic option toward cardiovascular protection in this population [139]. In the first clinical trial with hard cardiovascular outcomes using a β-blocker in hemodialysis, 114 patients with dilated cardiomyopathy were randomly assigned to carvedilol (titrated up to 25 mg twice daily) or placebo. Over a follow-up of 2 years, carvedilol

treatment improved LV systolic function and lowered by 56% the risk of all-cause hospitalization (HR, 0.44; 95% CI, 0.25–0.77) and by 49% the risk of all-cause death (HR, 0.51; 95% CI, 0.32–0.82) compared to placebo [149].

Additional support to the cardioprotective properties of β-blockade is provided by the Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril (HDPAL) trial [150], which performed a head-to-head comparison between the β-blocker atenolol and the ACEI lisinopril (both administered in a thrice-weekly regimen immediately postdialysis) in 200 hypertensive hemodialysis patients with echocardiographically documented LV hypertrophy (Table 24.1). This study was prematurely terminated for safety reasons due to significantly higher risk of cardiovascular events in the lisinopril group, although the number of events was generally not different from that recorded in registries of hemodialysis patients. The incidence of the combined outcome of MI, stroke, hospitalized CHF, and cardiovascular death was 2.29 times higher in lisinopril than in atenolol group [incidence rate ratio (IRR), 2.29; 95% CI, 1.07–5.21] [129]. LV mass index (the primary outcome) improved to a similar extent in the atenolol and lisinopril groups [150]. However, atenolol was shown to be superior to lisinopril in terms of its BP-lowering efficacy; although no significant differences in BP were noted between groups, lisinopril-treated patients had always numerically higher BP levels and required more aggressive volume management during dialysis and administration of higher number of antihypertensive drugs as add-on therapy to achieve the prespecified home BP target of 140/90 mmHg. In a secondary analysis of the HDPAL trial, atenolol was shown to be superior to lisinopril in improving aortic pulse wave velocity [87], which is a strong and independent cardiovascular risk predictor among dialysis patients [85]. This beneficial effect of atenolol on aortic stiffness was predominantly mediated through its potent BP-lowering efficacy.

The Beta-blocker to LOwer CArdiovascular Dialysis Events (BLOCADE) trial failed to advance our understanding on the cardioprotective role of β-blockade due to the low recruitment rate in the feasibility study that resulted in a small sample size [151]. The study aimed to enroll 150 patients; among 1443 patients screened, including 176 who were already on treatment with beta-blockers, only 354 were eligible, 91 consented, and 72 entered the 6-week active treatment run-in period. Of these, only 49 participants (68%; 95% CI, 57–79%) tolerated carvedilol therapy (6.25 mg twice daily) during the run-in and progressed to randomization [151]. Narrow inclusion criteria led to exclusion of high-risk patients, who were more likely to benefit from the cardioprotective actions of carvedilol.

Although actual data are scarce, some suggest vasodilating β-blockers (i.e., carvedilol) to be particularly useful in the setting of intradialysis hypertension, as they may favorably affect endothelial dysfunction, which is suggested as a major mechanistic pathway of intradialysis hypertension [152–154]. In an uncontrolled interventional study of 25 patients with intradialysis hypertension, Inrig et al. [155] showed that carvedilol treatment was associated with an improvement in endothelium-dependent flow-mediated vasodilatation; this effect was accompanied by reduced occurrence of intradialytic hypertensive episodes during follow-up and with a significant drop of 7 mmHg in 44-h interdialytic ambulatory systolic

BP. Again, it must be noted that there are differences in renal clearance and dialyzability between different β-blockers that need to be taken into account when prescribing these agents in hemodialysis patients [5].

#### 24.5.2.3 Calcium Channel Blockers

Calcium channel blockers (CCBs) can effectively lower BP, even in the volume-expanded state [156], and are often used as combination therapy for management of hypertension in dialysis patients. Tepel et al. [157] randomized 251 hypertensive hemodialysis patients to receive amlodipine (5–10 mg/day) or placebo for 30 months (Table 24.1). Amlodipine insignificantly improved survival as compared with placebo, but reduced by 47% the composite secondary end point of all-cause death, nonfatal stroke, MI, coronary revascularization, and angioplasty for peripheral vascular disease (HR, 0.53; 95% CI, 0.31–0.93) [157]. Other small studies suggested that dihydropyridine CCBs are equally effective with ACEIs or ARBs in reducing oxidative stress and regressing LV hypertrophy and carotid intima-media thickness [158]. Data on non-dihydropyridine CCB use in hemodialysis patients are scarce; using these agents should at least follow the recommendations for the general population. An important benefit of all CCBs is that they are practically not removed during standard hemodialysis and, thus, can be dosed once daily in these patients [5].

#### 24.5.2.4 Mineralocorticoid Receptor Antagonists

A cardioprotective action of mineralocorticoid receptor antagonist (MRA) therapy among dialysis patients is strongly supported by background evidence [159] and two recent trials (Table 24.1) [160, 161]. In the Dialysis Outcomes Heart Failure Aldactone Study (DOHAS), 309 oligoanuric hemodialysis patients were randomized to spironolactone (25 mg/day) or no add-on therapy for 3 years. Spironolactone reduced by 62% the risk of cardiovascular mortality or cardiovascular-related hospitalization (HR, 0.38; 95% CI, 0.17–0.83), with incidence of drug discontinuation due to serious hyperkalemia being 1.9% [160]. Another study randomized 253 patients without heart failure receiving hemodialysis or peritoneal dialysis to 2-year-long add-on therapy with spironolactone (25 mg/day) or placebo. Add-on MRA therapy reduced by 58% the occurrence of the composite primary end point of cardio-cerebrovascular mortality, aborted cardiac arrest, and sudden death (HR, 0.42; 95% CI, 0.26–0.78) [161]. The reduction in the risk of adverse clinical outcomes in these trials exceeded 50%, i.e., it was apparently superior to the effect of frequent in-center hemodialysis on the combined end point death and LVH progression [134] and largely unexpected in a population like the hemodialysis population that is notoriously less sensitive to interventions aimed at reducing death and cardiovascular events than other patient populations [162]. The safety profile of MRAs in the dialysis population was investigated in a recent study, in which 146 hemodialysis patients were randomly assigned to eplerenone (25–50 mg daily) or matching placebo for 13 weeks [163]. Eplerenone treatment significantly increased the incidence of hyperkalemia (defined as predialysis serum potassium >6.5 mmol/L) as compared with placebo (RR, 4.50; 95% CI, 1.0–20.2) [163], but permanent drug

discontinuation due to hyperkalemia or hypotension, which was the primary study end point, was no different between eplerenone and placebo groups [163]. Large, properly designed studies, like the ongoing ALCHEMIST [164] (ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial; NCT01848639), are needed to assess the safety and the effectiveness of mineralocorticoid receptor blockade in ESRD.

**Conclusion**

Hypertension in patients undergoing hemodialysis and peritoneal dialysis patients poses almost unique diagnostic, prognostic, and therapeutic problems. Evolution of studies using home or ambulatory BP monitoring is currently needed in order to better define the true burden of hypertension, to provide solid data on hypertension prevalence and prognostic associations, and to enable international organizations to propose objective thresholds for diagnosis and targets for treatment for these patients. As sodium and volume excess is the most important contributor to BP increase in the dialysis population, non-pharmacologic interventions targeting these factors are fundamental in this population and should precede pharmacological treatment. In patients whose BP remains unresponsive to the volume management strategies, the use of antihypertensive drugs is necessary. Among dialysis patents, BP lowering with the use of antihypertensive agents is associated with improvement in cardiovascular outcomes; the use of β-blockers followed by ACEIs and ARBs should be strongly considered, on the basis of evidence suggesting that these agents likely offer cardioprotection. Additional research efforts, mainly properly designed clinical trials, are warranted to identify the optimal non-pharmacologic and pharmacologic measures to treat hypertension and reduce cardiovascular disease in dialysis patients.

**Conflicts of Interest** None relevant to this work.

## References

1. Agarwal R, Flynn J, Pogue V et al (2014) Assessment and management of hypertension in patients on dialysis. J Am Soc Nephrol 25(8):1630–1646
2. Agarwal R (2010) Blood pressure and mortality among hemodialysis patients. Hypertension 55(3):762–768
3. Alborzi P, Patel N, Agarwal R (2007) Home blood pressures are of greater prognostic value than hemodialysis unit recordings. Clin J Am Soc Nephrol 2(6):1228–1234
4. Amar J, Vernier I, Rossignol E et al (2000) Nocturnal blood pressure and 24-hour pulse pressure are potent indicators of mortality in hemodialysis patients. Kidney Int 57(6):2485–2491
5. Levin NW, Kotanko P, Eckardt KU et al (2010) Blood pressure in chronic kidney disease stage 5D-report from a kidney disease: improving global outcomes controversies conference. Kidney Int 77(4):273–284
6. Zoccali C, Mallamaci F (2015) Hypertension. In: Daugirdas JT, Blake PG, Ing TS (eds) Handbook of dialysis, 5th edn. Wolters Kluwer, Philadelphia, pp 578–591
7. Agarwal R, Martinez-Castelao A, Wiecek A et al (2011) The lingering dilemma of arterial pressure in CKD: what do we know, where do we go? Kidney Int Suppl 1(1):17–20

8. Kidney Disease Outcomes Quality Initiative (K/DOQI) (2004) K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 43(5 Suppl 1):S1–290
9. Rahman M, Griffin V, Kumar A et al (2002) A comparison of standardized versus "usual" blood pressure measurements in hemodialysis patients. Am J Kidney Dis 39(6):1226–1230
10. Rohrscheib MR, Myers OB, Servilla KS et al (2008) Age-related blood pressure patterns and blood pressure variability among hemodialysis patients. Clin J Am Soc Nephrol 3(5): 1407–1414
11. Agarwal R (2009) Volume-associated ambulatory blood pressure patterns in hemodialysis patients. Hypertension 54(2):241–247
12. Inrig JK, Patel UD, Gillespie BS et al (2007) Relationship between interdialytic weight gain and blood pressure among prevalent hemodialysis patients. Am J Kidney Dis 50(1): 108–118.e4
13. Agarwal R, Peixoto AJ, Santos SF, Zoccali C (2006) Pre- and postdialysis blood pressures are imprecise estimates of interdialytic ambulatory blood pressure. Clin J Am Soc Nephrol 1(3):389–398
14. Zoccali C, Tripepi R, Torino C et al (2015) Moderator's view: ambulatory blood pressure monitoring and home blood pressure for the prognosis, diagnosis and treatment of hypertension in dialysis patients. Nephrol Dial Transplant 30(9):1443–1448
15. Sinha AD, Agarwal R (2009) Peridialytic, intradialytic, and interdialytic blood pressure measurement in hemodialysis patients. Am J Kidney Dis 54(5):788–791
16. Agarwal R, Metiku T, Tegegne GG et al (2008) Diagnosing hypertension by intradialytic blood pressure recordings. Clin J Am Soc Nephrol 3(5):1364–1372
17. Stergiou GS, Bliziotis IA (2011) Home blood pressure monitoring in the diagnosis and treatment of hypertension: a systematic review. Am J Hypertens 24(2):123–134
18. Parati G, Ochoa JE, Bilo G et al (2016) Hypertension in chronic kidney disease part 1: out-of-office blood pressure monitoring: methods, thresholds, and patterns. Hypertension 67(6):1093–1101
19. Agarwal R (2010) Managing hypertension using home blood pressure monitoring among haemodialysis patients—a call to action. Nephrol Dial Transplant 25(6):1766–1771
20. Agarwal R, Andersen MJ, Bishu K, Saha C (2006) Home blood pressure monitoring improves the diagnosis of hypertension in hemodialysis patients. Kidney Int 69(5):900–906
21. Agarwal R, Satyan S, Alborzi P et al (2009) Home blood pressure measurements for managing hypertension in hemodialysis patients. Am J Nephrol 30(2):126–134
22. Agarwal R, Light RP (2010) Median intradialytic blood pressure can track changes evoked by probing dry-weight. Clin J Am Soc Nephrol 5(5):897–904
23. Agarwal R, Brim NJ, Mahenthiran J et al (2006) Out-of-hemodialysis-unit blood pressure is a superior determinant of left ventricular hypertrophy. Hypertension 47(1):62–68
24. Moriya H, Ohtake T, Kobayashi S (2007) Aortic stiffness, left ventricular hypertrophy and weekly averaged blood pressure (WAB) in patients on haemodialysis. Nephrol Dial Transplant 22(4):1198–1204
25. Moriya H, Oka M, Maesato K, Mano T, Ikee R, Ohtake T, Kobayashi S (2008) Weekly averaged blood pressure is more important than a single-point blood pressure measurement in the risk stratification of dialysis patients. Clin J Am Soc Nephrol 3(2):416–422
26. da Silva GV, de Barros S, Abensur H et al (2009) Home blood pressure monitoring in blood pressure control among haemodialysis patients: an open randomized clinical trial. Nephrol Dial Transplant 24(12):3805–3811
27. Kauric-Klein Z, Artinian N (2007) Improving blood pressure control in hypertensive hemodialysis patients. CANNT J 17(4):24–28
28. Agarwal R (2015) Pro: ambulatory blood pressure should be used in all patients on hemodialysis. Nephrol Dial Transplant 30(9):1432–1437
29. Zoccali C, Benedetto FA, Tripepi G et al (1998) Nocturnal hypoxemia, night-day arterial pressure changes and left ventricular geometry in dialysis patients. Kidney Int 53(4):1078–1084

30. Tripepi G, Fagugli RM, Dattolo P et al (2005) Prognostic value of 24-hour ambulatory blood pressure monitoring and of night/day ratio in nondiabetic, cardiovascular events-free hemodialysis patients. Kidney Int 68(3):1294–1302
31. Agarwal R, Andersen MJ, Light RP (2008) Location not quantity of blood pressure measurements predicts mortality in hemodialysis patients. Am J Nephrol 28(2):210–217
32. Parati G, Ochoa JE, Bilo G et al (2016) Hypertension in chronic kidney disease part 2: role of ambulatory and home blood pressure monitoring for assessing alterations in blood pressure variability and blood pressure profiles. Hypertension 67(6):1102–1110
33. McManus RJ, Caulfield M, Williams B (2012) NICE hypertension guideline 2011: evidence based evolution. BMJ 344:e181
34. Piper MA, Evans CV, Burda BU et al (2015) Diagnostic and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: a systematic review for the U.S. Preventive Services Task Force blood pressure screening methods and consideration of rescreening intervals. Ann Intern Med 162(3):192–204
35. Georgianos PI, Sarafidis PA, Zoccali C (2015) Intradialysis hypertension in end-stage renal disease patients: clinical epidemiology, pathogenesis, and treatment. Hypertension 66(3): 456–463
36. Inrig JK (2010) Intradialytic hypertension: a less-recognized cardiovascular complication of hemodialysis. Am J Kidney Dis 55(3):580–589
37. Agarwal R, Light RP (2010) Intradialytic hypertension is a marker of volume excess. Nephrol Dial Transplant 25(10):3355–3361
38. Van Buren PN, Kim C, Toto R, Inrig JK (2011) Intradialytic hypertension and the association with interdialytic ambulatory blood pressure. Clin J Am Soc Nephrol 6(7):1684–1691
39. Agarwal R, Nissenson AR, Batlle D et al (2003) Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. Am J Med 115(4):291–297
40. Rahman M, Fu P, Sehgal AR, Smith MC (2000) Interdialytic weight gain, compliance with dialysis regimen, and age are independent predictors of blood pressure in hemodialysis patients. Am J Kidney Dis 35(2):257–265
41. Rocco MV, Yan G, Heyka RJ et al (2001) Risk factors for hypertension in chronic hemodialysis patients: baseline data from the HEMO study. Am J Nephrol 21(4):280–288
42. Salem MM (1995) Hypertension in the hemodialysis population: a survey of 649 patients. Am J Kidney Dis 26(3):461–468
43. Agarwal R (2011) Epidemiology of interdialytic ambulatory hypertension and the role of volume excess. Am J Nephrol 34(4):381–390
44. Sarafidis PA, Li S, Chen SC et al (2008) Hypertension awareness, treatment, and control in chronic kidney disease. Am J Med 121(4):332–340
45. Sarafidis PA, Sharpe CC, Wood E et al (2012) Prevalence, patterns of treatment, and control of hypertension in predialysis patients with chronic kidney disease. Nephron Clin Pract 120(3):c147–c155
46. Katzarski KS, Charra B, Luik AJ et al (1999) Fluid state and blood pressure control in patients treated with long and short haemodialysis. Nephrol Dial Transplant 14(2):369–375
47. Hypertension, by DOPPS country and cross-section. Available at: http://www.dopps.org/annualreport/html/MCOMHTN. Accessed 16 Jul 2016
48. Robinson B, Fuller D, Zinsser D et al (2011) The Dialysis Outcomes and Practice Patterns Study (DOPPS) Practice Monitor: rationale and methods for an initiative to monitor the new US bundled dialysis payment system. Am J Kidney Dis 57(6):822–831
49. Agarwal R, Bouldin JM, Light RP, Garg A (2011) Inferior vena cava diameter and left atrial diameter measure volume but not dry weight. Clin J Am Soc Nephrol 6(5):1066–1072
50. Port FK, Hulbert-Shearon TE, Wolfe RA et al (1999) Predialysis blood pressure and mortality risk in a national sample of maintenance hemodialysis patients. Am J Kidney Dis 33(3):507–517
51. Salem MM (1999) Hypertension in the haemodialysis population: any relationship to 2-years survival? Nephrol Dial Transplant 14(1):125–128

52. Zager PG, Nikolic J, Brown RH et al (1998) "U" curve association of blood pressure and mortality in hemodialysis patients. Medical Directors of Dialysis Clinic Inc. Kidney Int 54(2):561–569
53. Lacson E Jr, Lazarus JM (2007) The association between blood pressure and mortality in ESRD-not different from the general population? Semin Dial 20(6):510–517
54. Inrig JK, Patel UD, Toto RD, Szczech LA (2009) Association of blood pressure increases during hemodialysis with 2-year mortality in incident hemodialysis patients: a secondary analysis of the Dialysis Morbidity and Mortality Wave 2 Study. Am J Kidney Dis 54(5):881–890
55. Inrig JK, Patel UD, Toto RD, Reddan DN, Himmelfarb J, Lindsay RM, Stivelman J, Winchester JF, Szczech LA (2009) Decreased pulse pressure during hemodialysis is associated with improved 6-month outcomes. Kidney Int 76(10):1098–1107
56. Park J, Rhee CM, Sim JJ, Kim YL, Ricks J, Streja E, Vashistha T, Tolouian R, Kovesdy CP, Kalantar-Zadeh K (2013) A comparative effectiveness research study of the change in blood pressure during hemodialysis treatment and survival. Kidney Int 84(4):795–802
57. Cocchi R, Degli EE, Fabbri A et al (1999) Prevalence of hypertension in patients on peritoneal dialysis: results of an Italian multicentre study. Nephrol Dial Transplant 14(6):1536–1540
58. Atas N, Erten Y, Okyay GU et al (2014) Left ventricular hypertrophy and blood pressure control in automated and continuous ambulatory peritoneal dialysis patients. Ther Apher Dial 18(3):297–304
59. Cnossen TT, Konings CJ, Fagel WJ et al (2012) Fluid state and blood pressure control: no differences between APD and CAPD. ASAIO J 58(2):132–136
60. Enia G, Mallamaci F, Benedetto FA et al (2001) Long-term CAPD patients are volume expanded and display more severe left ventricular hypertrophy than haemodialysis patients. Nephrol Dial Transplant 16(7):1459–1464
61. Davies SJ (2015) What are the consequences of volume expansion in chronic dialysis patients? volume expansion in peritoneal dialysis patients. Semin Dial 28(3):239–242
62. Tonbul Z, Altintepe L, Sozlu C et al (2002) Ambulatory blood pressure monitoring in haemodialysis and continuous ambulatory peritoneal dialysis (CAPD) patients. J Hum Hypertens 16(8):585–589
63. Rodby RA, Vonesh EF, Korbet SM (1994) Blood pressures in hemodialysis and peritoneal dialysis using ambulatory blood pressure monitoring. Am J Kidney Dis 23(3):401–411
64. Hall JE (1991) The renin-angiotensin system: renal actions and blood pressure regulation. Compr Ther 17(5):8–17
65. Ritz E, Fliser D (1991) The kidney in congestive heart failure. Eur Heart J 12(Suppl C): 14–20
66. Machnik A, Neuhofer W, Jantsch J et al (2009) Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. Nat Med 15(5):545–552
67. Dahlmann A, Dorfelt K, Eicher F et al (2015) Magnetic resonance-determined sodium removal from tissue stores in hemodialysis patients. Kidney Int 87(2):434–441
68. Kelley K, Light RP, Agarwal R (2007) Trended cosinor change model for analyzing hemodynamic rhythm patterns in hemodialysis patients. Hypertension 50(1):143–150
69. Karpetas A, Sarafidis PA, Georgianos PI et al (2015) Ambulatory recording of wave reflections and arterial stiffness during intra- and interdialytic periods in patients treated with dialysis. Clin J Am Soc Nephrol 10(4):630–638
70. Koutroumbas G, Georgianos PI, Sarafidis PA et al (2015) Ambulatory aortic blood pressure, wave reflections and pulse wave velocity are elevated during the third in comparison to the second interdialytic day of the long interval in chronic haemodialysis patients. Nephrol Dial Transplant 30(12):2046–2053
71. Bazzato G, Coli U, Landini S et al (1984) Prevention of intra- and postdialytic hypertensive crises by captopril. Contrib Nephrol 41:292–298
72. Kornerup HJ, Schmitz O, Danielsen H et al (1984) Significance of the renin-angiotensin system for blood pressure regulation in end-stage renal disease. Contrib Nephrol 41:123–127

73. Henrich WL, Katz FH, Molinoff PB, Schrier RW (1977) Competitive effects of hypokalemia and volume depletion on plasma renin activity, aldosterone and catecholamine concentrations in hemodialysis patients. Kidney Int 12(4):279–284
74. Lifschitz MD, Kirschenbaum MA, Rosenblatt SG, Gibney R (1978) Effect of saralasin in hypertensive patients on chronic hemodialysis. Ann Intern Med 88(1):23–27
75. Agarwal R, Lewis R, Davis JL, Becker B (2001) Lisinopril therapy for hemodialysis hypertension: hemodynamic and endocrine responses. Am J Kidney Dis 38(6):1245–1250
76. Abd ElHafeez S, Tripepi G, Mallamaci F, Zoccali C (2015) Aldosterone, mortality, cardiovascular events and reverse epidemiology in end stage renal disease. Eur J Clin Invest 45(10):1077–1086
77. Converse RL Jr, Jacobsen TN, Toto RD et al (1992) Sympathetic overactivity in patients with chronic renal failure. N Engl J Med 327(27):1912–1918
78. Hausberg M, Kosch M, Harmelink P et al (2002) Sympathetic nerve activity in end-stage renal disease. Circulation 106(15):1974–1979
79. Ott C, Schmid A, Ditting T et al (2012) Renal denervation in a hypertensive patient with end-stage renal disease and small arteries: a direction for future research. J Clin Hypertens (Greenwich) 14(11):799–801
80. Papademetriou V, Doumas M, Anyfanti P et al (2014) Renal nerve ablation for hypertensive patients with chronic kidney disease. Curr Vasc Pharmacol 12(1):47–54
81. Schlaich MP, Bart B, Hering D et al (2013) Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with end-stage renal disease. Int J Cardiol 168(3):2214–2220
82. Desir GV, Wang L, Peixoto AJ (2012) Human renalase: a review of its biology, function, and implications for hypertension. J Am Soc Hypertens 6(6):417–426
83. Desir GV (2009) Regulation of blood pressure and cardiovascular function by renalase. Kidney Int 76(4):366–370
84. Malyszko J, Koc-Zorawska E, Malyszko JS et al (2012) Renalase, stroke, and hypertension in hemodialyzed patients. Ren Fail 34(6):727–731
85. Georgianos PI, Sarafidis PA, Lasaridis AN (2015) Arterial stiffness: a novel cardiovascular risk factor in kidney disease patients. Curr Vasc Pharmacol 13(2):229–238
86. Agarwal R, Light RP (2008) Arterial stiffness and interdialytic weight gain influence ambulatory blood pressure patterns in hemodialysis patients. Am J Physiol Renal Physiol 294(2):F303–F308
87. Georgianos PI, Agarwal R (2015) Aortic stiffness, ambulatory blood pressure, and predictors of response to antihypertensive therapy in hemodialysis. Am J Kidney Dis 66(2):305–312
88. Georgianos PI, Sarafidis PA, Haidich AB et al (2013) Diverse effects of interdialytic intervals on central wave augmentation in haemodialysis patients. Nephrol Dial Transplant 28(8):2160–2169
89. Townsend RR (2014) Pathogenesis of drug-resistant hypertension. Semin Nephrol 34(5):506–513
90. Vaziri ND, Ni Z, Wang XQ et al (1998) Downregulation of nitric oxide synthase in chronic renal insufficiency: role of excess PTH. Am J Physiol 274(4 Pt 2):F642–F649
91. Mallamaci F, Tripepi G, Maas R et al (2004) Analysis of the relationship between norepinephrine and asymmetric dimethyl arginine levels among patients with end-stage renal disease. J Am Soc Nephrol 15(2):435–441
92. Vallance P, Leone A, Calver A et al (1992) Accumulation of an endogenous inhibitor of nitric oxide synthesis in chronic renal failure. Lancet 339(8793):572–575
93. Raptis V, Kapoulas S, Grekas D (2013) Role of asymmetrical dimethylarginine in the progression of renal disease. Nephrology(Carlton) 18(1):11–21
94. Tada T, Kusano KF, Ogawa A et al (2007) The predictors of central and obstructive sleep apnoea in haemodialysis patients. Nephrol Dial Transplant 22(4):1190–1197
95. Ogna A, Forni OV, Mihalache A et al (2015) Obstructive sleep apnea severity and overnight body fluid shift before and after hemodialysis. Clin J Am Soc Nephrol 10(6):1002–1010

96. Abdel-Kader K, Dohar S, Shah N et al (2012) Resistant hypertension and obstructive sleep apnea in the setting of kidney disease. J Hypertens 30(5):960–966
97. Boyle SM, Berns JS (2014) Erythropoietin and resistant hypertension in CKD. Semin Nephrol 34(5):540–549
98. Carlini RG, Dusso AS, Obialo CI, Alvarez UM, Rothstein M (1993) Recombinant human erythropoietin (rHuEPO) increases endothelin-1 release by endothelial cells. Kidney Int 43(5):1010–1014
99. Kang DH, Yoon KI, Han DS (1998) Acute effects of recombinant human erythropoietin on plasma levels of proendothelin-1 and endothelin-1 in haemodialysis patients. Nephrol Dial Transplant 13(11):2877–2883
100. Eggena P, Willsey P, Jamgotchian N et al (1991) Influence of recombinant human erythropoietin on blood pressure and tissue renin-angiotensin systems. Am J Physiol 261(5 Pt 1):E642–E646
101. Hand MF, Haynes WG, Johnstone HA et al (1995) Erythropoietin enhances vascular responsiveness to norepinephrine in renal failure. Kidney Int 48(3):806–813
102. Kooman JP, van der Sande F, Leunissen K, Locatelli F (2003) Sodium balance in hemodialysis therapy. Semin Dial 16(5):351–355
103. Bibbins-Domingo K, Chertow GM, Coxson PG et al (2010) Projected effect of dietary salt reductions on future cardiovascular disease. N Engl J Med 362(7):590–599
104. Tomson CR (2001) Advising dialysis patients to restrict fluid intake without restricting sodium intake is not based on evidence and is a waste of time. Nephrol Dial Transplant 16(8):1538–1542
105. Santos SF, Peixoto AJ (2008) Revisiting the dialysate sodium prescription as a tool for better blood pressure and interdialytic weight gain management in hemodialysis patients. Clin J Am Soc Nephrol 3(2):522–530
106. Weiner DE, Brunelli SM, Hunt A et al (2014) Improving clinical outcomes among hemodialysis patients: a proposal for a "volume first" approach from the chief medical officers of US dialysis providers. Am J Kidney Dis 64(5):685–695
107. Cybulsky AV, Matni A, Hollomby DJ (1985) Effects of high sodium dialysate during maintenance hemodialysis. Nephron 41(1):57–61
108. Ogden DA (1978) A double blind crossover comparison of high and low sodium dialysis. Proc Clin Dial Transplant Forum 8:157–165
109. Munoz Mendoza J, Sun S, Chertow GM et al (2011) Dialysate sodium and sodium gradient in maintenance hemodialysis: a neglected sodium restriction approach? Nephrol Dial Transplant 26(4):1281–1287
110. Song JH, Lee SW, Suh CK, Kim MJ (2002) Time-averaged concentration of dialysate sodium relates with sodium load and interdialytic weight gain during sodium-profiling hemodialysis. Am J Kidney Dis 40(2):291–301
111. de Paula FM, Peixoto AJ, Pinto LV et al (2004) Clinical consequences of an individualized dialysate sodium prescription in hemodialysis patients. Kidney Int 66(3):1232–1238
112. Manlucu J, Gallo K, Heidenheim PA, Lindsay RM (2010) Lowering postdialysis plasma sodium (conductivity) to increase sodium removal in volume-expanded hemodialysis patients: a pilot study using a biofeedback software system. Am J Kidney Dis 56(1):69–76
113. Munoz MJ, Bayes LY, Sun S et al (2011) Effect of lowering dialysate sodium concentration on interdialytic weight gain and blood pressure in patients undergoing thrice-weekly in-center nocturnal hemodialysis: a quality improvement study. Am J Kidney Dis 58(6):956–963
114. Inrig JK, Molina C, D'Silva K et al (2015) Effect of low versus high dialysate sodium concentration on blood pressure and endothelial-derived vasoregulators during hemodialysis: a randomized crossover study. Am J Kidney Dis 65(3):464–473
115. Davies S, Carlsson O, Simonsen O et al (2009) The effects of low-sodium peritoneal dialysis fluids on blood pressure, thirst and volume status. Nephrol Dial Transplant 24(5):1609–1617
116. Paniagua R, Orihuela O, Ventura MD et al (2008) Echocardiographic, electrocardiographic and blood pressure changes induced by icodextrin solution in diabetic patients on peritoneal dialysis. Kidney Int Suppl 108:S125–S130

117. Agarwal R, Weir MR (2010) Dry-weight: a concept revisited in an effort to avoid medication-directed approaches for blood pressure control in hemodialysis patients. Clin J Am Soc Nephrol 5(7):1255–1260
118. Sinha AD, Agarwal R (2009) Can chronic volume overload be recognized and prevented in hemodialysis patients? The pitfalls of the clinical examination in assessing volume status. Semin Dial 22(5):480–482
119. Agarwal R, Andersen MJ, Pratt JH (2008) On the importance of pedal edema in hemodialysis patients. Clin J Am Soc Nephrol 3(1):153–158
120. Agarwal R, Alborzi P, Satyan S, Light RP (2009) Dry-weight reduction in hypertensive hemodialysis patients (DRIP): a randomized, controlled trial. Hypertension 53(3):500–507
121. Agarwal R, Bouldin JM, Light RP, Garg A (2011) Probing dry-weight improves left ventricular mass index. Am J Nephrol 33(4):373–380
122. Ozkahya M, Toz H, Qzerkan F et al (2002) Impact of volume control on left ventricular hypertrophy in dialysis patients. J Nephrol 15(6):655–660
123. Kayikcioglu M, Tumuklu M, Ozkahya M et al (2009) The benefit of salt restriction in the treatment of end-stage renal disease by haemodialysis. Nephrol Dial Transplant 24(3):956–962
124. Cirit M, Akcicek F, Terzioglu E et al (1995) 'Paradoxical' rise in blood pressure during ultrafiltration in dialysis patients. Nephrol Dial Transplant 10(8):1417–1420
125. Curatola G, Bolignano D, Rastelli S et al (2011) Ultrafiltration intensification in hemodialysis patients improves hypertension but increases AV fistula complications and cardiovascular events. J Nephrol 24(4):465–473
126. Movilli E, Gaggia P, Zubani R et al (2007) Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study. Nephrol Dial Transplant 22(12):3547–3552
127. Tattersall J, Martin-Malo A, Pedrini L et al (2007) EBPG guideline on dialysis strategies. Nephrol Dial Transplant 22(Suppl 2):ii5–21
128. Kalantar-Zadeh K, Unruh M, Zager PG et al (2014) Twice-weekly and incremental hemodialysis treatment for initiation of kidney replacement therapy. Am J Kidney Dis 64(2): 181–186
129. Kalantar-Zadeh K, Casino FG (2014) Let us give twice-weekly hemodialysis a chance: revisiting the taboo. Nephrol Dial Transplant 29(9):1618–1620
130. Foley RN, Gilbertson DT, Murray T, Collins AJ (2011) Long interdialytic interval and mortality among patients receiving hemodialysis. N Engl J Med 365(12):1099–1107
131. Tandon T, Sinha AD, Agarwal R (2013) Shorter delivered dialysis times associate with a higher and more difficult to treat blood pressure. Nephrol Dial Transplant 28(6):1562–1568
132. Georgianos PI, Sarafidis PA, Sinha AD, Agarwal R (2015) Adverse effects of conventional thrice-weekly hemodialysis: is it time to avoid 3-day interdialytic intervals? Am J Nephrol 41(4-5):400–408
133. Brunet P, Saingra Y, Leonetti F et al (1996) Tolerance of haemodialysis: a randomized cross-over trial of 5-h versus 4-h treatment time. Nephrol Dial Transplant 11(Suppl 8):46–51
134. Chertow GM, Levin NW, Beck GJ et al (2010) In-center hemodialysis six times per week versus three times per week. N Engl J Med 363(24):2287–2300
135. Ok E, Duman S, Asci G et al (2011) Comparison of 4- and 8-h dialysis sessions in thrice-weekly in-centre haemodialysis: a prospective, case-controlled study. Nephrol Dial Transplant 26(4):1287–1296
136. Chertow GM, Levin NW, Beck GJ et al (2016) Long-term effects of frequent in-center hemodialysis. J Am Soc Nephrol 27(6):1830–1836
137. Agarwal R, Sinha AD (2009) Cardiovascular protection with antihypertensive drugs in dialysis patients: systematic review and meta-analysis. Hypertension 53(5):860–866
138. Heerspink HJ, Ninomiya T, Zoungas S et al (2009) Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. Lancet 373(9668):1009–1015
139. Denker MG, Cohen DL (2015) Antihypertensive medications in end-stage renal disease. Semin Dial 28(4):330–336

140. Inrig JK (2010) Antihypertensive agents in hemodialysis patients: a current perspective. Semin Dial 23(3):290–297
141. Hayashi SY, Seeberger A, Lind B et al (2008) Acute effects of low and high intravenous doses of furosemide on myocardial function in anuric haemodialysis patients: a tissue Doppler study. Nephrol Dial Transplant 23(4):1355–1361
142. Lemes HP, Araujo S, Nascimento D et al (2011) Use of small doses of furosemide in chronic kidney disease patients with residual renal function undergoing hemodialysis. Clin Exp Nephrol 15(4):554–559
143. Zannad F, Kessler M, Lehert P et al (2006) Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. Kidney Int 70(7):1318–1324
144. Takahashi A, Takase H, Toriyama T et al (2006) Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis—a randomized study. Nephrol Dial Transplant 21(9):2507–2512
145. Suzuki H, Kanno Y, Sugahara S et al (2008) Effect of angiotensin receptor blockers on cardiovascular events in patients undergoing hemodialysis: an open-label randomized controlled trial. Am J Kidney Dis 52(3):501–506
146. Iseki K, Arima H, Kohagura K et al (2013) Effects of angiotensin receptor blockade (ARB) on mortality and cardiovascular outcomes in patients with long-term haemodialysis: a randomized controlled trial. Nephrol Dial Transplant 28(6):1579–1589
147. Zoccali C, Mallamaci F (2014) Pleiotropic effects of angiotensin II blockers in hemodialysis patients: myth or reality? Kidney Int 86(3):469–471
148. Zoccali C, Mallamaci F, Parlongo S et al (2002) Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. Circulation 105(11):1354–1359
149. Cice G, Ferrara L, D'Andrea A et al (2003) Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. J Am Coll Cardiol 41(9):1438–1444
150. Agarwal R, Sinha AD, Pappas MK et al (2014) Hypertension in hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial. Nephrol Dial Transplant 29(3):672–681
151. Roberts MA, Pilmore HL, Ierino FL et al (2016) The beta-blocker to lower cardiovascular dialysis events (BLOCADE) feasibility study: a randomized controlled trial. Am J Kidney Dis 67(6):902–911
152. El-Shafey EM, El-Nagar GF, Selim MF et al (2008) Is there a role for endothelin-1 in the hemodynamic changes during hemodialysis? Clin Exp Nephrol 12(5):370–375
153. Inrig JK, Van BP, Kim C et al (2011) Intradialytic hypertension and its association with endothelial cell dysfunction. Clin J Am Soc Nephrol 6(8):2016–2024
154. Raj DS, Vincent B, Simpson K et al (2002) Hemodynamic changes during hemodialysis: role of nitric oxide and endothelin. Kidney Int 61(2):697–704
155. Inrig JK, Van BP, Kim C et al (2012) Probing the mechanisms of intradialytic hypertension: a pilot study targeting endothelial cell dysfunction. Clin J Am Soc Nephrol 7(8):1300–1309
156. London GM, Marchais SJ, Guerin AP et al (1990) Salt and water retention and calcium blockade in uremia. Circulation 82(1):105–113
157. Tepel M, Hopfenmueller W, Scholze A et al (2008) Effect of amlodipine on cardiovascular events in hypertensive haemodialysis patients. Nephrol Dial Transplant 23(11):3605–3612
158. Aslam S, Santha T, Leone A, Wilcox C (2006) Effects of amlodipine and valsartan on oxidative stress and plasma methylarginines in end-stage renal disease patients on hemodialysis. Kidney Int 70(12):2109–2115
159. Pitt B, Rossignol P (2014) Mineralocorticoid receptor antagonists in patients with end-stage renal disease on chronic hemodialysis. J Am Coll Cardiol 63(6):537–538
160. Matsumoto Y, Mori Y, Kageyama S et al (2014) Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients. J Am Coll Cardiol 63(6):528–536

161. Lin C, Zhang Q, Zhang H, Lin A (2016) Long-term effects of low-dose spironolactone on chronic dialysis patients: a randomized placebo-controlled study. J Clin Hypertens (Greenwich) 18(2):121–128
162. Kramann R, Floege J, Ketteler M et al (2012) Medical options to fight mortality in end-stage renal disease: a review of the literature. Nephrol Dial Transplant 27(12):4298–4307
163. Walsh M, Manns B, Garg AX et al (2015) The safety of eplerenone in hemodialysis patients: a noninferiority randomized controlled trial. Clin J Am Soc Nephrol 10(9):1602–1608
164. Brest UH (2000–2016) ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST). In: ClinicalTrials.gov. National Library of Medicine (US), Bethesda, MD. Available from https://clinicaltrials.gov/show/NCT01848639: NCT01848639

# Renovascular Hypertension

# 25

Alexandre Persu and Patricia Van der Niepen

## 25.1 Pathophysiology of Renovascular Hypertension

Progressive atherosclerotic stenosis of the renal artery leads to hypoperfusion of the juxtaglomerular apparatus with release of renin and increased production of angiotensin II. The subsequent increases in sympathetic nerve activity and synthesis of intrarenal prostaglandin, aldosterone, and nitric oxide and the decrease in renal sodium excretion result in vasoconstriction and secondly in sodium and water retention, causing hypertension. Moreover, renal perfusion becomes volume and angiotensin II dependent, especially in bilateral RVD [1–3]. In the absence of renin increase or altered renin-angiotensin system modulation in patients with FMD compared to essential hypertensive patients, the applicability of this model to FMD-related renal artery stenosis has been recently questioned [4].

## 25.2 Atherosclerotic Renovascular Disease

### 25.2.1 Epidemiology

The prevalence of RVH is estimated at 5% of all hypertensive persons but varies depending on the screened cohort from <1% in mild to >50% in severe hypertension [5, 6]. In patients with extrarenal atherosclerosis, end-stage renal failure, and heart

A. Persu, M.D., Ph.D. (✉)
Cardiology Department, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, 10 avenue Hippocrate, 1200 Brussels, Belgium
e-mail: alexandre.persu@uclouvain.be

P. Van der Niepen, M.D., Ph.D.
Department of Nephrology and Hypertension, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium
e-mail: Patricia.VanderNiepen@uzbrussel.be



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_25

failure, the prevalence of ARAD is high and varies from 4 to18.4% in patients with proven coronary artery disease and from 12 to 45.5% in patients with peripheral artery disease or aortic disease [7]. The exact prevalence of atherosclerotic (A) RAS is unknown because the disease is often asymptomatic and few patients are screened unless they have symptoms or significant risk factors. Yet, among potential living kidney donors with normal BP and kidney function, renal artery narrowing or atherosclerosis, i.e., "incidental" RAS, can be identified in 5.3% by CT scan [8]. RVD, diagnosed with renal Doppler ultrasound (US) (>60% stenosis suggested by peak systolic velocity (PSV) >1.8 m/s in the main renal artery), was present in 6.8% of free-living, community-dwelling subjects above age 65 [9]. The prevalence of ARAD in autopsy series of patients died in hospital varies between 4.3 and 86% [6].

### 25.2.2 Clinical Presentation

Patients are often true treatment resistant, can present with recurrent ("flash") pulmonary edema, or suffer acute renal deterioration after BP lowering or administration of renin-angiotensin system blockers [5, 10].

The elevated BP due to RAD is responsible per se for an increased cardiovascular (CV) risk [11]. An increased rate of new CV events, including death, was observed in the 2 years after identification of new ARAS in patients aged >67 years in the United States. CV events were far more frequent than further loss of kidney function [12]. Progressive ARAS can indeed lead to ischemic nephropathy with progressive renal failure and occlusion with renal atrophy. However, it has been shown that renal outcomes in patients with ARAS are influenced by underlying hypertension and diabetes [6, 13]. The underlying mechanisms explaining why ARAD is a strong independent predictor of long-term mortality are not well understood, but excess neurohumoral activation (i.e., increased sympathetic nervous tone and stimulation of the renin-angiotensin-aldosterone axis) may be a major contributor to mortality in ARAD [6].

### 25.2.3 Diagnostic Evaluation

Not every patient with hypertension should be submitted to an extensive work-up for atherosclerotic RVH. The presence of an abdominal bruit, new onset hypertension or recent loss of BP control, a unilateral small kidney or a difference of at least 1.5 cm, grade 3 or 4 retinopathy, accelerated or malignant hypertension, unprovoked hypokalemia, increased serum creatinine after RAAS blockade or BP decline, absence of family history of hypertension, significant atherosclerotic disease in another vascular bed, elevated plasma renin activity, former or current cigarette smoking, flash pulmonary edema, proteinuria, older age, and true resistant hypertension are all clinical clues to RVH. Krijnen et al. proposed a "clinical prediction rule," derived from three small cohorts of patients with drug-resistant hypertension, based on patient's history (age, gender, presence of atherosclerotic

CV disease, onset of hypertension within 2 years, smoking), physical examination (BMI, abdominal bruit), and some laboratory values (serum creatinine and cholesterol). A nomogram provides the probability of RVH in patients with drug-resistant hypertension [14].

### 25.2.4 Screening and Diagnostic Tests

Screening for atherosclerotic RVH should be restricted to those patients with at least an intermediate risk for RVH.

Several tests, based on physiologic or anatomic or both parameters, have been evaluated to screen for RVH. Analyzing *plasma renin activity*, unstimulated or after stimulation by a captopril challenge test, is not very sensitive or specific. Determination of renin activity in the blood from renal veins compared to peripheral veins has been abandoned because of the invasive nature of the procedure.

*Renal scintigraphy*, using $^{99}$Tc-DTPA, $^{131}$I-hippurate, or $^{99}$Tc-MAG3, with and without captopril can be used but is no longer recommended by the American College of Cardiology/American Heart Association as a screening test for RVH. In 2003, the Society of Nuclear Medicine published updated interpretation criteria [15]. The most specific diagnostic criterion for RVH is an ACEI-induced change in the renogram. In patients with normal or minimally reduced renal function (creatinine <1.7 mg/dL) and in azotemic patients, ACEI renography has a sensitivity and specificity of about 90% and 80%, respectively, for diagnosis of RVH. Moreover, ACEI-induced renographic findings of RVH may indicate a high probability of hypertension cure or improvement after revascularization [16]. However, the latter has not been shown in the DRASTIC trial [17]. Furthermore, sensitivity and specificity of ACEI renography are affected by several factors that contribute to confusion in the literature, e.g., use of different isotopes, different clinical characteristics (azotemic and non-azotemic patients), as well as different antihypertensive treatment [16].

*Duplex ultrasonography* not only identifies renal arteries anatomically by using B-mode US but also provides hemodynamic information by using Doppler flow studies. The Doppler US criteria of RAS can be divided into two groups based on direct findings obtained at the level of the stenosis (proximal criteria: peak systolic velocity, PSV, and renal aortic ratio) or on flow changes observed in the renal vasculature distal to the site of stenosis (distal criteria: resistance index, RI, and acceleration time) (Table 25.1). The RI, determined from segmental arterial flow characteristics, reflects the status of the flow in the renal circulation beyond the main renal arteries. An elevated RI may reflect intrinsic parenchymal or small vessel disease. However, reliance upon RI as a predictive parameter for ARAS management remains controversial. Radermacher et al. reported that patients with RI >0.8 before angioplasty had less BP improvement and worse renal outcomes than those with RI <0.8 [19]. In contrast, Zeller et al. reported similar BP and renal outcomes for patients with RI >0.8 and those with RI <0.8 [20]. Finally, Bruno et al. reported that a RI within the contralateral kidney, and using a cut point of

**Table 25.1** Doppler ultrasound criteria for the classification of RA stenosis by color Doppler US

| Proximal criteria | Peak systolic velocity (cm/s) | Renal aortic ratio (renal PSV/aortic PSV) |
|---|---|---|
| Normal RA | <180 | <3.5 |
| RA diameter reduction <60% | <180 | <3.5 |
| RA diameter reduction ≥60% | >180 | ≥3.5 |
| Occlusion | No signal | Indeterminable |
| Distal criteria | Resistance index | Acceleration time (m/s) |
| RA diameter reduction ≥60% | Side-to-side differences in RI: >0.05 | >70 |

Adapted from Granata et al. [18]
*PSV* peak systolic velocity, *RA* renal artery, *RI* resistance index

0.73, was the best single predictor of functional outcome (recovery of estimated glomerular filtration rate (eGFR)). No US parameter predicted the response of BP [21]. In a hemodynamically significant stenosis, a "tardus parvus" wave can be observed, as the systolic acceleration of the waveform is slow and the systolic peak is of low height [18, 22].

A meta-analysis showed duplex US had 85% sensitivity and 92% specificity for detection of RAS. PSV had the highest performance characteristics, and additional measurements did not increase accuracy. Operator dependency and sometimes limited quality images because of patient characteristics are responsible for large variations in sensitivity (0–98%) and specificity (73–100%) [23].

Contrast-enhanced *magnetic resonance angiography* (*MRA*) provides good anatomical information with diagnostic sensitivity of 90% and specificity of 94% [24]. Limitations of MRA include a tendency to overestimate moderate stenosis and a reduced accuracy in small and distal arteries. In patients with CKD stage 3b or more, gadolinium has to be avoided because of the risk of nephrogenic fibrosing dermopathy; Dotarem instead can be used. New techniques such as blood-oxygen level-dependent MRI (BOLD-MRI) can identify critically ischemic kidneys and can predict change in renal function post-revascularization [25].

*Computed tomographic angiography* (*CTA*) has also good sensitivity of 84% and specificity of 91% [24]. A major limitation is the volume of intravenous contrast and the potential nephrotoxic risk. In contrast with MRA, obfuscation of signal by indwelling stents is not a concern. CTA is cost-effective in patients for whom there is low suspicion of RAS [26].

A meta-analysis showed CTA and gadolinium-enhanced MRA gave more accurate diagnosis than US or captopril scintigraphy [27].

The gold standard investigation remains catheter digital subtraction angiography (DSA). It can provide not only accurate anatomical and some functional information but also permits to intervene during the same examination. However, this test is invasive and carries the potential risk of access site complications, embolic events, and contrast-induced nephropathy [28]. Initial diagnostic testing by DSA may nevertheless be considered in those individuals with a high risk for RVH [29].

Figure 25.1 summarizes the diagnostic algorithm for renovascular hypertension.

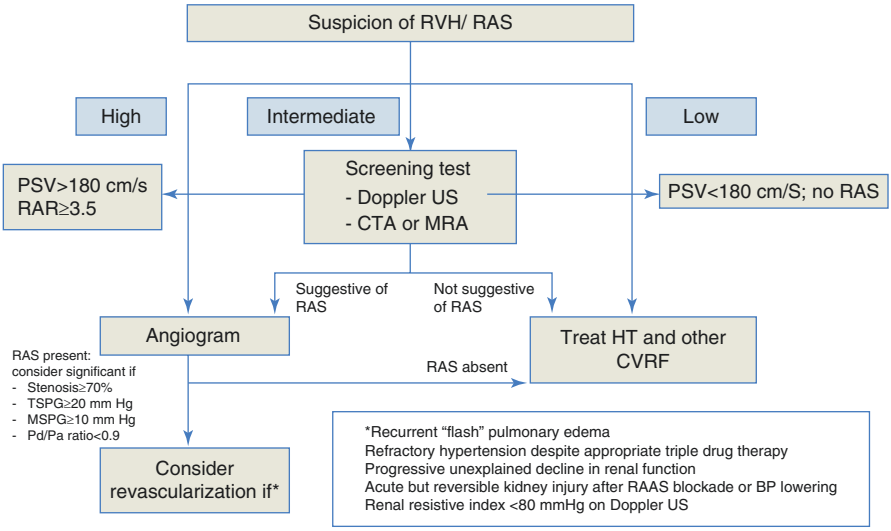



**Fig. 25.1** Diagnostic algorithm for renovascular hypertension. *BP* blood pressure, *CTA* computed tomographic angiography, *CVRF* cardiovascular risk factors, *MRA* magnetic resonance angiography, *RAAS* renin-angiotensin aldosterone system, *RAS* renal artery stenosis, *RVH* renovascular hypertension, *US* ultrasound

**Table 25.2** Possible indications and contraindications for revascularization

| |
|---|
| *Favorable response after revascularization* |
| Recurrent "flash" pulmonary edema |
| Refractory hypertension despite appropriate triple drug therapy |
| Progressive unexplained decline in renal function |
| Acute but reversible kidney injury after renin-angiotensin system blockade or blood pressure lowering |
| Renal resistive index <80 mmHg on Doppler ultrasound |
| *Unfavorable response after revascularization* |
| Normalized blood pressure with less than three antihypertensive drugs |
| Unilateral or bilateral small kidneys (<8 cm length) |
| Renal resistive index ≥80 mmHg on Doppler ultrasound |
| Long-standing hypertension (>10 years) |
| Renal artery stenosis <70% |

Adapted from Elliott [5]

### 25.2.5 Therapy

Despite decades of expertise in treating RAS, uncertainty still exists whether revascularization is warranted. Table 25.2 lists the most widely used potential indications and contraindications that can help in decision-making [30]. See also fig. 25.2 representing a clinical casus of an older patient with acute deterioration of kidney function due to ARAS who benefited from PTAS.

#### 25.2.5.1 Medical Management

Optimal medical therapy is mandatory in these high-risk patients to reduce CV risk. Besides BP lowering, control of other atherosclerotic CV risk factors is required. Maximal medical therapy, including low-dose aspirin, statins, and glycemic control, together with smoking cessation, is recommended [30].

A major concern about intensive BP lowering with or without RAAS blockers is the risk of acute kidney injury. A maximal increase in serum creatinine of 30% is allowed; discontinuing RAAS blockade or returning to a higher BP will reverse serum creatinine to baseline values [31]. Acute renal function degradation following RAAS blockade can be an indication for revascularization [5].

In an observational study, the use of ACEIs was associated with improved survival and a reduced risk of increasing serum creatinine in both revascularized and medically treated patients [32]. This observation emphasizes the need for RAAS blockers in the treatment of high-risk patients. However, the prevalent use of RAAS blockade prior to randomization in the CORAL trial was only 49% [33].

A population-based cohort study in 4040 patients >65 years with RVD suggests that statins are associated with improved prognosis as well [34].

#### 25.2.5.2 Angioplasty With or Without Stenting

Renal artery angioplasty alone was first performed by Gruntzig in 1978 [35].

*Angioplasty without stenting* is no longer preferred for atherosclerotic RAS due to high rate of technical failure, restenosis, and failure to lower BP, documented in observational studies and small RCTs. An even poorer outcome is observed in case of ostial stenosis, multiple and branch lesions. There is also little change in renal function after angioplasty [36]. However, large and randomized trials are lacking.

*Angioplasty with stenting* reduces the risk of restenosis as well as local dissection, prevents elastic recoil eventually responsible for acute restenosis and thrombosis, and can reduce pressure gradients across lesions after angioplasty.

In a multicenter registry including 1058 patients, stent revascularization of RAS, performed for poorly controlled hypertension, preservation of renal function, and/or congestive heart failure, was overall successful. At 4-year follow-up, BP had significantly decreased despite of a decrease in the number of antihypertensive medications, as well as serum creatinine. The cumulative probability of survival was 74% ± 3% at 4 years and was adversely affected by renal dysfunction despite adequate revascularization [37]. Similar results have been obtained in subsequent but smaller studies. In a retrospective analysis of patients treated for RVH, those who had a baseline eGFR of >40 mL/min/1.73 $m^2$ demonstrated a better response to RA stenting at each follow-up interval, with a significant difference at 2–4 years, compared with patients with a lower eGFR [38]. Another retrospective study in patients with chronic kidney disease (CKD) (creatinine clearance <50 mL/min) and RVD suggested that the rate of renal dysfunction progression before angioplasty with or without stenting is an independent and strong predictor of improvement in renal function after revascularization [39].

Restenosis rates vary between 10 and 50%, depending on location and severity of stenosis and on length of follow-up. Studies have suggested that secondary

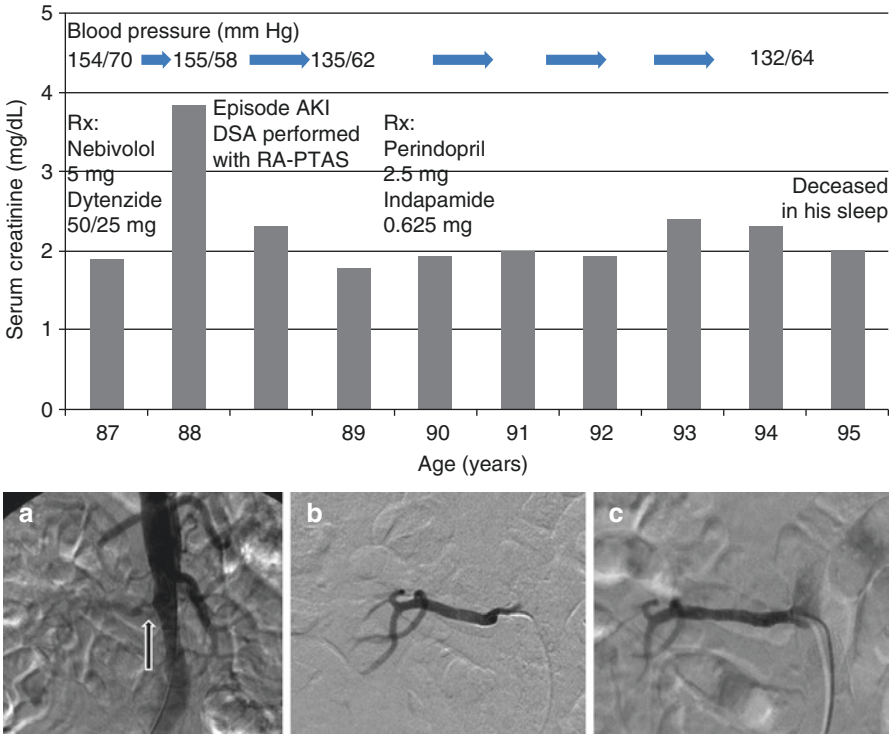



**Fig. 25.2** Serum creatinine, blood pressure, and medications over an 8-year period in an elderly patient with unilateral renovascular disease. This elderly atherosclerotic patient developed an acute rise in serum creatinine. Doppler US showed a smaller right kidney (10.1 cm) than the left kidney (11.2 cm) without hydronephrosis. Because of a high suspicion of renal artery stenosis, a DSA was performed, immediately followed by angioplasty and stenting. A marked decrease in serum creatinine was observed and remained stable till his death. An ACEI was started and BP was well controlled. **a** shows the ostial stenosis; **b** and **c** show the renal artery during and after angioplasty with stenting. *ACEI* angiotensin-converting enzyme inhibitor, *AKI* acute kidney injury, *BP* blood pressure, *DSA* digital subtraction angiography, *RA-PTAS* renal artery percutaneous transluminal angioplasty with stenting, *Rx* medical therapy, *US* ultrasound

interventions for recurrent RAS have outcomes that are comparable with those for primary interventions, whereas others have reported worse outcomes. In a retrospective analysis of 57 patients undergoing 65 secondary interventions for recurrent RAS, it was shown that these patients had outcomes (BP and renal function) comparable with 180 patients for 216 primary interventions. These data suggest that repeated endovascular procedures for RAS can be undertaken with similar expectations for clinical improvement [40]. Early renal artery PSV, within 1 week after renal artery percutaneous angioplasty and stenting (RA-PTAS), predicted renal artery restenosis and lower post-procedure renal function [41].

Statin use has been associated with decreased restenosis in 112 patients after primary RA-PTAS, whereby restenosis rates were 65% less likely with

pre-angioplasty statin use, as well as after secondary renal interventions in 51 patients [42, 43]. These findings support the routine use of statins in patients undergoing RA-PTAS.

One important concern of RA-PTAS is the risk of cholesterol embolization. According to the results of recent RCTs, acute atheroembolic renal disease, associated with clinical evident bad prognosis, is present in 0–2.2% of cases [44]. The majority of atheroembolic disease is subclinical and perhaps responsible for the frequently observed decline in kidney function, despite successful revascularization. Therefore, embolic devices have been developed. The frequency of atherosclerotic debris recovered in protection devices is >50% [45]. However, in a RCT of 100 patients undergoing RA-PTAS, renal artery stenting alone; stenting with Angioguard, an embolic protection device; and stenting with abciximab, a glycoprotein IIb/IIIa inhibitor, were associated with similar declines in GFR at a 1-month follow-up, whereas combination therapy with embolic protection and abciximab was better than no treatment or either treatment alone [46].

Several *randomized clinical trials comparing angioplasty with and/or without stenting* versus *medical treatment* have been performed. However, their interpretation is often complicated by various confounders, i.e., crossovers from medical to interventional arms, role of comorbid disease, hypertension vintage, proportion of patients with renal insufficiency or bilateral RAS, and different definitions of drug-resistant hypertension. Other limitations of these studies are related to patient selection (exclusion of patients with severe hypertension and progressive renal function decline, nonstandardized therapy for hypertension and dyslipidemia, nonstandardized BP measurement) or outcome (variable definitions of BP goals, variable measurements of kidney function, short duration of follow-up) [47]. The main results from these trials are summarized in Table 25.3.

The EMMA (Essai Multicentrique Medicaments vs. Angioplastie) study, the SNRASCG (Scottish and Newcastle Renal Artery Stenosis Collaborative Group) trial, and the DRASTIC (Dutch Renal Artery Stenosis Intervention Cooperative) study have compared angioplasty without stenting with medical therapy [17, 51, 52].

In the EMMA study, 49 of 76 eligible hypertensive patients with unilateral ARAS of ≥75% (or ≥60% with positive screening test) were randomized (26 patients were medically treated; 23 patients had angioplasty, of whom two had stents). The primary endpoint was ambulatory BP at 6 months or at study termination. Angioplasty reduced the number of antihypertensive drugs but was associated with more complications (one patient had renal artery dissection with segmental renal infarction, five had hematomas, and three developed restenosis, requiring re-intervention) than previously reported [51].

In the SNRASCG study, 55 of 135 eligible hypertensive patients treated with at least two antihypertensive drugs and with ≥50% RAS were randomized and stratified by unilateral (n, 27) or bilateral disease. The primary endpoints were the changes in BP and serum creatinine at baseline and at 6 months. A modest improvement in BP was seen with angioplasty in those with bilateral disease, again at the expense of a higher complication rate. No significant differences in serum creatinine were observed [52].

**Table 25.3** Prospective, randomized, clinical trials of balloon angioplasty, with and without stenting, versus medical therapy in atherosclerotic renal artery stenosis

| Study/author | Methods | Inclusion criteria | Primary and secondary endpoints | Participants | Results |
|---|---|---|---|---|---|
| *Surgery versus medical therapy* | | | | | |
| Uzzo et al. [48] | Single-center RCT<br>No blinding of intervention<br>No standardized medical treatment<br>FU: 74 months | BL RAS >75% or UL RAS >75% with azotemia (serum creatinine >1.5 and ≤4 mg/dL) | Poorly controlled hypertension, renal events, CV events, mortality | 52 patients | No significant difference in mortality or incidence of renal and CV events |
| *Surgery versus PTA* | | | | | |
| Weibull et al. [49] | Single-center RCT<br>No blinding of intervention<br>No standardized medical treatment<br>FU: 2 years | UL RAS (diameter stenosis ≤2 mm and renal vein ratio ≥1.5), untreated BP ≥160/100 mmHg, serum creatinine <3.39 mg/dL | Technical success, primary and secondary patency, effect on BP and renal function | 58 patients<br>≤70 years (mean age 57 years)<br>41% women<br>0% BL RAS<br>Baseline BP: 195/110 mmHg<br>>3 drugs: 81% | No significant difference in restenosis rate, BP, or renal function<br>Significant decrease in SBP and DBP in both groups<br>Stabilization of renal function |
| *Surgery versus PTA + stenting* | | | | | |
| RAOOD Balzer et al. [50] | Single-center RCT*<br>No blinding of intervention<br>No standardized medical treatment<br>FU: 4 years | UL or BL ostial AS-RAS >70% | Technical success, primary and secondary patency, effect on BP and renal function | 50 patients<br>Mean age, 64 years (range 44–84 years)<br>37% women<br>57% BL RAS<br>Baseline BP: 170/88 mmHg<br>Baseline N° drugs: 3.1 | No significant difference in mortality, restenosis rate, BP, or renal function<br>Significant decrease in SBP and DBP in both groups<br>Stabilization of renal function<br>*Final decision to perform revascularization was left to the radiologist or vascular surgeon<br>Six renal arteries were treated by PTRA only |

(continued)

**Table 25.3** (continued)

| Study/author | Methods | Inclusion criteria | Primary and secondary endpoints | Participants | Results |
|---|---|---|---|---|---|
| *PTA versus medical therapy* | | | | | |
| EMMA<br>Plouin et al. [51] | Multicenter RCT<br>No blinding of intervention<br>FU: 6 months<br>Standardized medical treatment | UL RAS ≥75% or ≥60% with positive lateralization test[a], DBP >95 mmHg or receiving antihypertensive treatment<br>CrCl >50 mL/min<br>Exclusion: malignant HTN | Mean 24 h ABP<br>Number and DDD of antihypertensive drugs, creatinine clearance<br>Rate of occluded arteries<br>Complications | 49 patients<br><75 years (mean age 59 years)<br>26% women<br>0% BL RAS<br>Baseline BP: 150/90 mmHg<br>Baseline N° drugs: ? | No significant difference in ambulatory BP<br>PTA: fewer antihypertensive drugs (1.0 vs. 1.78, $p$ <0.01), higher complication rate<br>27% crossover<br>8.7% stenting<br>Important exclusion criteria:<br>Malignant HT<br>Acute pulmonary edema<br>DBP >109 mmHg |
| SNRASCG<br>Webster et al. [52] | Multicenter RCT<br>No blinding of intervention<br>Standardized medical treatment<br>FU: 6 months | UL or BL RAS ≥50% stenosis, DBP ≥95 mmHg on ≥2 antihypertensive drugs<br>Serum creatinine <5.65 mg/dL | Office BP<br>Serum creatinine<br>Number antihypertensive drugs<br>Complications | 55 patients<br>40–75 years (mean age 61 years)<br>42% women<br>50.9% BL RAS<br>Baseline BP: 178/94 mmHg<br>Baseline N° drugs: 2.6 | PTA: significant BP reduction only if BL RAS; no significant difference in CV events or renal function<br>20% participants assigned to PTA had a surgery |
| DRASTIC<br>Van Jaarsveld et al. [17] | Multicenter RCT<br>No blinding of intervention<br>FU: 12 months | UL or BL RAS ≥50% stenosis, DBP ≥95 mmHg on ≥2 antihypertensive drugs or >0.2 mg/dL increase in serum creatinine with ACEI, serum creatinine ≤2.3 mg/dL (kidney length ≥8 cm) | Mean office BP<br>Number and DDD of antihypertensive drugs<br>Serum creatinine<br>Restenosis complications | 106 patients<br>18–75 years (mean age 60 years)<br>39% women<br>22.6% BL RAS<br>Baseline BP: 179/104 mmHg<br>Baseline N° drugs: 2.0 | No significant difference in systolic and diastolic BP<br>PTA: fewer antihypertensive drugs (1.9 vs. 2.4, $p$ <0.01)<br>44% participants assigned to medical therapy underwent revascularization at 3 months if DBP >95 mmHg despite ≥3 antihypertensive drugs<br>Only 3.6% stenting |

| | | | | | |
|---|---|---|---|---|---|
| *PTA versus PTA with stenting* | | | | | |
| Van de Ven et al. (1999) [53] | Single-center RCT<br>FU: 6 months | UL or BL ostial RAS >50% stenosis + positive scintigraphy or increase in serum creatinine ≥20% on ACEI | Restenosis | 84 patients | PTA with stenting: higher success and lower restenosis rates. No difference in systolic and diastolic BP or renal function |
| *PTA with stenting versus medical therapy* | | | | | |
| STAR<br>Bax et al. [54] | Multicenter RCT<br>No blinding of intervention<br>FU: 24 months | Ostial UL or BL AS-RAS ≥50% and C and G eCrCl <80 mL/min/1.7m$^2$ but ≥15 mL/min (kidney length ≥8 cm) | Worsening of renal function (>20% decline in eCrCl with C and G formula)<br>Office BP<br>Incidence of refractory or malignant HT<br>Pulmonary oedema<br>CV morbidity, CV mortality, total mortality | 140 patients<br>Mean age 66.5 years<br>55% women<br>48% BL RAS<br>Baseline BP: 162/82 mmHg<br>Baseline N° drugs: 2.9 | No significant difference in renal function, BP, CV mortality and morbidity<br>28% participants allocated to PTA did not undergo revascularization, mainly due to minimal stenosis<br>1.3% crossover<br>Important exclusion criteria:<br>Malignant HT |
| ASTRAL<br>Wheatley et al. [55] | Multicenter RCT<br>No blinding of intervention<br>Median FU: 34 months<br>Medical treatment was not standardized<br>Nonstandard imaging<br>42% <70%<br>58% ≥70% | Uncontrolled/refractory hypertension or unexplained renal dysfunction with UL or BL AS-RAS<br>Physician uncertain of clinical benefit | Renal outcome (reciprocal of serum creatinine)<br>Office BP<br>Time to renal and major CV events and mortality<br>Complications | 806 patients<br>42–88 years (mean age 70.5 years)<br>37% women<br>53.5% BL RAS<br>Baseline BP: 150/76 mmHg<br>Baseline N° drugs: 2.8 | No significant difference in renal function, BP, CV events and mortality<br>17% participants, allocated to PTA, did not undergo revascularization<br>6% crossover<br>Important exclusion criteria:<br>Need of surgery or high revascularization probability in 6 months |

(continued)

**Table 25.3** (continued)

| Study/author | Methods | Inclusion criteria | Primary and secondary endpoints | Participants | Results |
|---|---|---|---|---|---|
| CORAL<br>Cooper et al. [56] | Multicenter RCT<br>No blinding of intervention<br>Median FU: 43 months<br>Standardized medical treatment | UL or BL AS-RAS >80% or >60% with >2 mmHg systolic pressure gradient and SBP >155 mmHg with ≥2 antihypertensive drugs and/or eGFR <60 mL/min/1.73 $m^2$ (MDRD)<br>Kidney length >7 cm, serum creatinine ≤4 mg/dL | Composite of adverse fatal and nonfatal CV and renal events<br>Individual components of PEP<br>All-cause mortality<br>SBP<br>Restenosis<br>Renal resistance index<br>QOL<br>Cost-effectiveness | 947 patients<br>≥18 years (mean age 69 years)<br>50% women<br>20% BL RAS<br>Baseline BP: 150/− mmHg<br>Baseline N° drugs: 2.1 | No significant difference in primary composite endpoint, any of individual components of PEP, or all-cause mortality<br>Almost 17% of participants either withdrew or were lost to FU<br>5.4% participants, allocated to PTA, did not undergo revascularization<br>4% participants allocated to medical therapy crossed over<br>Possibly underpowered (1080 participants were required)<br>Important exclusion criteria:<br>DBP ≥120 mmHg and/or SBP ≥200 mmHg<br>Heart failure |
| *PTA with stenting versus medical therapy* (not fully published) | | | | | |
| NITER<br>Scarpioni et al. (2009) [57] | RCT<br>FU: 43 months | UL or BL AS-RAS ≥70%; serum creatinine ≤3 mg/dL and/or eGFR ≥30 mL/min/1.73 $m^2$ (MDRD); kidney length ≥8 cm;<br>BP ≤ 150/90 mmHg with <4 antihypertensive drugs | Death<br>Need for RRT<br>Reduction by 20% in eGFR<br>BP<br>Number antihypertensive drugs<br>Complications | 52 patients<br>45–80 years<br>Mean age 72 years<br>40% women<br>51.5% BL RAS<br>Baseline BP: 149/79 mmHg<br>Baseline N° drugs: 3.3 | Important exclusion criteria:<br>Heart failure |

| | | | | | |
|---|---|---|---|---|---|
| RADAR<br>Zeller et al. (2013) [58] | Multicenter RCT<br>FU 32 months | UL or BL AS-RAS<br>eGFR >10 mL/min/1.73 $m^2$ (MDRD)<br>Hypertension<br>Kidney length ≥7 cm | Change in eGFR after 12 months | 67 patients<br>≥18 years (mean age 67 years)<br>33% women | No significant difference in renal outcome<br>Study was prematurely terminated (reason not mentioned) |
| *Ongoing trials: PTA with stenting and standardized optimized medical treatment versus standardized optimized medical treatment* | | | | | |
| RAVE<br>Tobe et al. [59] | Single-center RCT (pilot)<br>Started 2007 | RAS and indication for revascularization* | Composite endpoint<br>Death or dialysis or doubling of serum creatinine<br>CV disease<br>BP<br>Antihypertensive drugs | 20 patients<br>Age ≥55 years | *Stenting is performed<br>At the discretion of the angiographer |
| METRAS<br>Rossi et al. [60] | Multicenter RCT<br>No blinding of intervention<br>FU: 60 months planned<br>Started 2012 | AS-RAS >70% and resistance index (RI) <0.55, and HTN | Change in eGFR<br>BP<br>Need for RRT<br>CV events<br>Quality of life | Estimated enrollment<br>N°: 120<br>Age: >18 years | |
| ANDORRA<br>Azizi et al. (2015) [61] | Multicenter RCT<br>FU: 12 months<br>Started Sept. 2015 | Resistant hypertension (daytime SBP ≥135 or DBP ≥85 mmHg) on ≥3 antihypertensive drugs and UL or BL AS-RAS ≥60%; kidney length ≥7 cm; eGFR ≥20 mL/min | Mean change in diurnal systolic BP (24 h ABPM) | Estimated enrollment<br>N°: 140<br>Age: 40–80 years | |

*AS-RAS* atherosclerotic renal artery stenosis, *BL* bilateral, *BP* blood pressure, *CrCl* creatinine clearance, *C and G*, Cockroft and Gault, *CV* cardiovascular, *DBP* diastolic BP, *DDD* defined daily doses, *eGFR* estimated glomerular filtration rate, *FU* follow-up, *MDRD* modification of diet in renal disease, *PEP* primary endpoint, *PTA* percutaneous angioplasty, *QOL* quality of life, *RAS* renal artery stenosis, *RCT* randomized controlled trial, *RRT* renal replacement therapy, *SBP* systolic BP, *UL* unilateral

[a]Intravenous pyelography, renal scintigraphy, or renal vein renin concentration performed according to the usual practice of each center

In the DRASTIC study, 106 of 169 eligible patients were randomized (50 patients were medically treated, 56 patients had angioplasty, of whom two with stent). All patients were either taking at least two antihypertensive drugs, or had previous deterioration of renal function with an ACEI, and had ≥50% RAS and serum creatinine <2.3 mg/dL at baseline. The primary endpoint, mean office BP at 3 and at 12 months, was not different between groups, although the number of antihypertensive drugs was lower in the angioplasty group. However, 20 of 50 patients initially assigned to the medical treatment group underwent angioplasty at 3 months, as diastolic BP was >95 mmHg despite ≥3 antihypertensive drugs. At 3 months, estimated creatinine clearance (Cockroft and Gault formula) was slightly but not significantly higher in the angioplasty group. Restenosis rate was high (52%) in the angioplasty group [17].

Several meta-analyses of these RCTs concluded that balloon angioplasty has a modest but significant effect on BP. However, no evidence of improving or preserving renal function was found, although none of the trials were designed to address this issue [36, 62, 63].

The ASTRAL (angioplasty and stenting for renal artery lesions), CORAL (cardiovascular outcomes in renal atherosclerotic lesions), RADAR, NITER (nephropathy ischemic therapy), and STAR (stent placement and blood pressure and lipid lowering for the prevention of progression of renal dysfunction caused by atherosclerotic ostial stenosis of the renal artery) randomized trials have compared initial angioplasty with stenting with medical therapy [54–56, 64, 65].

The STAR trial randomized 140 patients with ostial ARAS of >50% and estimated (Cockroft and Gault) creatinine clearance <80 mL/min/1.73m$^2$ (74 were assigned to medical therapy, 46 patients of the 64 assigned to balloon angioplasty with stent insertion underwent the allocated treatment). The primary endpoint was a 20% decline in estimated creatinine clearance. The intention-to-treat and the per protocol analysis revealed similar results in both arms after 2 years of follow-up [54].

The ASTRAL trial randomized 806 patients with uncontrolled or refractory hypertension or unexplained renal dysfunction with angiographically proven ARAS. Of the 403 patients assigned to RA-PTAS, only 301 were actually revascularized with stent placement. Of the 403 patients assigned to medical therapy, 24 (6%) crossed over to revascularization. The primary outcome was renal function, measured by the reciprocal of serum creatinine. No significant difference in the primary endpoint was observed. An important bias in this large study was the opinion of the physician: patients were only enrolled if their physician was uncertain as to whether revascularization would be of clinical benefits, which may have led to exclusion of patients most likely to benefit from revascularization [55].

The CORAL trial included 947 patients with ARAS of >80% or 60–79% with a systolic pressure gradient of >20 mmHg across the stenotic lesion on angiography and a systolic BP >155 mmHg on at least two antihypertensive drugs and/or eGFR (MDRD) <60 mL/min/1.73 m$^2$. The CORAL investigators factually selected patients with less severe RA stenosis but only with evidence of a significant translesional SP gradient. The latter is suggestive for a stenosis responsible

for an upregulation of renin production and, thus, for RVH and consequently may predict hypertension improvement after stenting of RAS [66]. Patients with renal FMD, nonischemic nephropathy, or a kidney length of <7 cm were excluded in the CORAL trial. 467 patients were assigned to RA-PTAS (embolic protection devices were used) and medical therapy (442 actually underwent revascularization) and 480 to medical therapy alone (4% crossover). Medical treatment was standardized. The primary endpoint was a composite of death from CV or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal failure, or the need for renal replacement therapy. The authors concluded that renal artery stenting did not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in patients with ARAS and hypertension or CKD [56].

The RADAR trial was designed to compare the best medical treatment versus the best medical treatment plus RA-PTAS in patients with hemodynamically significant ARAS (>70%). The primary endpoint is the change of eGFR over 12 months. The study was prematurely terminated, and the results of the trial, including 89 patients, have not been fully published [44, 47]. Also the results of the NITER trial have not been fully published [44, 53].

The Cochrane collaboration meta-analysis of Jenks et al. and other reviews all concluded that revascularization using balloon angioplasty, with or without stenting, is not superior to medical therapy for the treatment of ARAS in patients with hypertension. However, balloon angioplasty results in a small improvement in diastolic BP and a small reduction in antihypertensive drug requirements. Balloon angioplasty also appears to be safe and results in similar numbers of CV and renal adverse events as compared to medical therapy [44].

The primary objective of the ongoing METRAS trial is to determine whether RA-PTAS is superior or equivalent to optimal medical treatment for preserving GFR in the ischemic kidney as assessed by 99mTc-DTPA sequential renal scintigraphy [60].

The primary objective of the RAVE study is to determine the frequency of progression to the composite endpoint (death, dialysis, and doubling of serum creatinine) in patients with ARAD and indication for revascularization, randomized to medical therapy or renal revascularization over a minimum of 6 months. The study has been completed, but no results till now were published. [59].

The primary endpoint of the recently started ANDORRA study in resistant hypertension (daytime SBP ≥135 or DBP ≥85 mmHg on ≥3 antihypertensive drugs) and UL or BL ARAS ≥60%; kidney length ≥7 cm; eGFR ≥20 mL/min is the mean change in diurnal systolic BP on 24 h ABPM after 12 months [61].

#### 25.2.5.3 Surgical Revascularization

Surgical revascularization is no longer the first-choice treatment since angioplasty became widely available. Surgery is reserved for difficult and complex lesions or in case of a complication during angiography. To minimize atheroembolism, aortorenal bypass and renal endarterectomies have nowadays been superseded by nonaortic site bypasses (splenic, celiac, mesenteric, hepatic, or ileac arterial).

Few RCTs evaluated surgery versus medical therapy or angioplasty. A small randomized study including 52 patients with ARAS at risk for ischemic nephropathy, comparing surgery with medical therapy, did not show any difference in mortality at 5 years. No data on BP control or kidney function were published [48].

Another small study randomized 58 hypertensive patients with ARAS to surgery versus balloon angioplasty without stenting. The technical success rate was 83% in the RA-PTAS and 97% in the surgical group and not significantly different. The primary patency rate at 2 years was significantly higher for surgical than for angioplasty-treated patients (96% vs. 75%, $p < 0.05$). A significant decrease in BP in both groups was observed, but without intergroup differences. The number of patients receiving more than three antihypertensive drugs was reduced to a similar extent in both groups. There was also no difference between the two methods with regard to influence on renal function [49].

Balzer et al. randomized 50 patients with hypertension and renal artery ostial occlusive disease (RAOOD) to surgical revascularization or RA-PTAS. Four-year follow-up mortality was 18% in the stent group and 25% in the surgical group (NS). Both groups showed significant ($p < 0.01$) improvement of hypertension and nonsignificant improvement (surgery) or stabilization of renal function. Freedom from recurrent RAOOD (>70%) was achieved in 90.1% of the surgical group and 79.9% of the stent group (NS). Despite the nonsignificant differences in outcome, the authors concluded that surgical reconstruction remains the gold standard for patients with RAOOD [50]. Other advocates of surgery also question the predominance of endovascular intervention in ARAS and advance the need for more RCTs [67].

### 25.2.6 Future Perspectives

Despite the neutral results of the RCTs, it is obvious that patients with ARAD constitute a heterogeneous group. To date, the available RCTs have been subject to selection bias, excluding high-risk patients. Therefore, their data may not apply for all patients. Revascularization should still be considered in patients with true resistant hypertension, recurrent flash pulmonary edema, or rapid decline in kidney function [10, 68–70]. However, no hard evidence is available.

Which technique (US or DSA) or which parameter (i.e., RI, PSV, translesional pressure gradient) can reliably identify patients likely to benefit from revascularization remains controversial. Perhaps BOLD-MRI could help to resolve this problem [25].

Technical improvement of endovascular revascularization is continuing, with the use of drug-eluting stents, resulting in less complications [23, 28, 56, 68, 71].

It is increasingly recognized that atherosclerosis is a systemic disorder, characterized by inflammation. Poststenotic porcine and human kidneys release—even despite successful revascularization—several inflammatory cytokines and oxidative stress markers that may accelerate target organ injury. Recent research strategies try to ameliorate inflammation and oxidative stress by a single intrarenal infusion

of allogeneic adipose tissue-derived mesenchymal stem cells during PTRA. These experiments preserved stenotic kidney function, reduced systemic oxidative stress and inflammation, and thereby improved cardiac function, oxygenation, and myocardial injury 4 weeks after revascularization [72]. Endothelin-1 receptor blockers, angiogenic factors like vascular endothelial growth factor or hepatocyte growth factor, and mitochondria-targeted peptides also confer renoprotective effects in the stenotic kidney [73–76]. Whether these interventions might improve clinical outcome awaits further research.

## 25.3 Renal Artery Stenosis Due to Fibromuscular Dysplasia

### 25.3.1 Definition, Prevalence, and Classification

FMD-related renal artery stenosis has been for long considered a rare entity, with an estimated prevalence of <1% in the general population [77]. However, recent data suggest that FMD is much more common. A meta-analysis based on kidney donor data indeed found silent renal FMD lesions in 4% of the potential kidney donor population [78]. Furthermore, in the CORAL trial, where FMD was an exclusion criterion, the prevalence of FMD was 5.8% [78].

Three main histopathological types of renal FMD have been described according to the arterial wall involved, i.e., intimal FMD (5%), medial FMD (>85%), and perimedial FMD (10%) [79]. However, nowadays, as few cases of FMD require surgery and pathological documentation is lacking, this classification has become largely obsolete. Based on pathological-angiographic correlations, Kincaid proposed three types of renal artery FMD: multifocal ("string-of-beads" appearance), unifocal (solitary stenosis <1 cm in length), and tubular (stenosis at least 1 cm in length) FMD [80]. As the two last categories differ only by the length of the diseased segment, Savard et al. have proposed to group them under the generic term "unifocal" [81]. This pragmatic classification has been endorsed by the authors of the European consensus on FMD [82] and the American Heart Association [83].

Multifocal FMD accounts for over 80% of cases of renovascular FMD, and its histological substrate is medial FMD. It affects mainly women between 30 and 50 years old. The lesions commonly involve the middle or distal thirds of the main renal artery, and there is often extension into the proximal portion of the first-level branches. Lesions are bilateral in 60% of cases. Although the "string-of-beads" appearance is almost pathognomonic of multifocal (medial) FMD, the diagnosis requires exclusion of intoxication by sympathomimetic agents and ergotamine derivatives [77, 82].

Unifocal FMD can be found at the ostium, the trunk, or the bifurcation of the renal arteries. The diagnosis is suspected in young (usually <40 years old) patients with no atherosclerosis, after exclusion of other less frequent diseases. The differential diagnosis of unifocal FMD includes compression of the proximal renal artery by the median arcuate ligament; Takayasu or giant cell arteritis, usually associated with biological inflammation and vascular thickening; and rare monogenic or congenital

diseases (type 1 neurofibromatosis, tuberous sclerosis, pseudoxanthoma elasticum, vascular Ehlers-Danlos syndrome, Alagille syndrome, Williams syndrome, and Turner syndrome) [73, 78].

### 25.3.2 Clinical Presentation

Hypertension of variable severity is the most common clinical presentation of FMD. Occasionally, an epigastric or flank bruit at physical examination can also lead to the diagnosis. Flank pain may be a manifestation of renal artery dissection or aneurysm. FMD-associated arterial aneurysms at any location have been reported in 17% (33% in renal artery) and dissections in 20% (22% in renal artery) of patients in the US registry [84]. Renal insufficiency is uncommon and often due to renal artery dissection and renal infarction. Progression to end-stage renal disease is very rare. Finally, occurrence of FMD in at least another relative has been reported in 7–11% of cases [84, 85].

### 25.3.3 Diagnosis

The European consensus on fibromuscular dysplasia has recommended screening in patients <30 years old, especially in women and/or patients with severe, resistant, or malignant hypertension [82]. However, as the mean age at diagnosis of FMD in the US registry [84] and other recent cohorts is ~50 years, it appears reasonable to consider screening up to the fifth decade of life, especially in hypertensive women. Additional indications for screening include patients with small kidney in the absence of history of uropathy and abdominal bruit without apparent atherosclerosis and patients with demonstrated FMD in at least another vascular territory [82]. However, the true prevalence of FMD in these different subgroups has not been documented.

The diagnosis of renal FMD can be made by using noninvasive imaging studies including duplex ultrasonography and angiography by computed tomography or magnetic resonance. While, in the European consensus on FMD, renal duplex was still recommended as the first-line screening test [82], CT angiography—or, if contraindicated, MR angiography—is increasingly considered as a reasonable first-line imaging modality, in view of its higher resolution, especially for distal lesions, ability to detect FMD lesions without hemodynamic consequences, and decreasing costs and radiation exposure. This is especially true in case of high diagnostic probability or expected low performance of renal duplex (obese or hypo-echogenic patients, lack of local expertise, etc.).

Digital subtraction angiography remains the gold standard, but, in view of its invasiveness, it is usually reserved for patients in whom performing a simultaneous percutaneous angioplasty (PTA) is justified. DSA is also advised in the case of a high clinical suspicion of FMD-related stenosis, when the diagnosis remains uncertain after performing noninvasive tests [82]. In equivocal cases, intravascular

ultrasound (IVUS) and pressure measurements can help to assess the hemodynamic significance of a stenosis and the anatomical success after percutaneous intervention [86, 87].

### 25.3.4 Screening for FMD Lesions of Other Vascular Beds

Analysis of various cohorts of FMD patients from Europe and the United States suggests that up to one third of patients with FMD may harbor lesions of two or more vascular beds [82]. As vascular investigations were neither systematic nor standardized, these figures are likely underestimated. Notably, in the US registry, 65% of patients with renal FMD also have carotid FMD lesions [84]. Therefore, screening for cervico-cephalic FMD lesions in patients with renal FMD is recommended, provided there are arguments that identification of lesions in the second vascular bed could modify management [82]. CT- or, if contraindicated, MR angiography should be preferred to carotid duplex, first because cervical FMD lesions are often distal and thus may escape carotid duplex and secondly because CT angiography also allows detecting associated cerebral aneurysms [82, 88]. Screening of other, less often involved vascular beds (mesenteric, lower, or upper limb arteries) should also be considered in the presence of suggestive symptoms (claudication, abdominal angina, etc.) or medical history.

### 25.3.5 Therapy

The treatment of patients with renal FMD may include medical therapy with surveillance, endovascular therapy (angioplasty without stenting), or surgery. The decision depends on the nature and location of vascular lesions (stenosis/dissection/aneurysm), the presence and severity of symptoms, prior vascular events related to FMD, and comorbid conditions.

#### 25.3.5.1 Medical Management

Medical therapy includes antihypertensive drugs, preferably blockers of the renin-angiotensin system, treatment of other cardiovascular risk factors, and antiplatelet or antithrombotic drugs after angioplasty or in case of renal artery dissection or thrombosis. Furthermore, it has been suggested that smoking is associated with a more aggressive course of the disease [89, 90]. Accordingly, smoking cessation is strongly encouraged in patients with FMD.

#### 25.3.5.2 Angioplasty With or Without Stenting

There are no randomized controlled studies comparing revascularization to medical treatment only or revascularization by percutaneous angioplasty (PTA) to surgical revascularization in patients with FMD. In contrast with atherosclerotic RAS, hypertension cure is fairly common following revascularization of FMD-related RAS (30–50% according to the definition of normotension) [91]. As shown in a

meta-analysis, cure rates are higher in younger patients, those with more recent onset of hypertension, and in unifocal FMD compared with multifocal FMD [91]. It appears appropriate to propose revascularization in hypertensive patients with FMD-related RAS, especially if hypertension is of recent onset or in case of drug-resistant hypertension [82].

The two options available for renal artery revascularization are PTA and renal artery surgery. In view of its less invasive character and of the large experience acquired, PTA is currently the first-line revascularization technique. There is no evidence of superiority of renal artery PTA followed by stenting vs. PTA alone in FMD patients. Furthermore, cases of stent kinking of fracture have been reported in patients with renal FMD [92]. Therefore, stenting is not indicated after primary PTA unless needed due to a significant per-procedural dissection [82]. Surgery remains the primary approach for patients with complex lesions of arterial bifurcation or branches, stenoses associated with complex aneurysms, or following PTA failure. A second PTA may be attempted following PTA failure, but a third PTA is not recommended so as to prevent arterial trauma, which could jeopardize surgical results [82].

### 25.3.6 Future Perspectives

One of the major aims of current research is to identify the genetic and environmental factors involved in the pathogenesis of FMD. Besides candidate gene studies, which have proven disappointing so far [77], non-hypothesis-driven strategies such as genome-wide association studies performed in large discovery and replication cohorts and whole exome sequencing in selected familial, severe, early-onset cases [93] may contribute to unravel the genetic determinants of the disease. Environmental factors, including tobacco and hormones, and possible gene-environment interactions also need further evaluation. Additional research efforts should be devoted to identification of the disease subtypes more likely to progress, definition of an evidence-based screening and follow-up algorithm, and improvement in quantification of FMD-related renal artery stenosis. A common prerequisite of most of these investigations is to collect systematically and prospectively in a standardized way all FMD cases into national and international registries such as US [84], French [94], and European registries.

**Conclusions**

The prevalence of renovascular hypertension is highly variable according to the studied cohorts. Renal angiography remains the gold standard for the diagnosis of renal artery stenosis.

In atherosclerotic renal artery disease, medical therapy remains the cornerstone of treatment, and cardiovascular risk factors should be aggressively targeted. Revascularization with balloon angioplasty and stent placement should be considered for selected patients with atherosclerotic renal artery stenosis and poorly controlled hypertension and/or rapidly declining kidney function and/or

flash pulmonary edema. Recent research highlights the transition from a pure hemodynamic condition to a complex inflammatory process in the ischemic kidney, creating new opportunities for innovative therapies [95].

For FMD-related renal artery stenosis, angioplasty without stenting should be considered in most cases, especially in young patients with recent onset of hypertension and/or patients with resistant hypertension. FMD appears more and more as a systemic disease with a heritable component. Therefore, management should also include screening for lesions of other vascular beds, particularly cervicocephalic FMD, and careful family history taking [82].

**Acknowledgments** The authors are indebted to Dr. Elena Berra for her assistance in preparing and checking the references and to Mrs. Nadia Fenners for editing the tables.

## References

1. Textor SC, Novick A, Mujais SK et al (1983) Responses of the stenosed and contralateral kidneys to [Sar1, Thr8] AII in human renovascular hypertension. Hypertension 5:796–804
2. Textor SC, Lerman LO (2015) Paradigm shifts in atherosclerotic renovascular disease: where are we now? J Am Soc Nephrol 26:2074–2080
3. Kwon SH, Lerman LO (2015) Atherosclerotic renal artery stenosis: current status. Adv Chronic Kidney Dis 22:224–231
4. Conlon PJ, O'Riordan E, Kalra PA (2000) New insights into the epidemiologic and clinical manifestations of atherosclerotic renovascular disease. Am J Kidney Dis 35:573–578
5. Elliott WJ (2008) Renovascular hypertension: an update. J Clin Hypertens 10:522–533
6. Van Twist DJ, Houben AJ, de Haan MW et al (2016) Renal hemodynamics and renin-angiotensin system activity in humans with multifocal renal artery fibromuscular dysplasia. J Hypertens 34:1160–1169
7. De Mast Q, Beutler JJ (2009) The prevalence of atherosclerotic renal artery stenosis in risk groups: a systematic literature review. J Hypertens 27:1333–1340
8. Lorenz EC, Vrtiska TJ, Lieske JC et al (2010) Prevalence of renal artery and kidney abnormalities by computed tomography among healthy adults. Clin J Am Soc Nephrol 5:431–438
9. Hansen KJ, Edwards MS, Craven TE et al (2002) Prevalence of renovascular disease in the elderly: a population-based study. J Vasc Surg 36:443–451
10. Messerli FH, Bangalore S, Makani H et al (2011) Flash pulmonary oedema and bilateral renal artery stenosis: the Pickering syndrome. Eur Heart J 32:2231–2235
11. Shafique S, Peixoto AJ (2007) Renal artery stenosis and cardiovascular risk. J Clin Hypertens 9:201–208
12. Kalra PA, Guo H, Kausz AT et al (2005) Atherosclerotic renovascular disease in United States patients aged 67 years or older: risk factors, revascularization, and prognosis. Kidney Int 68:293–301
13. Yu TM, Sun CS, Lin CL et al (2015) Risk factors associated with end-stage renal disease (ESRD) in patients with atherosclerotic renal artery stenosis. a nationwide population-based analysis. Medicine (Baltimore) 94:e912 doi:https://doi.org/10.1097/MD.0000000000000912
14. Krijnen P, Steyerberg EW, Postma CT et al (2005) Validation of a prediction rule for renal artery stenosis. J Hypertens 23:1583–1588
15. Taylor A, Blaufox MD, Dubovsky EV et al (2003) Society of nuclear medicine procedure guideline for diagnosis of renovascular hypertension. Society of Nuclear Medicine and Molecular Imaging website http://interactivesnmorg/docs/pg_ch16_0403pdf Published August 2003. Accessed 29 Feb 2016

16. Taylor AT (2014) Radionuclides in nephrourology, part 2: pitfalls and diagnostic applications. J Nucl Med 55:786–798
17. Van Jaarsveld BC, Krijnen P, Pieterman H et al (2000) The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. Dutch Renal Artery Stenosis Intervention Cooperative Study Group. N Engl J Med 342:1007–1014
18. Granata A, Fiorini F, Andrulli S et al (2009) Doppler ultrasound and renal artery stenosis: an overview. J Ultrasound 12:133–143
19. Radermacher J, Chavan A, Bleck J et al (2001) Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. N Engl J Med 344:410–417
20. Zeller T, Muller C, Frank U et al (2003) Stent angioplasty of severe atherosclerotic ostial renal artery stenosis in patients with diabetes mellitus and nephrosclerosis. Catheter Cardiovasc Interv 58:510–515
21. Bruno RM, Daghini E, Versari D et al (2014) Predictive role of renal resistive index for clinical outcome after revascularization in hypertensive patients with atherosclerotic renal artery stenosis: a monocentric observational study. Cardiovasc Ultrasound 12:9. https://doi.org/10.1186/1476–7120–12-9
22. Schäberle W, Leyerer L, Schierling W et al (2016) Ultrasound diagnostics of renal artery stenosis. Stenosis criteria, CEUS and recurrent in-stent stenosis. Gefässchirurgie 21:S4–S13
23. Williams GJ, Macaskill P, Chan SF et al (2007) Comparative accuracy of renal duplex sonographic parameters in the diagnosis of renal artery stenosis: paired and unpaired analysis. Am J Roentgenol 188:798–811
24. Rountas C, Vlychou M, Vassiou K et al (2007) Imaging modalities for renal artery stenosis in suspected renovascular hypertension: prospective intraindividual comparison of color Doppler US, CT angiography, GD-enhanced MR angiography, and digital subtraction angiography. Ren Fail 29:295–302
25. Chrysochou C, Mendichovszky IA, Buckley DL et al (2012) BOLD imaging: a potential predictive biomarker of renal functional outcome following revascularization in atheromatous renovascular disease. Nephrol Dial Transplant 27:1013–1019
26. Van Helvoort-Postulart D, Dirksen CD, Nelemans PJ et al (2007) Renal artery stenosis: cost-effectiveness of diagnosis and treatment. Radiology 244:505–513
27. Vasbinder GB, Nelemans PJ, Kessels AG et al (2001) Diagnostic tests for renal artery stenosis in patients suspected of having renovascular hypertension: a meta-analysis. Ann Intern Med 135:401–411
28. Zeller T, Frank U, Müller C et al (2003) Technological advances in the design of catheters and devices used in renal artery interventions: impact on complications. J Endovasc Ther 10:1006–1014
29. Martin LG, Rundback JH, Wallace MJ et al (2010) Quality improvement guidelines for angiography, angioplasty, and stent placement for the diagnosis and treatment of renal artery stenosis in adults. J Vasc Interv Radiol 21:421–430
30. Bavishi C, de Leeuw PW, Messerli FH (2015) Atherosclerotic renal artery stenosis and hypertension: pragmatism, pitfalls, and perspectives. Am J Med 129:635.e5–635.e14
31. Bakris GL, Weir MR (2000) Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 160:685–693
32. Losito A, Errico R, Santirosi P et al (2005) Long-term follow-up of atherosclerotic renovascular disease. Beneficial effect of ACE inhibition. Nephrol Dial Transplant 20:1604–1609
33. Evans KL, Tuttle KR, Folt DA et al (2014) Use of renin-angiotensin inhibitors in people with renal artery stenosis. Clin J Am Soc Nephrol 9:1199–1206
34. Hackam DG, Wu F, Li P et al (2011) Statins and renovascular disease in the elderly: a population based cohort study. Eur Heart J 32:598–610
35. Gruntzig A, Vetter W, Meier B et al (1978) Treatment of renovascular hypertension with percutaneous transluminal dilation of a renal artery stenosis. Lancet 311:801–802
36. Ives NJ, Wheatley K, Stowe RL et al (2003) Continuing uncertainty about the value of percutaneous revascularization in atherosclerotic renovascular disease: a meta-analysis of randomized trials. Nephrol Dial Transplant 18:298–304

37. Dorros G, Jaff M, Mathiak L et al (2002) Multicenter Registry Participants. Multicenter Palmaz stent renal artery stenosis revascularization registry report: four-year follow-up of 1,058 successful patients. Catheter Cardiovasc Interv 55:182–188
38. Beck AW, Nolan BW, De Martino R et al (2010) Predicting blood pressure response after renal artery stenting. J Vasc Surg 51:380–385
39. Muray S, Martın M, Amoedo ML et al (2002) Rapid decline in renal function reflects reversibility and predicts the outcome after angioplasty in renal artery stenosis. Am J Kidney Dis 39:60–66
40. Simone TA, Brooke BS, Goodney PP et al (2013) Clinical effectiveness of secondary interventions for restenosis after renal artery stenting. J Vasc Surg 58:687–694
41. Christie JW, Conlee TD, Craven TE et al (2012) Early duplex predicts restenosis after renal artery angioplasty and stenting. J Vasc Surg 56:1373–1380
42. Corriere MA, Edwards MS, Pearce JD et al (2009) Restenosis after renal artery angioplasty and stenting: incidence and risk factors. J Vasc Surg 50:813–819
43. Davies MG, Saad WA, Bismuth JX et al (2009) Outcomes of endoluminal reintervention for restenosis after percutaneous renal angioplasty and stenting. J Vasc Surg 49:946–952
44. Jenks S, Yeoh SE, Conway BR (2014) Balloon angioplasty, with and without stenting, versus medical therapy for hypertensive patients with renal artery stenosis. Cochrane Database Syst Rev 12:CD002944. https://doi.org/10.1002/14651858.CD002944.pub2.
45. White CJ (2010) Optimizing outcomes for renal artery intervention. Circ Cardiovasc Interv 3:184–192
46. Cooper CJ, Haller ST, Colyer W et al (2008) Embolic protection and platelet inhibition during renal artery stenting. Circulation 117:2752–2760
47. Textor SC, Misra S, Oderich G (2013) Percutaneous revascularization for ischemic nephropathy: past, present and future. Kidney Int 83:28–40
48. Uzzo RG, Novick AC, Goormastic M et al (2002) Medical versus surgical management of atherosclerotic renal artery stenosis. Transplant Proc 34:723–725
49. Weibull H, Bergqvist D, Bergentz S-E et al (1993) Percutaneous transluminal renal angioplasty versus surgical reconstruction of atherosclerotic renal artery stenosis: a prospective randomized study. J Vasc Surg 18:841–852
50. Balzer KM, Pfeiffer T, Rossbach S et al (2009) Prospective randomized trial of operative vs interventional treatment for renal artery ostial occlusive disease (RAOOD). J Vasc Surg 49:667–675
51. Plouin PF, Chatellier G, Darné B et al (1998) Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis. A randomized trial. Hypertension 31:823–829
52. Webster J, Marshall F, Abdalla M et al (1998) Randomised comparison of percutaneous angioplasty vs continued medical therapy for hypertensive patients with atheromatous renal artery stenosis. Scottish and Newcastle Renal Artery Stenosis Collaborative Group. J Hum Hypertens 12:329–335
53. Van de Ven PJ, Kaatee R, Beutler JJ, Beek FJ, Woittiez AJ, Buskens E et al (1999) Arterial stenting and balloon angioplasty in ostial atherosclerotic renovascular disease: a randomised trial. Lancet 353(9149):282–286
54. Bax L, Woittiez A-JJ, Kouwenberg HJ et al (2009) Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function. A randomized trial. Ann Intern Med 150:840–848
55. Investigators TASTRAL, Wheatley K, Ives N et al (2009) Revascularization versus medical therapy for renal-artery stenosis. N Engl J Med 361:1953–1962
56. Cooper CJ, Murphy TP, Cutlip DE et al (2014) Stenting and medical therapy for atherosclerotic renal-artery stenosis. N Engl J Med 370:13–22
57. Scarpioni R, Michieletti E, Cristinelli L et al (2005) Atherosclerotic renovascular disease: medical therapy versus medical therapy plus renal artery stenting in preventing renal failure progression: the rationale and study design of a prospective, multicenter and randomized trial (NITER). J Nephrol 18:423–428

58. Zeller T (2013) RADAR—data of a prematurely terminated randomized, multi-centre, prospective study comparing best medical treatment versus best medical treatment plus renal artery stenting in patients with hemodynamically relevant atherosclerotic renal artery stenosis [Abstract]. Vasa 42:40
59. Tobe SW, Atri M, Perkins N et al (2007) Renal Atherosclerotic reVascularization Evaluation (RAVE Study): study protocol of a randomized trial [NCT00127738]. BMC Nephrol 8:4
60. Rossi GP, Seccia TM, Miotto D et al (2012) The medical and endovascular treatment of atherosclerotic renal artery stenosis (METRAS) study: rationale and study design. J Hum Hypertens 26:507–516
61. Azizi M (2015) Renal artery stenting in patients with documented resistant hypertension and atherosclerotic renal artery stenosis (ANDORRA). https://clinicaltrials.gov/show/NCT02539810
62. Nordmann AJ, Woo K, Parkes R et al (2003) Balloon angioplasty or medical therapy for hypertensive patients with atherosclerotic renal artery stenosis? A meta-analysis of randomized controlled trials. Am J Med 114:44–50
63. Caielli P, Frigo AC, Pengo MF et al (2015) Treatment of atherosclerotic renovascular hypertension: review of observational studies and a meta-analysis of randomized clinical trials. Nephrol Dial Transplant 30:541–555
64. Schwarzwälder U, Hauk M, Zeller T (2009) RADAR—a randomised, multi-centre, prospective study comparing best medical treatment versus best medical treatment plus renal artery stenting in patients with haemodynamically relevant atherosclerotic renal artery stenosis. Trials 10:60. https://doi.org/10.1186/1745–6215–10-60
65. Scarpioni R, Michieletti E, Pavone L, Gandolfi S, Ricardi M, Pecchini P et al (2009) Atherosclerotic renovascular disease (ARVD): medical therapy plus renal artery stenting (PTRS), compared with medical therapy alone, do not offer more chances in preventing cardio-vascular (CV) or renal events. Preliminary results of a prospective, multicenter and randomized trial [Abstract]. Presented at World Congress of Nephrology, Milan, Italy, 22–26 May 2009
66. De Bruyne B, Manoharan G, Pijls NHJ et al (2006) Assessment of renal artery stenosis severity by pressure gradient measurements. J Am Coll Cardiol 48:1851–1855
67. Abela R, Ivanova S, Lidder S et al (2009) An analysis comparing open surgical and endovascular treatment of atherosclerotic renal artery stenosis. Eur J Vasc Endovasc Surg 38:666–675
68. Chrysant GS, Bates MC, Sullivan TM et al (2014) Proper patient selection yields significant and sustained reduction in systolic blood pressure following renal artery stenting in patients with uncontrolled hypertension: long-term results from the HERCULES trial. J Clin Hypertens (Greenwich) 16:497–503
69. Bloch MJ, Trost DW, Pickering TG et al (1999) Prevention of recurrent pulmonary edema in patients with bilateral renovascular disease through renal artery stent placement. Am J Hypertens 12:1–7
70. Ritchie J, Green D, Chrysochou C et al (2014) High-risk clinical presentations in atherosclerotic renovascular disease: prognosis and response to renal artery revascularization. Am J Kidney Dis 63:186–197
71. Safian RD, Madder RD (2009) Refining the approach to renal artery revascularization. JACC Cardiovasc Interv 2:161–174
72. Eirin A, Zhu X-Y, Ferguson CM et al (2015) Intra-renal delivery of mesenchymal stem cells attenuates myocardial injury after reversal of hypertension in porcine renovascular disease. Stem Cell Res Ther 6:7. https://doi.org/10.1186/scrt541
73. Chade AR, Tullos N, Stewart NJ et al (2015) Endothelin-A receptor antagonism after renal angioplasty enhances renal recovery in renovascular disease. J Am Soc Nephrol 26:1071–1080
74. Chade AR, Kelsen S (2010) Renal microvascular disease determines the responses to revascularization in experimental renovascular disease. Circ Cardiovasc Interv 3:376–383
75. Stewart N, Chade AR (2013) Renoprotective effects of hepatocyte growth factor in the stenotic kidney. Am J Physiol Renal Physiol 304:F625–F633

76. Eirin A, Ebrahimi B, Zhang X et al (2014) Mitochondrial protection restores renal function in swine atherosclerotic renovascular disease. Cardiovasc Res 103:461–472
77. Plouin PF, Perdu J, La Batide-Alanore A et al (2007) Fibromuscular dysplasia. Orphanet J Rare Dis 2:28
78. Hendricks NJ, Matsumoto AH, Angle JF et al (2014) Is fibromuscular dysplasia underdiagnosed? A comparison of the prevalence of FMD seen in CORAL trial participants versus a single institution population of renal donor candidates. Vasc Med 19:363–367
79. Harrison EG, McCormack LJ (1971) Pathologic classification of renal arterial disease in renovascular hypertension. Mayo Clin Proc 46:161–167
80. Kincaid OW, Davis GD, Hallermann FJ et al (1968) Fibromuscular dysplasia of the renal arteries. Arteriographic features, classification, and observations on natural history of the disease. Am J Roentgenol Radium Ther Nucl Med 104:271–282
81. Savard S, Steichen O, Azarine A et al (2012) Association between 2 angiographic subtypes of renal artery fibromuscular dysplasia and clinical characteristics. Circulation 126:3062–3069
82. Persu A, Giavarini A, Touzé E et al (2014) European consensus on the diagnosis and management of fibromuscular dysplasia. J Hypertens 32:1367–1378
83. Olin JW, Gornik HL, Bacharach JM et al (2014) Fibromuscular dysplasia: state of the science and critical unanswered questions: a scientific statement from the American Heart Association. Circulation 129:1048–1078
84. Olin JW, Froehlich J, Gu X et al (2012) The United States Registry for fibromuscular dysplasia: results in the first 447 patients. Circulation 125:3182–3190
85. Pannier-Moreau I, Grimbert P, Fiquet-Kempf B et al (1997) Possible familial origin of multifocal renal artery fibromuscular dysplasia. J Hypertens 15:1797–1801
86. Gowda MS, Loeb AL, Crouse LJ et al (2003) Complementary roles of color-flow duplex imaging and intravascular ultrasound in the diagnosis of renal artery fibromuscular dysplasia: should renal arteriography serve as the "gold standard"? J Am Coll Cardiol 41:1305–1311
87. Prasad A, Zafar N, Mahmud E (2009) Assessment of renal artery fibromuscular dysplasia: angiography, intravascular ultrasound (with virtual histology), and pressure wire measurements. Catheter Cardiovasc Interv 74:260–264
88. Touze E, Oppenheim C, Trystram D et al (2010) Fibromuscular dysplasia of cervical and intracranial arteries. Int J Stroke 5:296–305
89. Savard S, Azarine A, Jeunemaitre X et al (2013) Association of smoking with phenotype at diagnosis and vascular interventions in patients with renal artery fibromuscular dysplasia. Hypertension 61:1227–1232
90. O'Connor S, Gornik HL, Froehlich JB et al (2016) Smoking and adverse outcomes in fibromuscular dysplasia: US Registry Report. J Am Coll Cardiol 67:1750–1751
91. Trinquart L, Mounier-Vehier C, Sapoval M et al (2010) Efficacy of revascularization for renal artery stenosis caused by fibromuscular dysplasia: a systematic review and meta-analysis. Hypertension 56:525–532
92. Raju MG, Bajzer CT, Clair DG et al (2013) Renal artery stent fracture in patients with fibromuscular dysplasia: a cautionary tale. Circ Cardiovasc Interv 6:e30–e31
93. Kiando SR, Barlassina C, Cusi D et al (2015) Exome sequencing in seven families and gene-based association studies indicate genetic heterogeneity and suggest possible candidates for fibromuscular dysplasia. J Hypertens 33:1802–1810
94. Toubiana L, Ugon A, Giavarini A et al (2015) A "pivot" model to set up large scale rare diseases information systems: application to the Fibromuscular Dysplasia Registry. Stud Health Technol Inform 210:887–891
95. Lerman LO, Textor SC (2015) Gained in translation protective paradigms for the poststenotic kidney. Hypertension 65:976–982

# Molecular Pathways in Hypertensive Renal Damage

# 26

John D. Imig, Md. Abdul H. Khan, and Ashraf El-Meanawy

## 26.1 Introduction

Hypertension is a chronic disease that afflicts close to one-third of the adult population worldwide [1–3]. This disease increases the risk for strokes, heart attacks, atherosclerosis, and chronic kidney disease. There are numerous drugs that are used to decrease blood pressure and control hypertension. These antihypertensive drugs fall into four major classes:β-blockers, vasodilators, renin-angiotensin system inhibitors, and diuretics. Antihypertensive drugs have been fairly effective in lowering blood pressure but have varying effects on progression of diseases associated with hypertension [3–6]. Patients with hypertension also become less responsive to drugs and can be treated with up to three antihypertensive drugs to control blood pressure [7, 8]. Moreover, there are a number of patients that eventually become resistant to antihypertensive drugs [3, 9, 10]. This suboptimal control of blood pressure results in a higher incidence of strokes, heart attacks, atherosclerosis, and chronic kidney disease [1–3]. This chapter will focus on the molecular pathways responsible for hypertensive renal damage that results in the progression of chronic kidney disease to end-stage renal disease (ESRD).

Chronic kidney disease and ESRD prevalence have been steadily increasing with the incidence of ESRD rising at a rate of 5–8% per year in the USA and worldwide [2]. Elevated blood pressure is clearly associated with chronic kidney disease, and decreasing blood pressure clearly slows but does not stop the progression of

J.D. Imig (✉) • M.A.H. Khan
Department of Pharmacology and Toxicology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA
e-mail: jdimig@mcw.edu

A. El-Meanawy
Division of Nephrology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI 53226, USA



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_26

chronic kidney disease [3, 7, 11]. To this end, the increase in ESRD is beginning to plateau and could be the result of improved rates of blood pressure control [3, 5]. In addition to elevated blood pressure, there are a number of molecular pathways that contribute to hypertensive renal damage. These factors include hormonal and paracrine factors, genetic and environmental factors, nephron number, renal hemodynamic changes, tubulointerstitial changes, and inflammatory factors (Fig. 26.1). Pathological changes in these factors during hypertension ultimately cause glomerulosclerosis and tubulointerstitial fibrosis in the kidney resulting in progression to chronic kidney disease.

Renal damage and chronic kidney disease in hypertension have become even more complex by the coexistence of these diseases and also the presence of other disease such as diabetes [12–16]. Patients in the category of uncomplicated hypertension will develop minimal renal damage in the absence of a severe elevation in blood pressure [12, 13, 16]. Kidney injury in uncomplicated hypertension has been separated into distinct clinical and histopathological categories of benign or malignant nephrosclerosis [12, 15, 16]. On the other hand, patients with diabetes and nondiabetic chronic kidney disease have increased susceptibility to even moderate

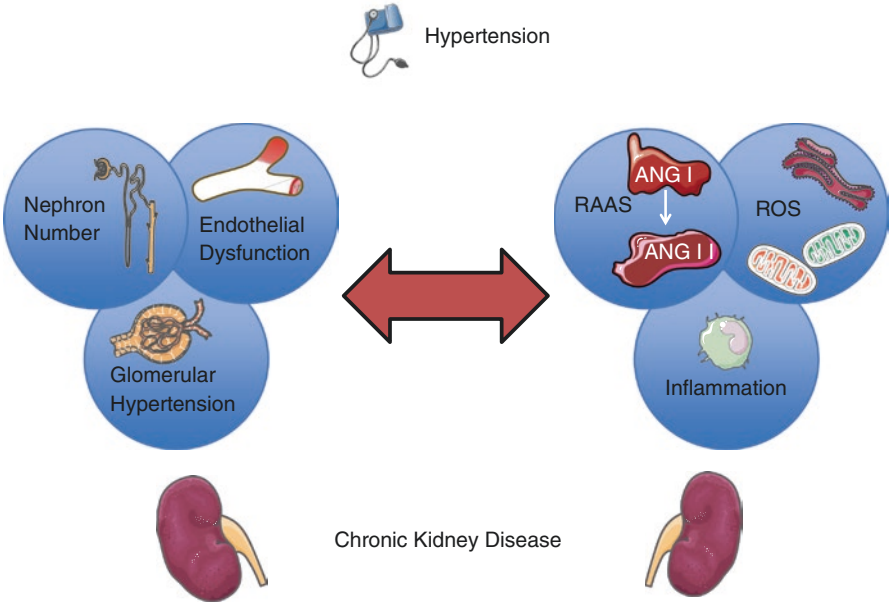



**Fig. 26.1** Schematic representation of mechanisms contributing to the development of hypertension-induced chronic kidney disease. Renal and vascular function and structural aspects contribute to progression of kidney disease. These include low nephron number, endothelial dysfunction, and glomerular hypertension. Hormonal and paracrine factors, for example, an elevated renin-angiotensin-aldosterone system (RAAS), oxidative stress (ROS), and inflammation, also contribute to chronic kidney disease in hypertension. Interactions between renal vascular functional and structural factors and hormonal and paracrine factors ultimately lead to glomerulosclerosis and tubulointerstitial fibrosis resulting in progressive chronic kidney disease

elevations in blood pressure [17–19]. The development of chronic kidney disease increases the risk for adverse cardiovascular events and death in patients with hypertension [2]. Kidney histopathology demonstrating vascular lesions of hyaline arteriosclerosis is a hallmark of hypertensive injury [14, 16]. This vascular pathology is not always prominent in chronic kidney disease; however, there can be accelerated segmental or global glomerulosclerosis evident in hypertension [14, 16]. Experimental investigations are beginning to understand the pathology observed under these different clinical pathologies of renal disease in hypertension. Relevant major underlying pathological and molecular mechanisms underlying hypertensive renal damage will be addressed.

## 26.2 Blood Pressure, Glomerular Hypertension, and Nephron Number

Elevated blood pressure and nephron number are major contributing factors to hypertensive renal damage and progression to chronic kidney disease (Fig. 26.2) [14–16]. A systemic elevation in blood pressure has consequences on the renal vascular bed and can eventually result in increased glomerular capillary pressure [15, 16]. The renal vasculature has autoregulatory mechanisms to maintain constant

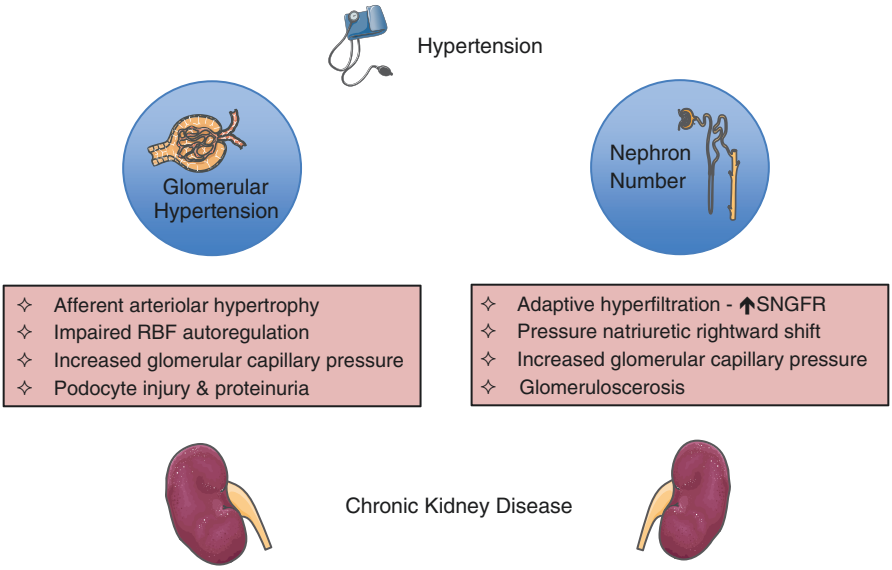



**Fig. 26.2** Elevated glomerular pressure and nephron deficiency contribute to hypertension-induced chronic kidney disease. Elevated vascular and glomerular pressure causes afferent arteriolar hypertrophy, impaired renal blood flow (RBF) autoregulation, and podocyte injury and proteinuria. Low nephron number results in an increase in single nephron glomerular filtration rate (SNGFR), rightward shift of the pressure-natriuretic relationship, and glomerular hypertension to result in glomerulosclerosis

renal blood flow and glomerular hydrostatic pressure [15]. Afferent arterioles respond to an increase in systemic blood pressure by contracting through the vascular smooth muscle cell myogenic response and the macula densa-mediated tubuloglomerular feedback response [15, 20]. A sustained elevation in blood pressure does not lead to glomerular lesions or damage as long as this afferent arteriolar autoregulatory response is properly maintained [15]. Glomerular nephron number, endothelial dysfunction, elevated renin-angiotensin system, oxidative stress, and inflammation contribute to changes in afferent autoregulation in hypertension [15, 20]. Renal blood flow autoregulation will ultimately be impaired and result in an elevated glomerular capillary pressure [20]. The increase in glomerular capillary pressure results in an increased filtration fraction and loss of glomerular filtration barrier. Glomerular barrier breakdown and an increased glomerular capillary hydrostatic pressure will lead to clinical proteinuria and glomerular destruction [14–16].

Glomerular hypertension is a critical component in progression of kidney damage in hypertension [13, 15, 21]. Afferent arterioles and glomerular capillaries will have structural adaptations to the elevated systemic blood pressure [15, 22]. Adaptive structural changes of the afferent arterioles include narrowing of the lumen diameter to combat the increase in wall stress [22–24]. Decreases in afferent arteriolar diameter will result in amplifying the already elevated blood pressure [15, 23]. Over time the afferent arteriole will develop hypertrophy in response to chronic blood pressure elevations [15, 23]. Afferent arteriolar hypertrophy leads to an ischemic injury in the glomeruli and tubulointerstitial structures [15, 22, 23]. At the level of the glomerulus, increased capillary pressure results in capillary stretching, endothelial damage, and breakdown of the capillary barrier [15, 23]. This leads to increased glomerular protein filtration that causes segmental necrosis and glomerulosclerosis [15, 22, 23]. Glomerular sclerosis and preglomerular vascular structural alterations can cause a further reduction in renal blood flow and enhancing the progression of chronic kidney disease [21–24].

Nephron number is another key component to the development of hypertension and the likelihood for the development of hypertension-induced chronic kidney disease [25–27]. The human kidney can have anywhere from 200,000 to 2.5million nephrons [25, 28, 29]. Brenner and colleagues proposed and provided convincing data that low nephron number increased the potential for a person to develop hypertension in adulthood [27, 28]. Approximately 50% of the children born with one kidney will have a reduced glomerular filtration rate and develop hypertension by the age of 18 [29, 30]. Hypertension occurs because a low nephron number leads to a maladaptive glomerular hyperfiltration [25, 26]. Congenital or acquired nephron deficiency reduces filtration surface area, thus reducing filtered load and renal excretory capacity [27, 31]. Ultimately, this shifts the pressure-natriuretic curve to the right and requires a higher arterial pressure to maintain proper sodium balance over time [25, 26].

There is a strong association between low nephron number and hypertension in humans [25–27]. Patients with primary hypertension have been demonstrated to have significantly fewer nephrons when compared to match control subjects [28, 32]. Australian Aboriginal population has a low nephron number and has been

extensively studied [33, 34]. This unique human population has a high prevalence of hypertension and chronic kidney disease [34]. There is still debate as to whether hypertension is the cause or the consequence of nephron deficiency. The contribution for nephron deficiency to a progressive decline in glomerular filtration rate and onset of hypertension is not clear. In line with decreased nephron number contributing to the hypertension, there are data from adult kidney donors. Normotensive adult kidney donors had a 5 mmHg greater increase in arterial pressure 5–10 years following donation compared to age-matched individuals with two intact kidneys [35, 36]. Although a small increase, this significantly increases the risk for cardiovascular diseases. Renal compensatory growth in congenital or acquired low nephron number could be a factor that leads to hypertension-induced kidney damage [25, 26]. The kidney compensates for low nephron number by increasing the glomerular filtration carried out by each glomerulus or the single nephron glomerular filtration rate [25, 27, 31]. This compensation results in the rightward shift in the pressure-natriuretic relationship and eventually leads to extracellular fluid volume expansion. To overcome this increase in extracellular volume, there is an increase in arterial pressure. Increases in arterial pressure in a setting of low nephron number have a feed forward effect of increasing glomerular capillary pressure and promoting hyperfiltration to the point where single nephron glomerular filtration rate can no longer be increased [25, 27]. The increase in glomerular capillary pressure results in glomerulosclerosis and further nephron loss and progression to chronic kidney disease [25, 27]. Human studies support this scenario because there is an inverse association between nephron number and glomerulosclerosis and intimal thickening of interlobular arteries [29, 37]. Therefore, renal adaptation in response to nephron deficiency increases the risk for developing hypertension and chronic kidney disease.

The podocyte and filtration barrier appears to be a critical component with glomerular hypertension and low nephron number in hypertension-induced chronic kidney disease [22, 38]. Podocyte density or insufficiency has been demonstrated to be a contributor to the rapid progression of diabetic nephropathy in Pima Indians [39]. Glomerular hyperfiltration associated with hypertension and low nephron number damages the glomerular filtration barrier [22]. Damage to the glomerular filtration barrier causes proteinuria and podocyte effacement [22, 38]. Podocytes respond to injurious stimuli in different ways including gradual simplification of the interdigitating process pattern until the cell flattens and lengthens [22, 38]. Podocyte injury progresses and the podocytes will detach from the basal membrane or undergo apoptosis [38]. Other factors such as an increased renin-angiotensin system and oxidative stress associated with hypertension can accelerate podocyte hypertrophy and apoptosis [22, 38]. This podocyte injury leads to passage of tubular-derived products into the interstitium and peritubular capillary spaces to accelerate tubulointerstitial injury and renal fibrosis [22, 38].

Progression of renal injury in hypertension can vary widely across animal models and human populations [14, 25]. The increase in blood pressure can cause renal structural adaptations that contribute to chronic kidney disease [14, 22]. These include vascular structural adaptations and responses to increases in glomerular

capillary pressure [22–24]. Another factor is nephron number and if nephron deficiency is congenital or acquired [25–27]. Other mechanisms responsible for susceptibility to hypertension-induced renal injury include the complex interaction between an elevated blood pressure, altered hormonal and paracrine factors, inflammation, and underlying endothelial function and renal diseases [14–16]. The contributions for endothelial function, renin-angiotensin system, oxidative stress, and inflammation to hypertension-induced progression of chronic kidney disease will be discussed in subsequent sections.

## 26.3 Endothelial Dysfunction

Endothelial cells are at an interface between circulating factors and organs including the kidney. The endothelial layer contributes importantly to vascular function and is critically involved in the control of vasomotor tone and permeability [40, 41]. It has become readily apparent that changes in the endothelial cells during diseases can be predictive of long-term health [14–16]. During the course of hypertension, there are changes in endothelial cells to a point where dysfunction occurs [14, 15]. Endothelial dysfunction is a precursor and predictor for chronic kidney disease as well as cardiovascular morbidity and mortality [15, 40].

Endothelial cells produce important autocrine and paracrine factors and respond to changes in circulating hormonal factors and cellular components such as inflammatory cells [40]. Major factors that vasodilate blood vessels and promote endothelial cell health include nitric oxide, prostacyclin, and epoxyeicosatrienoic acids (EETs) [40]. Generation of these endothelial factors tends to be decreased in disease states that result in endothelial dysfunction [15, 40]. On the other hand, endothelial cells generate or regulate vasoconstrictor factors such as thromboxane, angiotensin II, and endothelin-1. Endothelial dysfunction in hypertension is associated with elevated levels of these vasoconstrictor endothelial factors [15, 40]. Lastly, reactive oxygen species and oxidative stress contribute significantly to endothelial dysfunction in hypertension [42]. Endothelial cell nitric oxide synthase (eNOS) uncoupling and NADPH oxidase activity result in increased reactive oxygen species generation and oxidative stress [42]. Hypertension causes endothelial dysfunction by tilting the balance of the various endothelial cell factors (Fig. 26.3) [14, 40, 42].

Endothelial dysfunction in hypertension leads to renal vasoconstriction and vascular damage [14, 16, 43]. The capillary system in the renal medulla becomes damaged in hypertension [43]. Renal medulla hypoxia occurs with hypertension and endothelial damage resulting in vascular rarefaction of the capillaries [15, 43, 44]. Reduced nitric oxide synthesis by endothelial cells is a key event underlying damage to kidney arteries, arterioles, and capillaries [45, 46]. This reduced nitric oxide bioavailability can enhance the progression of chronic kidney disease in hypertension [43, 46].

Nitric oxide signaling is impaired in spontaneously hypertensive rats (SHR) and deoxycorticosterone (DOCA)-salt hypertensive rodents and is linked to renal injury [47, 48]. Factors that contribute to impaired nitric oxide signaling include decreased

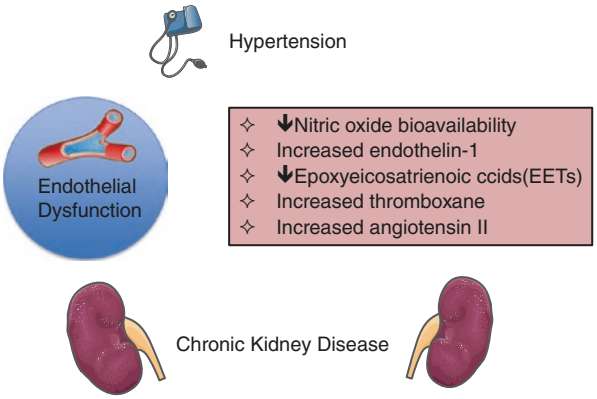



**Fig. 26.3** Endothelial dysfunction is an early event that precedes cardiovascular events and end-organ damage in hypertension. Generation of endothelial nitric oxide and epoxyeicosatrienoic acids (EETs) are decreased in hypertension. Endothelin-1, angiotensin II, and thromboxane generation are increased and contribute to endothelial dysfunction. Chronic kidney disease progression is accelerated in the presence of endothelial dysfunction

L-arginine bioavailability, decrease in cofactors required for nitric oxide synthesis, and increased production of superoxide [42, 43]. Nitric oxide production could be decreased due to inappropriate phosphorylation of eNOS to decrease enzymatic activity [49]. Endothelial cell oxidative stress during hypertension has been connected with renal damage [43, 47]. An increase in reactive oxygen species production and decreased antioxidant defense capacity predispose tissues to damage [43, 47]. Overall, there is strong evidence for decreased nitric oxide and increased oxidative stress that contributes to endothelial dysfunction and the progression of chronic kidney disease.

Decreased cyclooxygenase (COX) generation of prostacyclin ($PGI_2$) and epoxygenase generation of EETs by endothelial cells also contribute to renal vasoconstriction and endothelial dysfunction in hypertension [50, 51]. Decreased EET levels are a key factor early in the progression of endothelial dysfunction in hypertension [50, 52]. Angiotensin II hypertension is associated with an increased renal vascular expression of soluble epoxide hydrolase (sEH) enzyme that degrades EETs and results in decreased EET levels [52]. Likewise, sEH inhibition has been demonstrated to increase renal vascular EET levels, decrease blood pressure, and prevent hypertensive kidney injury [52–54]. Inflammatory responses are another factor critically involved in endothelial dysfunction [55, 56]. Endothelial cell upregulation of adhesion molecules, chemokine generation, and production of plasminogen activator inhibitor-1 occur in hypertension [57]. Elevated circulating IL-6 and TNF-α levels are key inflammatory factors leading to endothelial dysfunction and chronic kidney disease progression in hypertension [58–60]. Recent efforts have focused on increasing EETs and decreasing inflammation as a means to improve endothelial function in hypertension and prevent renal injury [61].

Vasoconstrictor factors also influence endothelial function in hypertension and the progression of kidney disease. Endothelin-1 (ET-1) is generated by endothelial

cells and is a potent renal vasoconstrictor [55, 62, 63]. Renal ET-1 levels are increased in hypertension and can contribute to arteriolar remodeling [62, 63]. Increased oxidative stress results from increased ET-1 levels [64–66]. ET-1 can also increase TGF-β that contributes to renal vascular inflammation and fibrosis in hypertension [62, 67]. Elevated angiotensin II levels contribute to endothelial dysfunction and renal damage in hypertension [14, 63, 68]. Angiotensin II causes renal vasoconstriction, increases oxidative stress and inflammation in endothelial cells, and results in vascular remodeling [42, 69]. An endothelial and vascular factor linked to angiotensin II is 20-hydroxyeicosatetraenoic acid (20-HETE). 20-HETE is a renal vasoconstrictor with pro-inflammatory actions. Endothelial cell angiotensin converting enzyme activity is increased by 20-HETE and contributes to angiotensin-dependent hypertension [70]. 20-HETE has also been associated with chronic kidney disease [50, 71, 72]. Taken together, there is strong evidence that increased endothelial cell 20-HETE, angiotensin II, and ET-1 in hypertension participate in endothelial dysfunction and chronic kidney disease.

## 26.4 Renin-Angiotensin-Aldosterone System

An inappropriate activation of the renin-angiotensin-aldosterone system (RAAS) contributes not only to hypertension but also to the progression of chronic kidney disease to ESRD (Fig. 26.4) [73, 74]. Angiotensin II has numerous hormonal actions that alter cardiovascular and renal function. Synthesis of angiotensin II depends on the release of renin by the juxtaglomerular cells in the kidney [73]. The hydrostatic pressure at the level of the afferent arterioles, angiotensin II levels, and salt delivery to the macula densa cells regulates renin release [20]. Angiotensinogen is converted to angiotensin I by renin. ACE then converts angiotensin I to angiotensin II at the level of endothelial cells and cell membranes in the heart, brain, and kidney [20, 73]. Angiotensin II has biological actions on the renal arterioles and epithelial cells that are mediated via the angiotensin type 1 (AT1) or angiotensin type 2 (AT2) receptors [20, 72]. AT1 receptors are responsible for the majority of the actions attributed to angiotensin II. Angiotensin II AT1 receptor activation mediates renal hemodynamic actions, endocrine actions, and mitogenic effects in the kidney [73]. AT2 receptors in the kidney can oppose the AT1 receptor activities [73]. Hypertension is accompanied by an inappropriate AT1 receptor activation that results in deleterious events and renal damage [72, 73].

Renal hemodynamic actions of angiotensin II are due to actions on the afferent and efferent arterioles [20]. Angiotensin II causes vasoconstriction of afferent and efferent arterioles leading to a reduction in renal blood flow and an elevated glomerular capillary in hypertension [20]. Increased intrarenal angiotensin II levels in hypertension enhance preglomerular arteriolar and tubuloglomerular feedback sensitivity [74, 75]. These angiotensin actions in hypertension increase renal vascular resistance, increase glomerular capillary pressure, and shift the pressure-natriuretic curve to the right [15, 76]. Angiotensin II also stimulates aldosterone secretion that causes a further shift in the pressure-natriuretic curve [15, 74, 76]. The renal

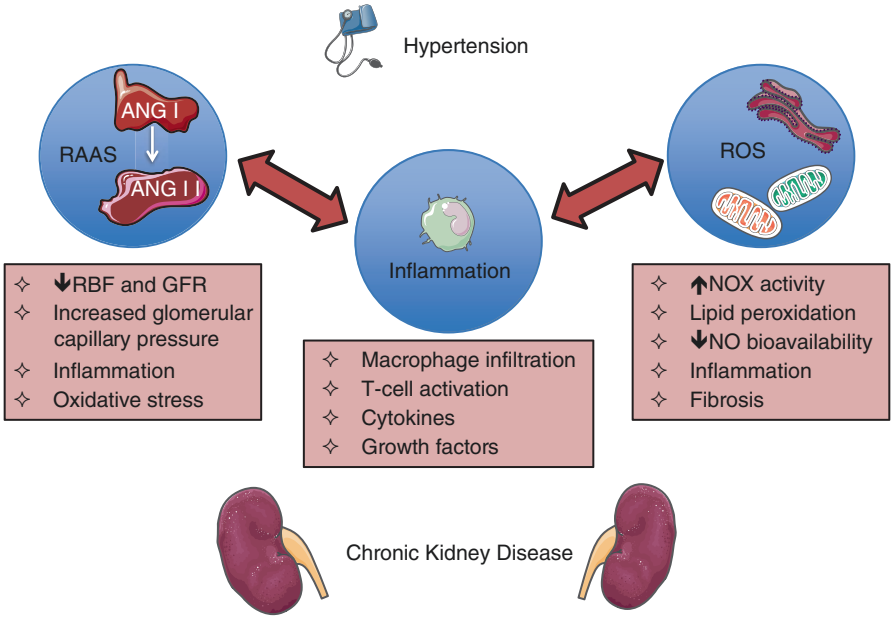



**Fig. 26.4** Hormonal and paracrine factors contribute to hypertension-induced chronic kidney disease. Elevated renin-angiotensin-aldosterone system (RAAS) leads to decreased renal blood flow (RBF) and glomerular filtration rate (GFR), inflammation, and oxidative stress. Inflammation involves macrophage infiltration and T-cell activation with generation of cytokines and growth factors. Reactive oxygen species (ROS) increases NADPH oxidase (NOX) activity, decreases nitric oxide (NO) bioavailability, and causes lipid peroxidation and inflammation. There are extensive interactions between RAAS, inflammation, and ROS that contribute to hypertension-induced chronic kidney disease

hemodynamic actions of angiotensin II are not the only actions contributing to hypertension-induced chronic kidney damage.

Angiotensin II has potent inflammatory actions that contribute to the pathogenesis of chronic kidney disease [72, 73]. Immune and inflammatory responses in renal endothelial and epithelial cells are intensified by angiotensin II [58, 59, 77, 78]. Chemotaxis, proliferation, and differentiation of monocytes into macrophages are stimulated by angiotensin II [59, 78]. Angiotensin II stimulation of pro-fibrotic cytokines and growth factors have detrimental effects on the kidney [59, 74]. Activation of TGF-β causes hypertrophy and proliferation of mesangial cells [59, 79]. TGF-β upregulates type 1 procollagen, plasminogen activator inhibitor-1, and fibronectin [59, 79]. Increases in growth factors such as TGF-β, VEGF, and IGF cause proliferation of fibroblasts and increase extracellular matrix protein synthesis as well as by decreasing apoptosis of resident interstitial cells leading to glomerulosclerosis and renal interstitial fibrosis [14, 59, 79]. Likewise, aldosterone potentiates TGF-β mitogenic activity and exerts pro-inflammatory and pro-fibrotic actions [55, 59]. Consequently, an elevated RAAS in hypertension makes a critical contribution to renal fibrosis and glomerulosclerosis.

In addition to and linked to the inflammatory actions, angiotensin II stimulates ET-1 generation and increases oxidative stress [67, 80]. Angiotensin II via AT1 receptors is a potent stimulator of NADPH oxidase and increases ET-1 generation in renal arterioles [67, 68, 80]. ET-1 is a factor that in the kidney recruits T cells and macrophages and increases NF-kB in activated B cells [59, 67, 77, 78]. Increases in reactive oxygen species lead to additional renal injury that enhances inflammation and fibrosis [43, 47]. Angiotensin II actions in hypertension include inflammation, accumulation of cells and matrix, and exacerbation by increased cell adhesion to result in renal injury [73, 74]. Glomerulosclerosis and tubulointerstitial fibrosis in response to an elevated RAAS create a progressive course of chronic kidney disease, proteinuria, decline in glomerular filtration rate, and a vicious cycle of continuous RAAS activation [73, 74].

RAAS inhibition is a common and effective treatment for hypertension. Evidence in humans suggests that blockade of the RAAS provides renal protection beyond blood pressure lowering in hypertension [6, 81, 82]. RAAS blockade reduces urinary protein and overall renal risk to a greater degree than other blood pressure-lowering therapies [81, 82]. This additional renal protection could be in part due to the anti-inflammatory actions demonstrated for RAAS inhibitors [73, 82, 83]. RAAS inhibition reduces renal cell proliferation, circulating T cells, and cytokine production [56, 84, 85]. The renin inhibitor, aliskiren, markedly reduces TGF-β, albuminuria, and renal fibrosis in hypertensive mice independently of a change in blood pressure [14, 16]. On the other hand, AT2 receptor activation could combat hypertension-induced chronic kidney disease [73]. AT2 receptor activation reduces renal inflammation in a mouse model of renal fibrosis [72, 73]. Taken together, RAAS inhibition appears to be a therapeutic approach that can combat progressive kidney disease in hypertension by mechanisms independent of blood pressure lowering.

## 26.5 Reactive Oxygen Species

Oxidative stress and the generation of reactive oxygen species are due to an imbalance between oxidants and antioxidants that can result in kidney damage (Fig. 26.4) [42, 86, 87]. Patients with mild to moderate renal insufficiency or ESRD have oxidative stress [14, 16, 88]. Elevated reactive oxygen species production has been shown in humans with renovascular, essential, and malignant hypertension [14, 16]. Increased plasma malondialdehyde levels, a marker of oxidative stress, are increased in patients with chronic renal failure when compared to those with essential hypertension despite similar blood pressures suggesting that inflammation and an altered redox state could be the reason for the increase in oxidative stress [16, 88].

Hypertension and chronic kidney disease have increased levels of oxidant molecules including hydrogen peroxide or hydroxyl radicals and decreased antioxidants like catalase, glutathione dismutase, or superoxide dismutase [42, 43, 87]. Asymmetric dimethylarginine, a nitric oxide synthase inhibitor, is increased in chronic kidney

disease [86, 87]. These changes result in reactive oxygen species generation by the arterioles, macula densa, podocytes, and epithelial cells [86, 87]. NADPH oxidase (NOX) has surfaced as the main source for reactive oxygen species in renal arterioles [87]. Vasoactive agents such as angiotensin II, shear stress, and inflammation can induce NOX or mitochondrial reactive oxygen species generation [87]. Reactive oxygen species have renal vascular actions to cause afferent arteriolar constriction, reduce nitric oxide levels, and contribute to hypertension and kidney injury [87, 89].

Indeed, elevated reactive oxygen species production by NOX and hypertension is closely associated with kidney damage as shown in different models of hypertension Dahl salt-sensitive rats, deoxycorticosterone acetate (DOCA) salt rats, and angiotensin II hypertensive rats [90, 91]. In regard to a prominent role of oxidative stress in hypertensive kidney injury, it is important to note that NOX-mediated reactive oxygen species production in hypertension is linked to endoplasmic reticulum (ER) stress. Accumulating evidence shows that during ER stress, reactive oxygen species production by NOX is increased [92, 93]. It is also demonstrated that in a setting of ER stress, reactive oxygen species are produced by NOX2 and NOX4 and play a critical role in hypertension [94]. Indeed, hypertension has been recently linked to ER stress, and there is accumulating evidence that ER stress is an important factor in hypertensive kidney injury [95–97]. The role of NOX-mediating ER stress in the above models of hypertensive renal injury remains to be explored, but a role of NOX2 has been shown to be associated with ERstress-induced renal cell death [98]. These findings provide a link between oxidative stress and ER stress in hypertensive renal injury.

Interactions between oxidative stress, renal vascular function, and inflammation are contributing factors to kidney disease progression in hypertension. Excess reactive oxygen species leads to oxidative stress and predisposes the kidney to tissue damage [14, 42, 43]. Reactive oxygen species enzyme activation in renal arterioles results in redox signaling to generate inflammation transcription factors [86, 87]. A subsequent decrease in nitric oxide bioavailability leads to lipid peroxidation and production of growth factors to induce renal fibrosis [42, 87]. Reactive oxygen species also promote accumulation of myofibroblasts via epithelial-mesenchymal transition of proximal tubular and mesangial cells [99]. This results in remodeling of the extracellular matrix of the tubulointerstitium leading to renal fibrosis, a common feature of hypertensive renal injury [99]. In addition to direct actions to constrict the afferent arteriole, reactive oxygen species can enhance tubuloglomerular feedback responses to further increase renal vascular resistance [87]. Endothelial cell generation of COX-derived thromboxane increases in response to elevations in oxidative stress [87]. Thromboxane causes afferent arteriolar vasoconstriction and increases platelet activity [86, 87]. At the level of kidney epithelial transport, reactive oxygen species diminishes oxygen utilization for sodium transport [87]. Overall, increases in reactive oxygen species cause endothelial dysfunction, afferent arteriolar constriction, and renal inflammation resulting in progression of chronic kidney disease to ESRD in hypertension.

## 26.6 Inflammation

Inflammation is an important contributing aspect to endothelial dysfunction and renal injury in hypertension. In addition, there have been a number of rodent studies that have demonstrated that the adaptive immune response and renal inflammation participate in the development of hypertension [56, 59]. Multiple studies with immunosuppressive agents such as mycophenolate mofetil (MMF) and the TNF-α receptor blocker etanercept lower blood pressure and decrease renal damage [59, 100–102]. A role for T cells and B cells in hypertension and progression of kidney disease has also been examined [56, 103, 104]. Mice deficient in T and B cells demonstrate attenuated angiotensin-dependent hypertension [59, 104, 105]. Interestingly, adoptive transfer of T cells but not B cells restored the hypertensive response to angiotensin II [59, 78]. Mice lacking T and B cells also attenuated renal injury associated with angiotensin hypertension [59, 78]. MMF inhibition of T and B cell proliferation was demonstrated to lower blood pressure in Dahl salt-sensitive hypertension [106]. Other studies have determined a potential contribution for CCR5-positive cells and RANTES [59, 60, 106]. As a whole, experimental studies have supported the concept that activated T cells in the kidney and cytokine release contribute to the development of hypertension.

Cytokine activation has deleterious actions on renal vascular and tubular epithelial cells that contribute to hypertension and progression of chronic kidney disease (Fig. 26.4). Elevations in Th1 cytokines such as TNF-α and IL-6 associate with increased blood pressure [58, 59, 107]. Likewise, hypertensive patients have an upregulation of the T-cell renin-angiotensin system [77]. Glomerular epithelial and endothelial cell has an increased production of TNF-α in angiotensin hypertension [108]. TNF-α receptor antagonism decreases blood pressure and reduces renal injury in DOCA-salt, angiotensin, and autoimmune-associated hypertension [102, 107, 108]. Renal injury prevention by etanercept can be independent of blood pressure lowering. IL-6 is another cytokine that can contribute to renal inflammation, hypertension, and progressive renal damage [56, 58]. Angiotensin-dependent hypertension is attenuated in IL-6-deficient mice [58]. These findings have demonstrated that T-cell infiltration into the kidney and generation of TNF-α and IL-6 contribute to hypertension and kidney damage.

MCP-1 and activation of CCR2 receptor can contribute to hypertension and chronic kidney disease. The MCP-1 inhibitor bindarit decreases renal inflammation and fibrosis and improves renal endothelial function independent of blood pressure lowering [109]. CCR2 inhibition also decreases renal inflammation and delays the progression of angiotensin hypertension [107]. The inflammatory cytokine IL-17 produced by Th17m CD8+ cells, neutrophils, and T cells also contributes to hypertension [110]. Angiotensin-dependent hypertension and renal inflammation are decreased in IL-17-deficient mice (110). Finally, Tregs are another cell type that influences blood pressure control and progressive renal injury in hypertension [59, 60]. Tregs reduce T-cell activation and are protective in hypertension. Dahl salt-sensitive hypertensive rats that harbor Brown Norway chromosome 2 have increased Treg cells and increased generation of the cytokine IL-10 to reduce blood pressure

and decrease renal injury [60]. Taken together, T-cell activation of pro-inflammatory cytokines contributes to hypertension and kidney disease progression that can be opposed by Tregs that limit T-cell activation.

The actions of renal inflammatory cytokines on the renal vascular and epithelial cells contribute significantly to kidney disease associated with hypertension. Renal hemodynamic consequences for elevated kidney cytokines are a reduced renal blood flow and rightward shift of the pressure-natriuretic relationship [56, 111]. Although the contribution for specific cytokines has been difficult to determine, renal inflammation decreases renal blood flow and glomerular filtration rate and leads to a progressive decline that results in ESRD [56]. One cytokine that could contribute to impaired renal hemodynamics is MCP-1 and CCR2 receptors. CCR2 receptor inhibition improves renal hemodynamics in hypertension [107]. TNF-α that is administered acutely can lower renal blood flow and glomerular filtration rate [112]. TGF-β is a growth factor that impairs afferent arteriolar autoregulatory responses [113]. The impaired afferent arteriolar autoregulatory responses have been attributed to TGF-β stimulation of reactive oxygen species [113]. IL cytokines also have renal vascular actions. IL-2 has been demonstrated to decrease glomerular filtration rate when given to patient [114]. Overall, these findings demonstrate that cytokines and inflammation can have detrimental actions on renal hemodynamics that contribute to the progression of chronic kidney disease in hypertension.

Glomerular and interstitial macrophage infiltrations are characteristic to progressive chronic kidney disease in hypertension [14–16]. Glomerular hypertension and increased angiotensin II can stimulate renal inflammation [14–16]. Cytokines and chemokines including MCP-1 and VEGF have direct actions on renal tubular and glomerular cells [56]. Macrophage infiltration increases production of IL-1, TNF-α, and MCP-1 contributing to the progressive renal injury [115, 116]. All glomerular cell types such as podocytes, mesangial cells, and endothelial cells contribute to the progression of glomerular injury in hypertension [56]. VEGF has been demonstrated to be increased in podocytes and contributes to the development of glomerular sclerosis [56, 117]. IL-1, RANTES, MCP-1, and TGF-β are activated at the level of mesangial cells to result in mesangial cell proliferation [117, 118]. Mesangial cells fibroblast phenotype then secretes extracellular matrix and further contributes to glomerular sclerosis in hypertension [117, 119, 120]. Endothelin-1, TGF-β, and PDGF increase in glomerular endothelial cells in response to increased shear stress in hypertension [117, 121]. Glomerular endothelial cell activation can also increase TNF-α and MCP-1 to increase inflammatory cell infiltration [122, 123]. Endothelial cell inflammation can result in microthrombi, hyaline deposition, and destruction of the glomerular basement membrane in hypertension [117, 124]. Renal inflammation also is involved in tubulointerstitial damage in hypertension. Interstitial infiltration of inflammatory cells occurs in the early phases of kidney disease associated with hypertension [117, 124, 125]. Macrophages and T and B cells and their migration to the interstitium in hypertension are driven by tubular expression of chemokines and adhesion molecules [124, 125]. Thus, inflammation and cytokines contribute significantly to progressive glomerular and tubulointerstitial injury in hypertension.

**Conclusion**

Renal damage and progression to ESRD in hypertension is due to the interaction of complex mechanisms. Factors such as blood pressure, elevated glomerular pressure, and low nephron number can accelerate renal damage in hypertension. Although blood pressure is a contributing factor to hypertensive renal damage, other mechanisms act independent of blood pressure.Endothelial dysfunction and altered regulation of endothelial-derived factors contribute to chronic kidney disease progression. A central role for the RAAS in hypertensive renal damage has been demonstrated, and pharmacological RAAS blockade is an extremely valuable approach to decrease progressive kidney disease in hypertension. There is also a complex interaction between the RAAS, reactive oxygen species, and inflammation that accelerate renal damage in hypertension. A deeper understanding of the molecular mechanisms that contribute to chronic kidney disease in hypertension will identify novel therapeutic targets to prevent renal damage in hypertension.

**Acknowledgments** This work is supported by the Dr. Ralph and Marian Falk Medical Research Trust Bank of America, N.A., Trustee grant and National Institute of Health (NIH) grant (DK103616) to John D. Imig and Research and a Starter Grant from PhRMA Foundation USA to Md. A.H. Khan.



## References

1. Schoenborn C (2009) Health characteristics of adults aged 55 years and over: United States, 2004–2007. Natl Health Stat Report 16:1–31
2. U.S. Renal Data System (2009) USRDS 2009 annual data report: Atlas of chronic kidney disease and end-stage renal disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda
3. Appel LJ (2010) Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med 363:918–929
4. Agodoa LY, Appel L, Bakris GL et al (2001) Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA 6:2719–2728
5. Tocci G, Volpe M (2011) End-organ protection in patients with hypertension: focus on the role of angiotensin receptor blockers on renal function. Drugs 71:1003–1017
6. Arici M (2009) Dual blockade of the renin-angiotensin system for cardio-renal protection: an update. Am J Kidney Dis 53:332–345
7. Klag MJ, Whelton PK, Randall BL et al (1996) Blood pressure and end-stage renal disease in men. N Engl J Med 334:13–18
8. Bakris GL (1996) Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. Kidney Int 50:1641–1650
9. Chobanian AV (2003) Joint committee on prevention, definition, evaluation and treatment of high blood pressure. Hypertension 42:1206–1256
10. Kaplan NM (2005) Treatment of hypertension: drug therapy. In: Kaplan NM, Flynn JT (eds) Clinical hypertension, 9th edn. Lippincott Williams & Wilkins, Philadelphia, pp 217–230
11. Acosta JH (1982) Hypertension in chronic renal disease. Kidney Int 22:702–712

12. Segura J, Campo C, Gil P et al (2004) Development of chronic kidney disease and cardiovascular prognosis in essential hypertensive patients. J Am Soc Nephrol 15:1616–1622
13. Olson JL (2007) Renal disease caused by hypertension. In: Jennette JC, Olson JL, Schwartz MM, Silva FG (eds) Heptinstall's pathology of the kidney, 6th edn. Lippincott Williams & Wilkins, Philadelphia, pp 937–988
14. Morgado E, Neves PL (2012) Hypertension and chronic kidney disease: cause and consequence—therapeutic considerations. In: Babaei H, editor. antihypertensive drugs. InTech. doi: 10.5772/36916.
15. Bidani AK, Griffin KA (2004) Pathophysiology of hypertensive renal damage: implications for therapy. Hypertension 44:595–601
16. Udani S, Lazich I, Bakris GL (2011) Epidemiology of hypertensive kidney disease. Nat Rev Nephrol 7:11–21
17. Romagnani P, Remuzzi G (2013) Renal progenitors in non-diabetic and diabetic nephropathies. Trends Endocrinol Metab 24:13–20
18. Cushman WC, Evans GW, Byington RP et al (2010) Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 362:1575–1585
19. Atkins RC, Briganti EM, Lewis JB et al (2005) Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. Am J Kidney Dis 45:281–287
20. Navar LG, Inscho EW, Majid DSA et al (1996) Paracrine regulation of the renal microcirculation. Physiol Rev 76:425–536
21. Hemmelgarn BR, Manns BJ, Lloyd A et al (2010) Relation between kidney function, proteinuria, and adverse outcomes. JAMA 303:423–429
22. Shankland SJ (2006) The podocyte's response to injury: role in proteinuria and glomerulosclerosis. Kidney Int 69:2131–2147
23. Folkow B, Gothberg G, Lundin S, Ricksten SE (1977) Structural "resetting" of the renal vascular bed in spontaneously hypertensive rats (SHR). Acta Physiol Scand 100:270–272
24. Campese VM (1991) Abnormal renal hemodynamics in black salt-sensitive patients with hypertension. Hypertension 18:805–812
25. Fong D, Denton KM, Moritz KM et al (2014) Compensatory responses to nephron deficiency: adaptive or aladaptive? Nephrology (Carlton) 19:119–128
26. Bertram JF, Douglas-Denton RN, Diouf B et al (2011) Human nephron number: implications for health and disease. Pediatr Nephrol 26:1529–1533
27. Luyckx VA, Brenner BM (2010) The clinical importance of nephron mass. J Am Soc Nephrol 21:898–910
28. Brenner BM, Garcia DL, Anderson S (1988) Glomeruli and blood pressure. Less of one, more the other? Am J Hypertens 1:335–347
29. Puelles VG, Hoy WE, Hughson MD et al (2011) Glomerular number and size variability and risk for kidney disease. Curr Opin Nephrol Hypertens 20:7–15
30. Schreuder MF, Langemeijer ME, Bokenkamp A et al (2008) Hypertension and microalbuminuria in children with congenital solitary kidneys. J Paediatr Child Health 44:363–368
31. Brenner BM, Lawler EV, Mackenzie HS (1996) The hyperfiltration theory: a paradigm shift in nephrology. Kidney Int 49:1774–1777
32. Keller G, Zimmer G, Mall G et al (2003) Nephron number in patients with primary hypertension. N Engl J Med 348:101–108
33. Hoy WE, Wang Z, VanBuynder P et al (2001) The natural history of renal disease in Australian aborigines: part 1. Changes in albuminuria and glomerular filtration rate over time. Kidney Int 60:243–248
34. Hoy WE, Wang Z, VanBuynder P et al (2001) The natural history of renal disease in Australian aborigines: part 2. Albuminuria predicts natural death and renal failure. Kidney Int 60:249–256
35. Abdi R, Slakey D, Kittur D et al (1998) Baseline glomerular size as a predictor of function in human renal transplantation. Transplantation 66:329–333
36. Sommerer C, Morath C, Andrassy J, Zeier M (2004) The long-term consequences of living-related or unrelated kidney donation. Nephrol Dial Transplant 19(Suppl 4):iv45–iv47

37. Manalich R, Reyes L, Herrera M et al (2000) Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. Kidney Int 58:770–773
38. Pavenstädt H, Kriz W, Kretzler M (2003) Cell biology of the glomerular podocyte. Physiol Rev 83:253–307
39. Lemley KV (2003) A basis for accelerated progression of diabetic nephropathy in pima Indians. Kidney Int Suppl 63:S38–S42
40. Luscher TF, Barton M (1997) Biology of the endothelium. Clin Cardiol 20(11 Suppl 2):II3–II10
41. Ignarro LJ (1999) Nitric oxide: a unique endogenous signaling molecule in vascular biology. Biosci Rep 19:51–71
42. Griendling KK, Sorescu D, Ushio-Fukai M (2000) NAD(P)H oxidase: role in cardiovascular biology and disease. Circ Res 86:494–501
43. Agarwal R (2004) Chronic kidney disease is associated with oxidative stress independent of hypertension. Clin Nephrol 61:377–383
44. Johnson RJ, Lanaspa MA, Gabriela Sánchez-Lozada L, Rodriguez-Iturbe B (2015) The discovery of hypertension: evolving views on the role of the kidneys, and current hot topics. Am J Physiol Renal Physiol 308:F167–F178
45. Vaziri ND (1997) Altered nitric oxide metabolism and increased oxygen free radical activity in lead-induced hypertension: effect of lazaroid therapy. Kidney Int 52:1042–1046
46. Vaziri ND (2002) Enhanced nitric oxide inactivation and protein nitration by reactive oxygen species in renal insufficiency. Hypertension 39:135–141
47. Tian N (2008) NADPH oxidase contributes to renal damage and dysfunction in Dahl salt-sensitive hypertension. Am J Physiol Regul Integr Comp Physiol 295:R1858–R1865
48. Hirata Y, Hayakawa H, Kakoki M et al (1996) Nitric oxide release from kidneys of hypertensive rats treated with imidapril. Hypertension 27:672–678
49. Fulton D, Gratton JP, Sessa WC (2001) Post-translational control of endothelial nitric oxide synthase: why isn't calcium/calmodulin enough? J Pharmacol Exp Ther 299:818–824
50. Roman RJ (2002) P-450 metabolites of arachidonic acid in the control of cardiovascular function. Physiol Rev 82:131–185
51. Imig JD, Falck JR, Wei S, Capdevila JH (2001) Epoxygenase metabolites contribute to nitric oxide-independent afferent arteriolar vasodilation in response to bradykinin. J Vasc Res 38: 247–255
52. Zhao X, Pollock DM, Inscho EW et al (2003) Decreased renal cytochrome P450 2C enzymes and impaired vasodilation are associated with angiotensin salt-sensitive hypertension. Hypertension 41:709–714
53. Imig JD, Zhao X, Zaharis CZ et al (2005) An orally active epoxide hydrolase inhibitor lowers blood pressure and provides renal protection in salt-sensitive hypertension. Hypertension 46:975–981
54. Imig JD, Zhao X, Capdevila JH et al (2002) Soluble epoxide hydrolase inhibition lowers arterial blood pressure in angiotensin II hypertension. Hypertension 39:690–694
55. Luft FC (2002) Proinflammatory effects of angiotensin II and endothelin: targets for progression of cardiovascular and renal diseases. Curr Opin Nephrol Hypertens 11:59–66
56. Imig JD, Ryan MJ (2013) Immune and inflammatory role in renal disease. Compr Physiol 3: 957–976
57. Imig JD, Inscho EW (2002) Adaptations of the renal microcirculation to hypertension. Microcirculation 9:315–328
58. Brands MW, Banes-Berceli AK, Inscho EW et al (2010) Interleukin 6 knockout prevents angiotensin II hypertension: role of renal vasoconstriction and janus kinase 2/signal transducer and activator of transcription 3 activation. Hypertension 56:879–884
59. Harrison DG, Guzik TJ, Lob HE et al (2011) Inflammation, immunity, and hypertension. Hypertension 57:132–140
60. Viel EC, Lemarie CA, Benkirane K et al (2010) Immune regulation and vascular inflammation in genetic hypertension. Am J Physiol Heart Circ Physiol 298:H938–H944

61. Imig JD (2012) Epoxides and soluble epoxide hydrolase in cardiovascular physiology. Physiol Rev 92:101–130
62. Ammarguellat F, Larouche I, Schiffrin EL (2001) Myocardial fibrosis in DOCA-salt hypertensive rats: effect of endothelin ET(a) receptor antagonism. Circulation 103:319–324
63. Ergul S, Parish DC, Puett D, Ergul A (1996) Racial differences in plasma endothelin-1 concentrations in individuals with essential hypertension. Hypertension 28:652–655
64. Wedgwood S, Dettman RW, Black SM (2001) ET-1 stimulates pulmonary arterial smooth muscle cell proliferation via induction of reactive oxygen species. Am J Physiol Lung Cell Mol Physiol 281:L1058–L1067
65. Elmarakby AA, Loomis ED, Pollock JS, Pollock DM (2005) NADPH oxidase inhibition attenuates oxidative stress but not hypertension produced by chronic ET-1. Hypertension 45:283–287
66. Elmarakby AA, Loomis DE, Pollock JS, Pollock DM (2004) ETA receptor blockade attenuates hypertension and decreases reactive oxygen species in ETB receptor-deficient rats. J Cardiovasc Pharmacol 44:S7–S10
67. Pollock DM (2000) Renal endothelin in hypertension. Curr Opin Nephrol Hypertens 9:157–164
68. Rajagopalan S, Kurz S, Munzel T et al (1996) Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. J Clin Invest 97:1916–1923
69. Kawada N, Imai E, Karber A et al (2002) A mouse model of angiotensin II slow pressor response: role of oxidative stress. J Am Soc Nephrol 13:2860–2868
70. Alonso-Galicia M, Maier KG, Greene AS et al (2002) Role of 20-hydroxyeicosatetraenoic acid in the renal and vasoconstrictor actions of angiotensin II. Am J Physiol Regul Integr Comp Physiol 283:R60–R68
71. Stec DE, Mattson DL, Roman RJ (1997) Inhibition of renal outer medullary 20-HETE production produces hypertension in Lewis rats. Hypertension 29:315–319
72. Pueyo ME, Gonzalez W, Nicoletti A et al (2000) Angiotensin II stimulates endothelial vascular cell adhesion molecule-1 via nuclear factor kappaB activation induced by intracellular oxidative stress. Arterioscler Thromb Vasc Biol 20:645–651
73. Ruster C, Wolf G (2006) Renin-angiotensin-aldosterone system and progression of renal disease. J Am Soc Nephrol 17:2985–2991
74. Imig JD (2000) Afferent arteriolar reactivity to angiotensin II is enhanced during the early phase of angiotensin II hypertension. Am J Hypertens 13:810–818
75. de Paula RB, da Silva AA, Hall JE (2004) Aldosterone antagonism attenuates obesity-induced hypertension and glomerular hyperfiltration. Hypertension 43:41–47
76. Raij L (2005) The pathophysiologic basis for blocking the renin-angiotensin system in hypertensive patients with renal disease. Am J Hypertens 18:95S–99S
77. Coppo M, Bandinelli M, Berni A et al (2011) Ang II upregulation of the T-lymphocyte renin-angiotensin system is amplified by low-grade inflammation in human hypertension. Am J Hypertens 24:716–723
78. Guzik TJ, Hoch NE, Brown KA et al (2007) Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. J Exp Med 204:2449–2460
79. Ruiz-Ortega M, Egido J (1997) Angiotensin II modulates cell growth-related events and synthesis of matrix proteins in renal interstitial fibroblasts. Kidney Int 52:1497–1510
80. Sasser JM, Pollock JS, Pollock DM (2002) Renal endothelin in chronic angiotensin II hypertension. Am J Physiol Regul Integr Comp Physiol 283:R243–R248
81. Mann JF, Schmieder RE, McQueen M et al (2008) Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet 372:547–553
82. Pohl MA, Blumenthal S, Cordonnier DJ et al (2005) Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. J Am Soc Nephrol 16: 3027–3037

83. Campbell R (2003) Effects of combined ACE inhibitor and angiotensin II antagonist treatment in human chronic nephropathies. Kidney Int 63:1094–1103
84. Norris K, Vaughn C (2003) The role of renin-angiotensin-aldosterone system inhibition in chronic kidney disease. Expert Rev Cardiovasc Ther 1:51–63
85. Hilgers KF, Mann JF (2002) ACE inhibitors versus AT(1) receptor antagonists in patients with chronic renal disease. J Am Soc Nephrol 13:1100–1108
86. Baylis C (2012) Nitric oxide synthase derangements and hypertension in kidney disease. Curr Opin Nephrol Hypertens 21:1–6
87. Wilcox CS (2005) Oxidative stress and nitric oxide deficiency in the kidney: a critical link to hypertension? Am J Physiol Regul Integr Comp Physiol 289:R913–R935
88. Bakris GL (2003) Hypertension and nephropathy. Am J Med 115(Suppl 8A):49S–54S
89. Montezano AC, Touyz RM (2012) Molecular mechanisms of hypertension-reactive oxygen species and antioxidants: a basic science update for the clinician. Can J Cardiol 28:288–295
90. Chabrashvili T, Tojo A, Onozato ML et al (2002) Expression and cellular localization of classic NADPH oxidase subunits in the spontaneously hypertensive rat kidney. Hypertension 39:269–274
91. Montezano AC, Touyz RM (2012) Oxidative stress, Noxs, and hypertension: experimental evidence and clinical controversies. Ann Med 44:S2–S16
92. Chen K, Kirber MT, Xiao H et al (2008) Regulation of ROS signal transduction by NADPH oxidase 4 localization. J Cell Biol 181:1129–1139
93. Cullinan SB, Diehl JA (2004) PERK-dependent activation of Nrf2 contributes to redox homeostasis and cell survival following endoplasmic reticulum stress. J Biol Chem 279:20108–20117
94. Pedruzzi E, Guichard C, Ollivier V et al (2004) NAD(P)H oxidase Nox-4 mediates 7-ketocholesterol-induced endoplasmic reticulum stress and apoptosis in human aortic smooth muscle cells. Mol Cell Biol 24:10703–10717
95. Hasty AH, Harrison DG (2012) Endoplasmic reticulum stress and hypertension—a new paradigm? J Clin Invest 122:3859–3861
96. Kassan M, Galan M, Partyka M et al (2012) Endoplasmic reticulum stress is involved in cardiac damage and vascular endothelial dysfunction in hypertensive mice. Arterioscler Thromb Vasc Biol 32:1652–1661
97. Hye Khan MA, Neckár J, Manthati V et al (2013) Orally active epoxyeicosatrienoic acid analog attenuates kidney injury in hypertensive Dahl salt-sensitive rat. Hypertension 62:905–913
98. Li G, Scull C, Ozcan L, Tabas I (2010) NADPH oxidase links endoplasmic reticulum stress, oxidative stress, and PKR activation to induce apoptosis. J Cell Biol 191:1113–1125
99. Eddy AA (2000) Molecular basis of renal fibrosis. Pediatr Nephrol 15:290–301
100. Boesen EI, Williams DL, Pollock JS, Pollock DM (2010) Immunosuppression with mycophenolate mofetil attenuates the development of hypertension and albuminuria in deoxycorticosterone acetate-salt hypertensive rats. Clin Exp Pharmacol Physiol 37:1016–1022
101. Dzielak DJ (1991) Immune mechanisms in experimental and essential hypertension. Am J Phys 260:R459–R467
102. Elmarakby AA, Quigley JE, Imig JD et al (2008) TNF-alpha inhibition reduces renal injury in DOCA-salt hypertensive rats. Am J Physiol Regul Integr Comp Physiol 294:R76–R83
103. Duffield JS (2010) Macrophages and immunologic inflammation of the kidney. Semin Nephrol 30:234–254
104. De Miguel C, Das S, Lund H, Mattson DL (2010) T lymphocytes mediate hypertension and kidney damage in Dahl salt-sensitive rats. Am J Physiol Regul Integr Comp Physiol 298:R1136–R1142
105. Barhoumi T, Kasal DA, Li MW, Shbat L, Laurant P, Neves MF, Paradis P, Schiffrin EL (2011) T regulatory lymphocytes prevent angiotensin II-induced hypertension and vascular injury. Hypertension 57:469–476
106. Mattson DL, James L, Berdan EA, Meister CJ (2006) Immune suppression attenuates hypertension and renal disease in the Dahl salt-sensitive rat. Hypertension 48:149–156

107. Elmarakby AA, Quigley JE, Olearczyk JJ et al (2007) Chemokine receptor 2b inhibition provides renal protection in angiotensin II—salt hypertension. Hypertension 50:1069–1076
108. Elmarakby AA, Quigley JE, Pollock DM, Imig JD (2006) Tumor necrosis factor alpha blockade increases renal Cyp2c23 expression and slows the progression of renal damage in salt-sensitive hypertension. Hypertension 47:557–562
109. Muller DN, Shagdarsuren E, Park JK et al (2002) Immunosuppressive treatment protects against angiotensin II-induced renal damage. Am J Pathol 161:1679–1693
110. Madhur MS, Lob HE, McCann LA et al (2010) Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunction. Hypertension 55:500–507
111. Knight SF, Imig JD (2007) Obesity, insulin resistance, and renal function. Microcirculation 14:349–362
112. Shahid M, Francis J, Majid DS (2008) Tumor necrosis factor-alpha induces renal vasoconstriction as well as natriuresis in mice. Am J Physiol Renal Physiol 295:F1836–F1844
113. Sharma K, Cook A, Smith M et al (2005) TGF-beta impairs renal autoregulation via generation of ROS. Am J Physiol Renal Physiol 288:F1069–F1077
114. Shalmi CL, Dutcher JP, Feinfeld DA et al (1990) Acute renal dysfunction during interleukin-2 treatment: suggestion of an intrinsic renal lesion. J Clin Oncol 8:1839–1846
115. Holdsworth SR, Summers SA (2008) Role of mast cells in progressive renal diseases. J Am Soc Nephrol 19:2254–2261
116. Wilson HM, Walbaum D, Rees AJ (2004) Macrophages and the kidney. Curr Opin Nephrol Hypertens 13:285–290
117. Harris RC, Neilson EG (2006) Toward a unified theory of renal progression. Annu Rev Med 57:365–380
118. Taal MW, Omer SA, Nadim MK, Mackenzie HS (2000) Cellular and molecular mediators in common pathway mechanisms of chronic renal disease progression. Curr Opin Nephrol Hypertens 9:323–331
119. Floege J, Burns MW, Alpers CE et al (1992) Glomerular cell proliferation and PDGF expression precede glomerulosclerosis in the remnant kidney model. Kidney Int 41:297–309
120. Johnson RJ, Raines EW, Floege J et al (1992) Inhibition of mesangial cell proliferation and matrix expansion in glomerulonephritis in the rat by antibody to platelet-derived growth factor. J Exp Med 175:1413–1416
121. Malek AM, Greene AL, Izumo S (1993) Regulation of endothelin 1 gene by fluid shear stress is transcriptionally mediated and independent of protein kinase C and cAMP. Proc Natl Acad Sci U S A 90:5999–6003
122. Hirschberg R, Wang S (2005) Proteinuria and growth factors in the development of tubulointerstitial injury and scarring in kidney disease. Curr Opin Nephrol Hypertens 14:43–52
123. Lee LK, Meyer TW, Pollock AS, Lovett DH (1995) Endothelial cell injury initiates glomerular sclerosis in the rat remnant kidney. J Clin Invest 96:953–964
124. Noronha IL, Fujihara CK, Zatz R (2002) The inflammatory component in progressive renal disease—are interventions possible? Nephrol Dial Transplant 17:363–368
125. Sanchez-Lozada LG, Tapia E, Johnson RJ et al (2003) Glomerular hemodynamic changes associated with arteriolar lesions and tubulointerstitial inflammation. Kidney Int Suppl (86):S9–S14

# Determinants of Hypertensive Renal Disease and Its Progression

# 27

Karen A. Griffin, Aaron J Polichnowski, and Anil K. Bidani

Hypertensive kidney disease, a consequence of exposure to increased macro- or microvascular pressures, is second only to diabetic nephropathy as a primary etiology for end-stage renal disease (ESRD) accounting for ~30% of ESRD [1]. However, it needs to be emphasized that this large population risk is primarily attributable to the huge prevalence of hypertension (HTN) in the general population. The individual risk for ESRD is strikingly small in those with uncomplicated essential HTN (~0.5%) [2, 3]. And, even this risk is disproportionately distributed, with certain ethnic groups such as African-Americans, accounting for a substantial fraction of the ESRD that is ascribed to essential HTN [1–3]. The recent identification of certain genetic loci in the African-American population associated with chronic kidney disease and end-stage renal disease (ESRD) [4, 5] has led some to question whether essential HTN per se leads to ESRD in the absence of such genetic predispositions [5, 6] or the development of malignant HTN [7–9]. Fortunately, the wide availability of effective antihypertensive agents has greatly reduced the incidence of malignant HTN and its contribution to the ESRD population [8, 9]. However, such interpretations greatly underestimate the extent to which hypertension-induced renal damage (HIRD) contributes to the development of ESRD. Abundant evidence now indicates that coexistent HTN, even if moderate in severity, plays a predominant role in the progression of most other forms of chronic kidney disease (CKD) including diabetic nephropathy, indicating an enhanced renal sensitivity to the adverse effects of HTN in CKD states [8–14].

K.A. Griffin (✉) • A.J. Polichnowski • A.K. Bidani
Edward Hines Jr. VA Hospital, Hines, IL 60141, USA

Loyola University Medical Center, 2160 South First Avenue, Maywood, IL 60153, USA
e-mail: kgriffi@lumc.edu



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_27

## 27.1 Clinical Patterns of HIRD Susceptibility and Pathologic Correlates

Any increase in blood pressure (BP) within the intrarenal vasculature, if of sufficient magnitude and regardless of cause, is expected to result in barotrauma and local vascular injury as happens in malignant HTN [7, 15]. Therefore, susceptibility to HIRD needs to be defined in terms of BP threshold for HIRD and the slope of the relationship between BP and HIRD (the increase in HIRD for a given increase in BP) [8, 14]. Figure 27.1 schematically illustrates the relative resistance to HIRD in individuals with essential hypertension in the absence of genetic predisposition or malignant HTN. This is in contrast to the markedly increased susceptibility in CKD states as manifested in a greatly reduced BP threshold at which HIRD starts to develop and a steeper slope of relationship between BP and HIRD [8, 12, 14]. Given this enhanced susceptibility to even moderate hypertension and the very high prevalence of hypertension in the CKD population, the dominant role played by hypertension in CKD progression is not unexpected. Indeed, despite extensive efforts to identify additional therapeutic targets, optimal BP control and renin-angiotensin system (RAS) blockade remain the mainstays of CKD management [8, 10–14]. And, even the beneficial effects of RAS blockade are at least in large part mediated by its antihypertensive effects as discussed in a subsequent section.

These contrasting clinical patterns of HIRD susceptibility are associated with distinct histologic phenotypes and characteristic time courses. The histologic pattern of renal injury in malignant HTN is characterized by acute disruptive vascular injury and fibrinoid necrosis of the small arteries, arterioles, and glomerular capillaries that has been collectively described as malignant nephrosclerosis [7–9, 16]. Ischemic glomeruli are frequent because of the upstream vascular injury. The syndrome evolves rapidly over days and weeks resulting in acute renal failure and, despite treatment, is frequently followed by residual CKD or even ESRD. By contrast, the renal pathology in individuals with nonmalignant essential HTN progresses slowly over decades and consists of thickening, hypertrophy, and hyaline arteriosclerosis of the renal resistance vessels with focal global ischemic glomerular obscelence, a pattern that has historically been termed benign nephrosclerosis [8, 9, 16]. In contrast to these predominantly vascular sites of renal pathology in benign

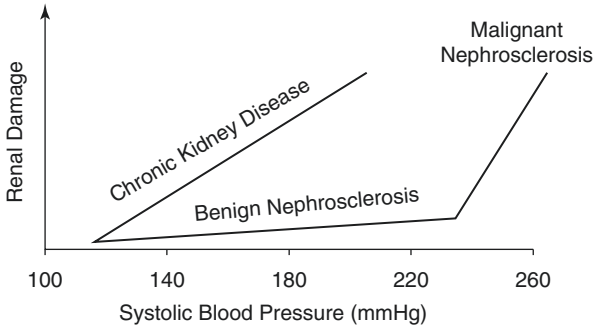



**Fig. 27.1** The differing BP thresholds and slopes of the relationship between BP and renal damage in patients with uncomplicated hypertension (benign and malignant nephrosclerosis) and those with diabetic and nondiabetic CKD (Reproduced from Ref. [8] with permission)

and malignant nephrosclerosis, the site of HIRD in CKD states is predominantly glomerular, with a pattern of accelerated segmental or global glomerulosclerosis (GS) often superimposed on the intrinsic phenotype of the underlying disease [8, 9, 12, 14]. Progression to ESRD usually occurs over months to years. As discussed in the following section, investigations in experimental models have indicated that these contrasting clinicopathologic patterns of HIRD stem from differences in underlying pathophysiology and pathogenesis. The use of BP radiotelemetry to define ambient 24 h BP phenotypes for the assessment of quantitative relationships between BP and HIRD combined with renal hemodynamic measurements has been critical to the achievement of these insights.

## 27.2 Pathophysiology of HIRD: Insights from Animal Models

Given that the pathogenesis of HIRD critically depends on local vascular exposure to increased pressures, it is important to note that unlike cardiovascular end points, which reflect macrovascular events and their consequences (stroke, myocardial infarction, heart failure), renal end points (ESRD, doubling of serum creatinine) primarily reflect microvascular pathology (loss of glomerular capillaries and/or filtration capacity) [8, 9, 14]. Unlike macrovascular pressures which fluctuate in parallel with BP, increases in BP, episodic or sustained, within the renal autoregulatory range lead to proportionate preglomerular autoregulatory vasoconstriction such that renal blood flow (RBF), GFR, and glomerular capillary pressures ($P_{GC}$) remain relatively stable (Fig. 27.2, pattern A) [8, 17–19]. The vast majority of patients with essential HTN have preserved renal autoregulation (AR). Therefore, as long as BP remains within the autoregulatory range and renal autoregulation is intact, glomerular HTN does not develop, and significant proteinuria and glomerular injury are not seen. But, the preglomerular vasculature exposed to HTN does develop the slowly progressive vascular pathology of benign nephrosclerosis [8, 9, 14, 16–18]. The glomerular capillary and nephron loss that occurs over time are usually not sufficient to result in a major impairment of renal function. But, if the BP elevations become so severe as to exceed the autoregulatory range, acute disruptive vascular and glomerular injury (malignant nephrosclerosis) develops with proteinuria, hematuria, and renal failure [7–9, 14]. The spontaneously hypertensive rat (SHR) and its stroke-prone counterpart ($SHR_{sp}$) provide the experimental illustrations for this phenomenon. Both have intact autoregulation, but the salt-supplemented $SHR_{sp}$ develops more severe HTN that exceeds the BP threshold for disruptive vascular injury resulting in stroke and malignant nephrosclerosis [14, 17, 18, 20–22]. Moreover, even suboptimal antihypertensive therapy prevents malignant nephrosclerosis as long as BP is prevented from exceeding the critical threshold [21, 22]. Even after malignant nephrosclerosis has developed, relatively modest BP reductions result in substantial repair and recovery [22] emphasizing the barotrauma-mediated pathogenesis of this syndrome. With chronic hypertension, the autoregulatory range is shifted to the right and serves to protect against malignant HTN [8, 17]. Thus, severe acute increases in BP have greater potential for such target organ injury than slower

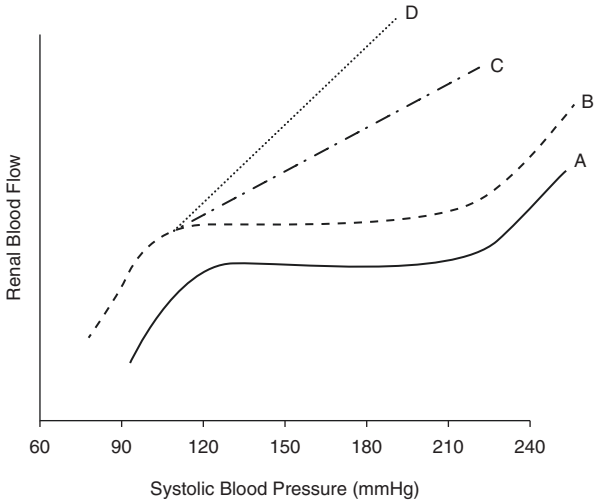



**Fig. 27.2** Illustration of the spectrum of pressure/flow relationships in the renal vascular bed in hypertension. *Pattern A* represents the normal renal autoregulatory responses observed in uncomplicated hypertension and shows the constancy of renal blood flow (RBF) despite BP changes within the autoregulatory range. *Pattern B* indicates the ambient renal vasodilation but preserved autoregulation after uninephrectomy. *Pattern C* illustrates the impaired RBF autoregulatory responses observed in the 5/6 renal ablation model. *Pattern D* shows the complete loss of renal autoregulation in 5/6 renal-ablated rats treated with dihydropyridine CCBs. Although RBF is depicted as the dependent variable, the same relationships are expected for glomerular pressures, given that the autoregulatory resistance changes are confined to the preglomerular vasculature (Reproduced from Ref. [8] with permission)

increases. Conversely, when renal AR is impaired as it is inrenal mass reduction (RMR) models of CKD [23, 24] (Fig. 27.2, pattern C), even modest BP increases are expected to be transmitted to the glomerular capillaries with resultant barotrauma, proteinuria, progressive GS, and a greatly reduced BP threshold at which hypertensive GS starts to develop, similar to the pattern observed in CKD states [8, 14, 17, 18, 25]. Thus, in CKD states, the severity of HIRD depends not on the extent of increase in systemic BP per se but rather on the degree to which such increases are transmitted to the renal microvasculature [8, 12, 14, 17].

In this context, it is important to note that the hypertensive 5/6 renal ablation model was initially employed to replicate the phenomenon of progressive injury to initially normal remnant nephrons believed to underlie the autonomous progression of human CKD [14, 23, 25–27]. Based on micropuncture studies, the concept was formulated by Brenner and colleagues that glomerular hyperfiltration, a compensatory adaptation in response to a reduction in functional nephron number irrespective of cause, was in fact per se "maladaptive" [26–28]. It was postulated that "the elevated single nephron glomerular filtration rate (SNGFR) common to these pathophysiologic conditions is usually caused by increases in the glomerular capillary plasma flow rate ($Q_A$) and mean glomerular capillary hydraulic pressure ($P_{GC}$), which in turn are due to adaptive reductions in pre-glomerular and post-glomerular

arteriolar resistances" and "that—systemic hypertension is not required for glomerular capillary hyperfiltration and hypertension." Similar hyperfiltration, increased $P_{GC}$, and GS were described in experimental diabetes [28]. The increases in $P_{GC}$ were ascribed to the greater dilation of the afferent than efferent arteriole. This relative efferent vasoconstriction was attributed to the tonic vasoconstrictor effects of angiotensin II (Ang II), because angiotensin-converting enzyme (ACE) inhibitors were shown to dilate the efferent arteriole, reduce $P_{GC}$, and ameliorate glomerulosclerosis [27, 28]. Studies from our laboratory have questioned the concept that glomerular hyperfiltration per se is intrinsically injurious in the absence of glomerular HTN or that glomerular HTN is necessary for hyperfiltration [14, 29]. Hyperfiltration in normotensive models of RMR, pregnancy, and kidney donors is accomplished without significant $P_{GC}$ increases through coordinated increases in glomerular filtration surface area (hypertrophy) and increases in single-nephron plasma flow through proportionate afferent and efferent vasodilation [14, 29–33]. In fact, increases in $P_{GC}$ are not even very effective in increasing SNGFR due to the inverse relationship between $P_{GC}$ and the ultrafiltration coefficient K*f* [14, 29]. We have therefore interpreted the glomerular HTN in hypertensive RMR models to be a superimposed consequence of an enhanced glomerular transmission of coexistent systemic HTN through a dilated and poorly autoregulating preglomerular vasculature [8, 12, 14, 18, 23]. We have suggested that the contribution of angiotensin II-mediated efferent constriction to glomerular HTN in these models has likely been greatly overestimated during micropuncture studies due to renin release and efferent constriction triggered by anesthesia, surgery, and neurohormonal activation [8, 12, 14, 29, 34].

The importance of renal autoregulatory capacity as a determinant of HIRD susceptibility is further demonstrated by the adverse effects of calcium channel blockers (CCB), particularly the dihydropyridine CCBs in the 5/6 ablation model of CKD [8, 14, 35]. Given that pressure-induced vascular wall stretch, depolarization, activation of voltage-gated $Ca^{2+}$ channels, and $Ca^{2+}$ entry are involved in activation of the myogenic mechanism, CCBs predictably impair renal autoregulation [17–19]. Although the mechanisms responsible for the impaired renal autoregulation in CKD models remain obscure [8, 14, 17–19], CCBs cause a further impairment of renal autoregulation (Fig. 27.2, pattern D), reduce the BP threshold for GS, and increase the slope of the relationship between BP and GS such that greater GS are observed in CCB-treated animals at any given level of HTN as compared to untreated controls (Fig. 27.3). Note that these qualitative relationships between BP and GS are unaltered in 5/6 ablated rats treated with RAS blockade indicating the BP dependence of the renoprotection provided by RAS blockade [12, 14, 34–36]. Conversely, substitution of a low (8%)-protein diet for the standard 24% protein diet preserves autoregulatory capacity after 5/6 renal ablation and substantially ameliorates GS despite continued HTN [23, 37]. However, if the low-protein-fed rats are also given CCBs, the protection against renal autoregulatory impairment and GS is both abolished [37]. Recent studies have further emphasized the protective importance of the myogenic component of renal autoregulation [14, 17, 18]. The rapid activation kinetics of the afferent arteriolar myogenic response and its potential triggering by the systolic rather than

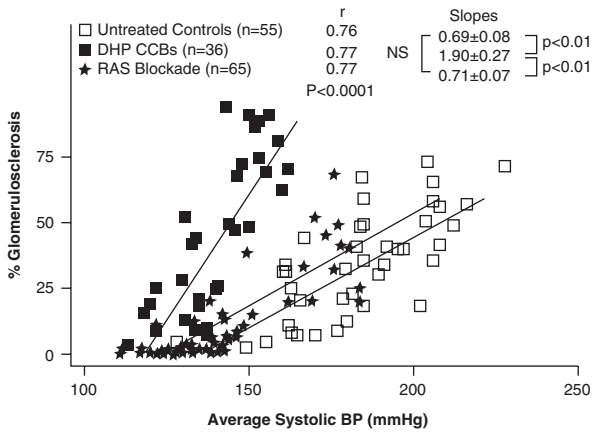



**Fig. 27.3** Compilation of data obtained in our laboratory which illustrate the quantitative relationships between BP and glomerulosclerosis (GS) in rats with 5/6 renal ablation who were left untreated or received either calcium channel blockers or RAS blockade. The deleterious effects of calcium channel blockers on GS as compared to untreated or RAS blockade-treated rats are evident (Reproduced from Ref. [12, 14] with permission)

the mean BP are consistent with this protective function, given that systolic BP may have the greatest potential for target organ damage. It is also important to note that BP is fundamentally labile and exhibits spontaneous, rapid, and often large BP fluctuations even in normotensive individuals [17, 38]. Such fluctuations are prevented from reaching the glomerular capillary by the normal preglomerular autoregulatory responses. Therefore, in states of impaired renal autoregulation, glomerular pressure exposure may not be normalized even if normotension is achieved and modest glomerular barotrauma may continue to occur [14, 39].

In this context, it needs to be emphasized that these adverse effects of impaired renal autoregulation on HIRD susceptibility only occur in a vasodilated vascular bed. Vasodilation alone, with preserved autoregulation such as observed after uninephrectomy [24], only modestly increases the susceptibility to hypertensive injury (Fig. 27.2, pattern B). However, when combined with impaired AR, it substantially amplifies the effects on HIRD susceptibility [8]. Conversely, preglomerular vasoconstriction is expected to protect against glomerular BP transmission and reduce HIRD severity but may also reduce the capacity to maintain renal perfusion when BP falls [8]. Although somewhat counterintuitive, the Ang II infusion models of HTN provide a fairly dramatic illustration of this phenomenon. Despite severe HTN and a plethora of postulated Ang II-mediated BP-independent mechanisms of injury [11, 40], Ang II infusions produce surprisingly little renal damage [41]. Recent studies in conscious Ang II-infused rats have indicated that this limited renal injury is a consequence of Ang II-induced vasoconstriction, potentiation of myogenic responses, and attenuation of intrarenal BP transmission [41]. Figure 27.4 using data from the $SHR_{sp}$ model of malignant nephrosclerosis, the 5/6 ablation model of CKD, and the angiotensin II infusion model of severe HTN but limited HIRD provide an illustrative summary of these insights and emphasizes the critical importance of physical BP transmission in the pathogenesis of HIRD.

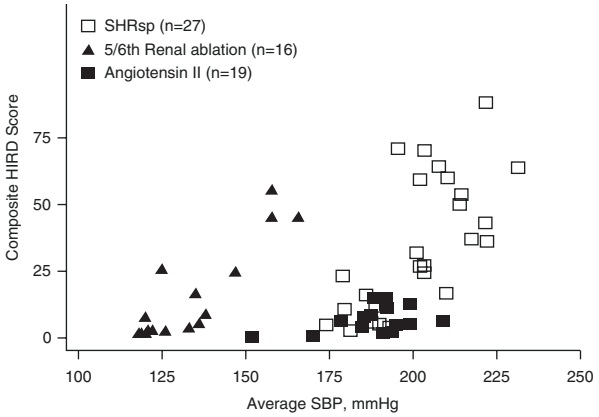



**Fig. 27.4** Compilation of data obtained in our laboratory which depicts the qualitative relationships between SBP and HIRD in three commonly employed rodent models: (1) the salt-supplemented stroke-prone spontaneously hypertensive rat ($SHR_{sp}$) model of malignant HTN, (2) the hypertensive 5/6 renal ablation model of CKD in Sprague-Dawley rats, and (3) the continuous exogenous angiotensin infusion model of HTN (300–500 ng/kg/min for 4 weeks). These data illustrate the differences in the BP threshold for HIRD and/or the slope of the relationship between average systolic BPs (final 4 weeks) and HIRD (increase in HIRD/mmHg increase in average systolic BP) between the three models. The $SHR_{sp}$ exhibits intact renal autoregulation, and a strong correlation between BP and HIRD is only observed after 4 weeks of salt supplementation when BP exceeds the critical renal autoregulatory threshold ($r^2 = 0.46$, slope 1.13 ± 0.24; $p < 0.0001$). The rats with 5/6 renal ablation and impaired renal autoregulation display a similar strong correlation between average systolic BP and HIRD ($r^2 = 0.77$, slope 1.03 ± 0.15; $p < 0.0001$) but exhibit a much lower BP threshold for HIRD consistent with the enhanced renal microvascular BP transmission [25]. By contrast, the rats with Ang II-induced HTN exhibit very limited HIRD despite average systolic BP that are high as the $SHR_{sp}$ with a much weaker correlation and a flatter slope ($r^2 = 0.27$, slope 0.28 ± 0.11; $p < 0.025$). As discussed in the text, this paucity of HIRD is most plausibly due to the angiotensin II-induced renal vasoconstriction and potentiation of myogenic autoregulation that reduces BP transmission to the renal microvasculature [41] (Adapted with permission from the cited references)

## 27.3 Other Major Postulated Modulators of HIRD Progression

Over the years, a large number of factors/mechanisms have been proposed to modulate and promote HIRD through BP-independent pathways. A detailed discussion of these is beyond the scope of this chapter, so only a few major ones are briefly addressed here.

1. *Renin-angiotensin system (RAS)*: It is widely believed that RAS plays a predominant role in CKD progression, and therefore, its blockade is recommended as a primary strategy to retard CKD progression [8–14]. Although RAS activation and/or its inadequate suppression despite volume expansion are critical to the pathogenesis of HTN in human and experimental CKD, it is the BP-independent mechanisms of CKD progression that have received the greater emphasis [8–12,

14, 40–42]. However, the evidence for such pathways is much less definitive than claimed [13, 14, 42]. The fact that RAS activation by a low-salt diet in vivo does not activate the deleterious pathways initiated by angiotensin II in in vitro systems indicates a context-appropriate regulation of these signaling pathways in vivo [42]. And, given that many of the deleterious downstream pathways can also be activated by HTN, much of the in vivo evidence of BP independence is compromised by the limitations of the tail-cuff BP measurements that have been used to support such interpretations [42, 43]. When direct BP radiotelemetry has been employed, little evidence of BP-independent effects has been found (Fig. 27.3) [21, 34, 36]. The apparent discrepancy between such experimental data and clinical trial results is addressed in a subsequent section.

2. *Endothelial dysfunction and NO availability*: Although less emphasized, substantial evidence indicates that endothelial dysfunction and reduced NO availability have important adverse effects on HIRD [44]. The two pathways that may be particularly relevant are (a) the increased severity of hypertension in states of impaired NO generation and (b) the local hemodynamic effects of NO on the renal microvasculature. There is topographic evidence of significant expression of nitric oxide synthases 1 and 3 in the efferent arteriolar endothelial cells [45]. It has been suggested that these cells may act as shear stress sensors with the released NO serving an important efferent arteriolar vasodilatory protective function in states of glomerular HTN [45, 46]. An impairment of efferent arteriolar NO production may thereby promote exaggerated $P_{GC}$ elevations in such states [46].
3. *Glomerular capillary hypertrophy and reduced podocyte density*: The compensatory hypertrophy of glomerular capillaries results in a reduction of podocyte density due to the limited replication potential of this terminally differentiated cell [47]. It has been proposed that the resultant loss of structural support may limit the ability of glomerular capillaries to maintain physical integrity and mechanical stability during hypertensive stress [47, 48]. An increase in wall tension (Laplace law: tension = pressure x radius) may also add to the hypertensive stress [30].

## 27.4 Clinical Parallels and Correlates

The validity of these concepts/insights derived from animal models has generally been borne out by the clinical data [49]. To illustrate, an impairment of GFR autoregulation similar to that observed in renal mass reduction models of CKD has been observed in patients with diabetic and nondiabetic nephropathies [50, 51]. Similarly, as would be predicted from the experimental data, substantially greater success has been achieved clinically with antihypertensive therapy in preventing malignant nephrosclerosis than in slowing CKD progression [8, 9, 14, 22]. Moreover, the adverse impact of BP on proteinuria has been recently shown to increase with progressive reduction in GFR in humans as would be predicted by the data from RMR models [52]. The benefits from a lower BP target in patients with proteinuric renal

disease and the lesser effectiveness of CCBs in preventing CKD progression in such patients are also consistent with the experimental data [8, 12, 14, 53–58]. Given that an absence of proteinuria implies a pathogenesis that is less dependent on glomerular HTN, the lack of demonstrable benefits of lower BP targets in non-proteinuric CKD is in agreement with these insights [39, 53–57]. However, the recently released results of the SPRINT trial may render most such distinctions moot [59]. Although CKD patients with the greatest risk of progression (proteinuria >1gm) were unfortunately excluded from the trial precluding a direct demonstration of the renal benefits of lower BP targets (<120 mmHg systolic), the significant cardiovascular and mortality benefits observed support a general implementation of lower targets in all individuals at increased CV risk including CKD patients. However, these benefits need to be weighed against the significantly increased risks for hypotension, syncope, electrolyte abnormalities, and acute renal failure that were observed in the more intensively treated group [59]. Even though the incidence of an adverse composite renal outcome was low (1.1%) and not more frequent in the intensive treatment group in participants with CKD at baseline, definitive judgements may need to await the release of additional detailed data from the SPRINT trial regarding kidney function and CKD progression. Meanwhile, it may be prudent to take into consideration the risk/benefit ratios in individual patients when selecting BP targets. It is also worth noting that the BP measurement protocol used in SPRINT that included 5 min of rest before BP measurements likely yielded systolic BP values that may be ~5–10 mmHg lower than that obtained during routine office practice [59, 60].

A major apparent discrepancy does exist with respect to BP-independent benefits of RAS blockade seen in clinical trials but not in experimental models when BP radiotelemetry is used (Fig. 27.3). However, the discrepancy is more apparent than real as the clinical trial evidence is more ambiguous and the magnitude of BP-independent benefits is likely much smaller than claimed [8, 12, 14, 61]. To illustrate, the original interpretation of the landmark trial of captopril in diabetic nephropathy conducted by the Collaborative Study Group [62] might have been seriously compromised by the disproportionately greater randomization of the nephrotic patients at the highest risk of renal end points into the placebo group [8, 12, 14, 61, 62]. This likely accounted for most of the excess of end points observed for the placebo group compared with the captopril group. Likewise, other such clinical trials are confounded either by a 2–6 mmHg lower-systolic BP in the RAS blockade groups or the use of dihydropyridine CCBs with their adverse effects on glomerular BP transmission in the comparator groups [8, 12, 14, 61–67]. The post hoc statistical adjustments for BP differences between RAS blockade and comparator arms are substantially limited by the potential for effect modifications given that the small BP differences are more likely to have larger impact in the more susceptible individuals who are expected to be the primary contributors to the end points in these trials [55, 61]. Moreover, small differences in clinical BP, which are often not controlled for time of day and/or timing relative to drug dosing, may reflect larger differences in nocturnal BP [61, 68].

The claims of class-specific BP-independent protection by RAS blockade have been further weakened by the results of several clinical trials that have employed

dual RAS blockade so as to achieve more complete RAS blockade in at-risk populations. In addition to the once widely acclaimed results of cooperate study having been discredited and withdrawn [69], the other more recent clinical trials of dual RAS blockade (ONTARGET, ALTITUDE, and VA NEPHRON D) have also failed to show greater benefits than monoblockade. Moreover, a greater risk of serious adverse effects was noted (hyperkalemia, acute renal failure) [70–72], as is also true for the addition of a mineralocorticoid antagonist to RAS blockade [73]. Collectively, such data indicate that the guidelines for RAS blockade use should be similar to that for other antihypertensive agents with the titration of BP effects being balanced against the potential for adverse effects, rather than being targeted to surrogate markers of renoprotection.

Nevertheless, it needs to be emphasized that there are other compelling rationale for the use of RAS blockade in CKD patients. HTN in most CKD patients is primarily volume dependent with relative RAS suppression. Therefore, adequate and sustained BP reductions cannot be achieved without effective diuresis. Because effective diuresis activates RAS, combining diuretics with RAS blockade is very effective antihypertensive therapy in CKD. Additionally, RAS blockade counteracts the tendency to potassium and magnesium wasting that occurs with such diuretic use. Therefore, the antihypertensive synergy of diuretics and RAS blockade and their antagonism of each other's adverse effects make this combination an effective and logical initial antihypertensive regimen for CKD patients [8, 12, 14].

Given that glomerular BP transmission is expected to be an *around-the-clock* phenomenon and that masked daytime and/or nocturnal HTN and BP lability are both widely prevalent and more difficult to control in CKD patients [74, 75], failure to achieve 24 h BP control has likely contributed to the suboptimal results in preventing CKD progression [39]. The limitations of clinic BP measurements alone to ensure BP control are illustrated by the results of the ambulatory blood pressure monitoring (ABPM) that was performed at the end of the African American Study of Kidney Disease (AASK) trial before entry into the AASK cohort trial phase [75]. Masked HTN (elevated day or night time BP levels but controlled clinic BP) was present in 80% of the participants with CKD. Forty percent of the patients in fact demonstrated a reverse dipping pattern with a systolic BP at night that was on average ~14 mmHg higher than their clinic systolic BP. Wider use of home and ABPM is accordingly being advocated to improve renal outcomes [74, 76].

## References

1. U.S. Renal Data system (USRDS) (2012) 2012 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD
2. Klag MJ, Whelton PK, Randall BL et al (1997) End-stage renal disease in African-American and white men: 16-year MRFIT findings. JAMA 277:1293–1298
3. Hsu CY, McCulloch CE, Darbinian J et al (2005) Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. Arch Intern Med 165:923–928
4. Genovese G, Friedman DJ, Ross MD et al (2010) Association of trypanolytic apoL1 variants with kidney disease in African-Americans. Science 329:841–845

5. Freedman BI, Sedor JR (2008) Hypertenison-associated kidney disease: perhaps no more. J Am Soc Nephrol 19:2047–2051
6. Kopp JB (2013) Rethinking hypertensive kidney disease: arterionephrosclerosis as a genetic, metabolic, and inflammatory disorder. Curr Opin Nephrol Hypertens 22:266–272
7. Byrom FB (1969) The hypertensive vascular crisis: an experimental study [Heinemann monograph]. William Heinemann Medical Books, London
8. Bidani AK, Griffin KA (2004) Pathophysiology of hypertensive renal damage: implications for therapy. Hypertension 44:595–601
9. Olson JL (2007) Renal disease caused by hypertension. In: Jennette JC, Olson JL, Schwartz MM, Silva FG (eds) Heptinstall's pathology of the kidney, vol II, Sixth edn. Lippincott Williams & Wilkins, Philadelphia, pp 937–990
10. Bakris GL, Williams M, Dworkin Elliott WJ et al (2000) Preserving renal function in adults with hypertension and diabetes: a consensus approach. Am J Kidney Dis 36:646–661
11. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, de Zeeuw D, Shahinfar S, Toto R, Levey AS, for the AIPRD Study Group (2003) Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition. A patient-level meta-analysis. Ann Intern Med 139:244–252
12. Griffin KA, Bidani AK (2006) Progression of renal disease: the renoprotective specificity of renin angiotensin system blockade (invited review). Clin J Am Soc Nephrol 1:1054–1065
13. Lv J, Ehte P, Sarnak MJ et al (2013) Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ 185:949–957
14. Bidani AK, Polichnowski AJ, Loutzenhiser R, Griffin KA (2013) Renal microvascular dysfunction, hypertension and CKD progression. Curr Opin Nephrol Hypertens 22:1–9
15. Hill GS (1970) Studies on the pathogenesis of hypertensive vascular disease. Effect of high-pressure intra-arterial injections in rats. Circ Res 27:657–668
16. Bohle A, Wehrmann M, Greschniok A, Junghans R (1998) Renal morphology in essential hypertension: analysis of 1177 unselected cases. Kidney Int 54(Suppl 67):S205–S206
17. Loutzenhiser GKA, Williamson G, Bidani AK (2006) Renal autoregulation: new perspectives regarding the protective and regulatory roles of the underlying mechanisms. Am J Physiol 290:R1153–R1167
18. Bidani AK, Griffin KA, Williamson G et al (2009) Protective importance of the myogenic response in the renal circulation. Hypertension 54:393–398
19. Carlstrom M, Wilcox CS, Arendshorst WJ (2015) Renal autoregulation in health and disease. Physiol Rev 95:405–511
20. Abu-Amarah I, Bidani AK, Hacioglu R et al (2005) Differential effects of salt on renal hemodynamics and potential pressure transmission in stroke-prone and stroke-resistant spontaneously hypertensive rats. Am J Physiol Renal Physiol 289:F305–F313
21. Griffin KA, Abu-Amarah I, Picken M, Bidani AK (2003) Renoprotection by ACE inhibition or aldosterone blockade is blood pressure dependent. Hypertension 41:201–206
22. Griffin KA, Polichnowski A, Litbarg N et al (2014) Critical blood pressure threshold dependence of hypertensive injury and repair in a malignant nephrosclerosis model. Hypertension 64(4):801–807
23. Bidani AK, Schwartz MM, Lewis EJ (1987) Renal autoregulation and vulnerability to hypertensive injury in remnant kidney. Am J Physiol 252:1003–1010
24. Bidani AK, Hacioglu R, Abu-Amarah I et al (2003) 'Step' vs 'dynamic' autoregulation: implications for susceptibility to hypertensive injury. Am J Physiol 285:F113–F120
25. Bidani AK, Griffin KA, Picken M, Lansky DM (1993) Continuous telemetric blood pressure monitoring and glomerular injury in the rat remnant kidney model. Am J Physiol 265(3 Pt 2):F391–F398
26. Hostetter TH, Olson JL, Rennke HG et al (1981) Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. Am J Physiol 241:F85–F93
27. Anderson S, Rennke H, Brenner BM (1986) Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. J Clin Invest 77:1993–2000

28. Brenner BM, Lawler EV, Mackenzie HS (1996) The hyperfiltration theory: a paradigm shift in nephrology. Kidney Int 49:1774–1777
29. Griffin KA, Kramer H, Bidani AK (2008) Adverse renal consequences of obesity. Am J Physiol 94:F685–F696
30. Bidani AK, Mitchell KD, Schwartz MM et al (1990) Absence of progressive glomerular injury in a normotensive rat remnant kidney model. Kidney Int 38:28–38
31. Griffin KA, Picken MM, Churchill M et al (2000) Functional and structural correlates of glomerulosclerosis after renal mass reduction in the rat. J Am Soc Nephrol 11:497–506
32. Baylis C, Wilson CB (1989) Sex and the single kidney. Am J Kidney Dis 13:290–298
33. Lenihan CR, Busque S, Derby G et al (2015) Longitudinal study of living kidney donor glomerular dynamics after nephrectomy. J Clin Invest 125:1311–1318
34. Bidani AK, Picken MM, Bakris G, Griffin KA (2000) Lack of evidence of BP independent protection by renin-angiotensin system blockade after renal ablation. Kidney Int 57:1651–1661
35. Griffin KA, Picken MM, Bidani AK (1995) Deleterious effects of calcium channel blockade on pressure transmission and glomerular injury in rat remnant kidneys. J Clin Invest 96:793–800
36. Griffin KA, Picken M, Bidani AK (1994) Radiotelemetric BP monitoring, antihypertensives and glomeruloprotection in remnant kidney model. Kidney Int 46:1010–1018
37. Griffin KA, Picken M, Giobbie-Hurder A, Bidani AK (2003) Low protein diet mediated renoprotection in remnant kidneys: renal autoregulatory vs hypertrophic mechanisms. Kidney Int 63:607–616
38. Griffin KA, Picken MM, Bidani AK (2004) Blood pressure lability and glomerulosclerosis after normotensive 5/6 renal mass reduction in the rat. Kidney Int 65:209–218
39. Bidani AK, Griffin KA, Epstein M (2012) Hypertension and chronic kidney disease progression: why the suboptimal outcomes? Am J Med 125:1057–1062
40. Harris RC, Neilson EG (2006) Toward a unified theory of renal progression. Annu Rev Med 57:365–380
41. Polichnowski AJ, Griffin KA, Picken MM et al (2015) Hemodynamic basis for the limited renal injury in rats with angiotensin II-induced hypertension. Am J Physiol 308:F252–F260
42. Griffin KA, Bidani AK (2009) Angiotensin II type 2 receptor in chronic kidney disease: the good side of angiotensin II? (Commentary). Kidney Int 75:1006–1008
43. Kurtz TW, Griffin KA, Bidani AK et al (2005) AHA scientific statement. Recommendation for blood pressure measurements in humans and animals. Part 2: blood pressure measurements in experimental animals. Hypertension 45:299–310. (Also reprinted in: Artheroscler Thromb Vasc Biol 25(3):e22-33)
44. Baylis C (2012) Nitric oxide synthase derangements and hypertension in kidney disease. Curr Opin Nephrol Hypertens 21:1–6
45. Bachmann S, Bosse HM, Mundel P (1995) Topography of nitric oxide synthesis by localizing constitutive NO synthesis in mammalian kidney. Am J Physiol 268:F885–F898
46. Griffin K, Polichnowski A, Licea-Vargas H et al (2012) Large BP-dependent and -independent differences in susceptibility to nephropathy after nitric oxide inhibition in Sprague-Dawley rats from two major suppliers. Am J Physiol Renal Physiol 302:F173–F182
47. Fries JU, Sandstrom DJ, Meyer TW, Rennke HG (1989) Glomerular hypertrophy and epithelial cell injury modulate progressive glomerulosclerosis in the rat. Lab Investig 60:205–218
48. Kriz W, Elger M, Mundel P, Lemley KV (1995) Structure-stabilizing forces in the glomerular tuft. J Am Soc Nephrol 51:1731–1739
49. Griffin KA, Bidani AK (2004) Hypertensive renal damage: insights from animal models and clinical relevance. Curr Hypertens Rep 6(2):145–153
50. Christensen PK, Hansen HP (1997) Impaired autoregulation of GFR in hypertensive non-insulin dependent diabetic patients. Kidney Int 52:1369–1374
51. Christensen PK, Hommel EE (1999) Impaired autoregulation of the glomerular filtration rate in patients with nondiabetic nephropathy. Kidney Int 56:1517–1523
52. Fotheringham J, Odudu A, McKane W, Ellam T (2015) Modification of the relationship between blood pressure and renal albumin permeability by impaired excretory function and diabetes. Hypertension 65:510–516

53. Appel LI, Wright JT Jr., Green T et al; for the AASK Collaborative Research Group (2010) Intensive blood pressure control in hypertensive chronic kidney disease. N Engl J Med 363:918–929
54. Upadhyay A, Earley A, Haynes SM, Uhlig K (2011) Systemic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. Ann Intern Med 154:541–548
55. Bidani AK, Griffin KA (2011) Chronic kidney disease: blood pressure targets in chronic kidney disease. Nat Rev Nephrol 7(3):128–130
56. KDIGO (2012) 2012 Clinical practice guidelines for the management of blood pressure in chronic kidney disease. Kidney Int Suppl 2:337–414
57. Wright JT Jr, Bakris G, Greene T et al (2002) Effect of blood pressure and antihypertensive drug class on progression of hypertensive kidney disease. Results from AASK trial. JAMA 288:2421–2431
58. Ruggenenti P, Perna A, Loriga G et al (2005) Blood pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomized controlled trial. Lancet 365:939–946
59. The SPRINT Research Group (2015) A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 373:2103–2116
60. Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Kaczorowski J (2010) Measurements of blood pressure in the office. Recognizing the problem and proposing the solution. Hypertension 55:195–200
61. Bidani AK, Griffin KA (2006) The benefits of renin-angiotensin blockade in hypertension are dependent on blood-pressure lowering (viewpoint). Nature Clin Prac Nephrol 2:542–543
62. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD, Collaborative Study Group (1993) The effects of angiotensin converting enzyme inhibition on diabetic nephropathy. N Engl J Med 329:1456–1462
63. Hebert LA, Bain RP, Verme D et al (1994) Remission of nephrotic range proteinuria in type I diabetes. Kidney Int 46:1688–1693
64. Maschio G, Aeti D, Janin G et al (1996) The angiotensin-converting-enzyme inhibition in progressive renal insufficiency study group: effects of the angiotensin-converting-enzyme inhibition benazepril on the progression of chronic renal insufficiency. N Engl J Med 334: 939–945
65. Lewis EJ, Hunsicker LG, Clarke WR et al (2001) Renoprogressive effect of the angiotensin receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 345:851–860
66. Brenner BM, Cooper ME, de Zeeuw D et al (2001) Effect of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 345:861–869
67. Hou FF, Zhang X, Zhang GH et al (2006) Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med 354:131–140
68. Svensson P, de Faire U, Sleight P et al (2001) Comparison of the effects of Ramipril on ambulatory and office blood pressures. A HOPE substudy. Hypertension 38:E28–E32
69. Nakao N, Yoshimura A, Morita H et al (2003) Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomized controlled trial. Lancet 361:117–124
70. Mann JF, Schmieder RE, McQueen M et al; ONTARGET Investigators (2008) Renal outcomes with telmisartan, Ramipril or both in people at high vascular risk (the ONTARGET study): a multicentre, randomized, double-blind, controlled trial. Lancet 372:547–553
71. Parving HH, Brenner BM, McMurray JJ et al; ALTITUDE Investigators (2012) Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med 367:2204–2213
72. Fried LF, Emanuele N, Zhang JH et al; VA NEPHRON-D Investigators (2013) Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med 369:1892–1903
73. Juurlink DN, Mamdani MM, Lee DS et al (2004) Rates of hyperkalemia after publication of the randomized aldactone evaluation study. N Engl J Med 351:543–551
74. Agarwal R (2007) Ambulatory blood pressure and cardiovascular events in chronic kidney disease. Semin Nephrol 27:538–543

75. Pogue V, Rahman M, Lipkowitz M et al; for the African American Study of Kidney Disease (2009) Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. Hypertension 53:20–27
76. Drawz PE, Alper AB, Anderson AH et al (2016) Masked hypertension and elevated nighttime blood pressure in CKD: prevalence and association with target organ damage. Clin J Am Soc Nephrol 11:642–652

# Part VII

# Hypertension Phenotypes: Endocrine Causes

# Cushing's Syndrome and Glucocorticoid Excess

# 28

Christian A. Koch

## 28.1 Introduction

Cushing's syndrome (CS) is considered a rare disease and results from exposure to excess glucocorticoids. This chapter represents an update from previous chapters on this topic [1–5]. The most frequent form of CS is related to exogenous glucocorticoid excess triggered and caused by physicians prescribing and/or administering glucocorticoids (oral, intravenous, intranasal, transdermal, inhalation, rectal) in dosages exceeding the threshold generally accepted to be equivalent to 5–7.5 mg of prednisone. For instance, dexamethasone is a very potent glucocorticoid with a much higher affinity to the glucocorticoid receptor and a longer biological half-life than hydrocortisone (1 mg dexamethasone is equivalent to 25 mg of hydrocortisone with regard to anti-inflammatory potency). To facilitate calculating equipotent steroid doses, one could use the corticosteroid conversion calculator (http://clincalc.com/corticosteroids/). Therefore, one should consider inter- and intraindividual susceptibility to glucocorticoid receptor affinity and duration of action when prescribing glucocorticoids and assessing individuals for the presence of CS. The prevalence and incidence of endogenous CS depend on sociodemographic and ethnic factors with approximately 2–5 new cases per million of population per annum [6–8]. The annual incidence of endogenous CS can be further subdivided to 1.2–2.4 cases per million coming from pituitary causes and 0.6 cases of CS from adrenal causes [8]. As reviewed in various large series including the one from the National Institutes of Health in Bethesda, MD, USA, signs and/or symptoms in

C.A. Koch
Department of Internal Medicine, Division of Endocrinology, Diabetes and Metabolism, University of Mississippi Medical Center, Jackson, MS, 39216, USA

G.V. (Sonny) Montgomery VA Medical Center, Jackson, MS, USA

Department of Medicine, Med Klinik 3, University of Dresden, Dresden, Germany
e-mail: Christian_albert_koch@yahoo.com



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_28

**Table 28.1** Signs and symptoms of Cushing's syndrome (reproduced with permission from ref. [7], Nieman 2015)

| More common | Less common |
|---|---|
| Decreased libido | ECG abnormalities or atherosclerosis |
| Obesity or weight gain | Dorsal fat pad |
| Plethora | Edema |
| Round face | Abnormal glucose tolerance |
| Menstrual changes | Osteopenia or fracture |
| Hirsutism | Headache |
| Hypertension | Backache |
| Ecchymoses | Recurrent infections |
| Lethargy, depression | Abdominal pain |
| Striae | Acne |
| Proximal muscle weakness | Female balding |

patients with CS are not pathognomonic, although clinical sensitivity has been reported high (>80%) for weight gain, impaired short-term memory, plethora, round face, thin, and fragile skin. Specificity (>80%) is thought to be high for osteopenia/fracture, ecchymoses, proximal muscle weakness, and hypertension (Table 28.1) [7, 9, 10].

A recent observational, prospective, multicenter study including 353 patients attending endocrinology units for outpatient visits reported developing a risk score to predict CS in an at risk population which potentially helps identifying at risk patients in non-endocrinological settings (primary care). This risk score included muscular atrophy, osteoporosis, dorsocervical fat pad, and late-night (11 PM) salivary cortisol concentrations, all of which would provide an estimated area under the receiver operating characteristic curve of 0.93 with a sensitivity of 96% and specificity of 83% [11]. The authors underscore the importance of signs and symptoms of CS in the screening process rather than overly reliance on biochemical tests such as late-night salivary cortisol. This is also demonstrated by the occurrence of neuroendocrine alterations in obese patients (which can mimic CS) including elevated concentrations of adrenocorticotropic hormone (ACTH), leptin, insulin, and aldosterone and reduction of other hormones including growth hormone and testosterone [12]. Furthermore, cross-sectional analyses from a cohort of 264 obese children showed that slightly increased urinary free cortisol concentrations were measured in 31% [13]. In the pediatric age group up two 18 years of age, approximately 10% of new CS cases occur each year with 80% of cases being caused by Cushing's disease [14, 15]. Weight gain and delayed growth/short stature are frequent findings in children and adolescents [16–18]. The prevalence of hypertension in children and adolescents with endogenous CS has been reported to be up to 60% and in adults up to 80% [10, 19]. Patients with exogenous CS develop hypertension depending on the duration and dose of glucocorticoids administered which may or may not be associated with steroid-induced diabetes mellitus, depending on individual body composition and insulin resistance risk factors. Generally, about 20% of such patients are found to be hypertensive depending on the population studied [20].

## 28.2 Illustrative Case Studies

### 28.2.1 Case 1

An 18-year-old boy was referred for short stature and growth hormone deficiency. He had initially been evaluated at the age of 16 years for hypertension (treated with clonidine) and delayed growth after his mom had noticed that the patient's younger sibling surpassed his height. His bone age assessed by the standards of Greulich and Pyle was more than 2 years behind his chronologic age. His thyroid function tests had been normal. He was started on growth hormone therapy but nonresponsive when receiving 0.26 mg/kg body weight per week. His weight was approximately 53 kg and his blood pressure 140/98 mm Hg (134/89 mm Hg is approximately the 95th BP percentile reading) when clonidine therapy was tapered and amlodipine (5–10 mg daily) started. His father's height is 170 cm and his mother's 155 cm, providing a calculated midparental height of approximately 170 cm. His family history was significant for short stature in maternal great aunts who were born triplets and are all 149 cm as adults. When we evaluated him in the clinic, his voice was deep, but his total testosterone was 64 ng/dL with a free testosterone of 2.9 ng/dL, both low. His height was measured at 137.5 cm and bone age was at 16 years with chronologic age being 18 years and 8 months. He presented with clinical features of CS and partial collapse of the L1–L3 vertebral bodies (Fig. 28.1a–c). He had gynecomastia, facial plethora, buffalo hump, acne, and purple stretch marks more than 1 cm wide [21, 22].

Noon serum cortisol was elevated at 32 μg/dL, ACTH at 71 pg/mL, insulin-like growth factor-1 (IGF-1) at 215 ng/mL, 24-h urinary free cortisol at 280 μg (normal, less than 45 μg), and serum cortisol at 8 AM after 1-mg dexamethasone high at 26 μg/dL. A pituitary magnetic resonance scan showed a 5 × 3 × 3 mm hypoenhancing oval structure in the right anterior lateral pituitary suggestive of a microadenoma (Fig. 28.2).

The young man underwent transsphenoidal surgery with removal of this microadenoma and had a serum cortisol of 1.3 μg/dL with a concomitant ACTH of 1.9 pg/mL on postoperative day 1. Pathology revealed an ACTHoma (ACTH-secreting pituitary adenoma) with a Ki-67 index of less than 3% and negative p53 immunostain. Because of postoperative nausea and symptoms of adrenal insufficiency/glucocorticoid withdrawal, he received hydrocortisone 10 mg in the morning and 5 mg at 5 PM for a few weeks and was unable to taper hydrocortisone off. He developed several kidney stones postoperatively and had an elevated uric acid level for several months. Kidney stones appear to be an underrecognized clinical sign in pediatric Cushing's disease, as 19% of such patients either have radiographic evidence or a history of kidney stones [23]. Our patient's breast tissue/bilateral gynecomastia regressed, he became more energetic with growing muscle mass, and he grew approximately 4 cm on follow-up 6 months postoperatively. His IGF-1 level then increased to 261 ng/mL (normal, 104–484 ng/mL) and his total testosterone to 457 ng/dL with a free testosterone of 15 ng/dL. His weight declined to 45 kg, and

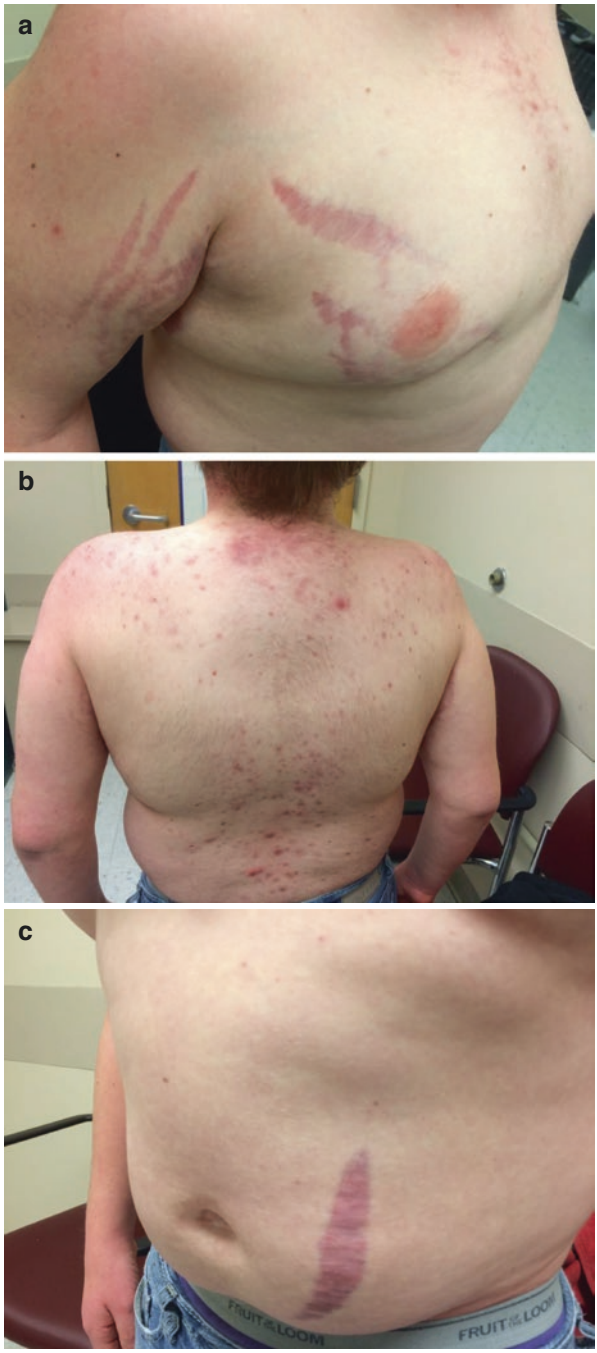



**Fig. 28.1** Clinical features of CS (**a**–**c**)

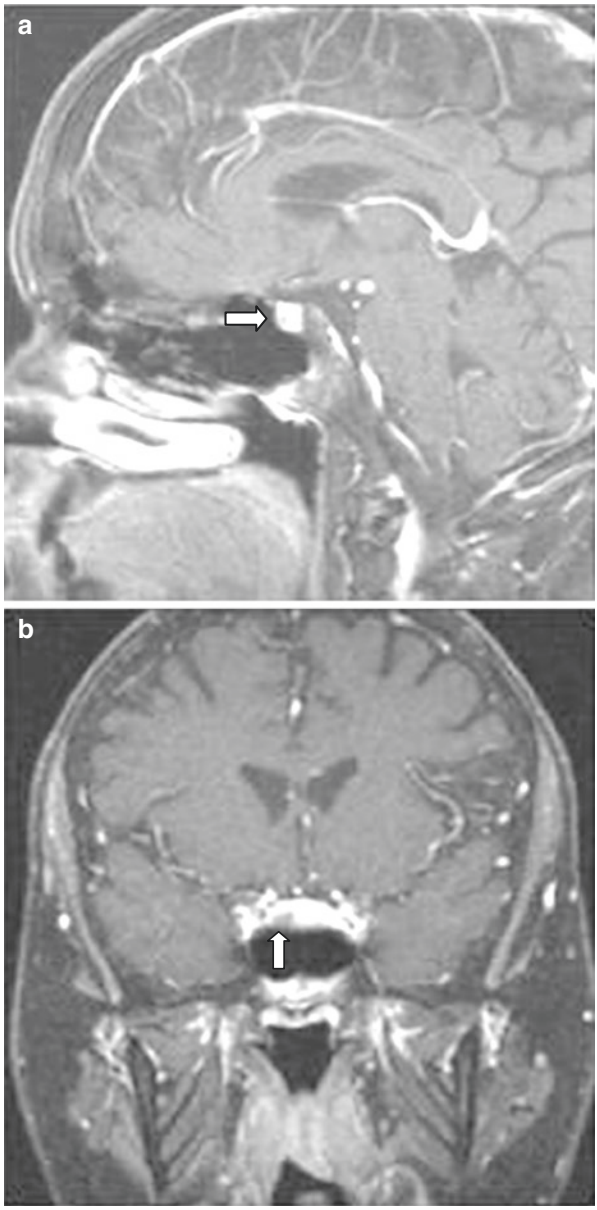



**Fig. 28.2** Pituitary MRI scan, sagittal (**a**) and coronal (**b**) view

he no longer has stretch marks or a dorsocervical fat pad. He no longer takes antihypertensives and now has a BP of 114/61 mm Hg. He continues taking hydrocortisone for now, and it is known that full recovery of the hypothalamic-pituitary-adrenal axis in children and adolescents after surgical cure of Cushing's disease can be

expected in 75% of patients by 12 months and in 95% of cases by 18 months. An ACTH stimulation test is pending [24].

### 28.2.2 Case 2

Another young man, a 19-year-old male was admitted because of inexplicable severe back pain for the last 3 months. On presentation, the young man had a plethoric moon face, red striae, and hypertension (Fig. 28.3).

He reported increased appetite, mood irritability, latent agitation, erectile dysfunction, sleep impairment, recent proximal muscle weakness of the limbs, and a 15 kg weight gain during the last 6 months. Furthermore, he experienced a reduction of his body height from 182 to 177 cm. A radiograph of the spine showed multiple osteoporotic vertebral fractures (Fig. 28.4).

Abdominal ultrasound demonstrated mild hepatomegaly and nephrocalcinosis. Laboratory evaluation showed impaired glucose tolerance, mild secondary hyperparathyroidism, and ACTH levels throughout the day and nighttime being elevated at above 26 pmol/L including peaks of 45 pmol/L (reference range, 1.98–11.4 pmol/L) with high basal serum cortisol levels up to 1367 nmol/L (reference, 187–724 nmol/L). A 24-h urinary free cortisol (UFC) (normal 22–212 nmol per day) was constantly above 1055 nmol/day. Several overnight dexamethasone suppression tests demonstrated no suppression of serum cortisol. 100 μg of corticotropin-releasing hormone (CRH) stimulated plasma ACTH to less than 30% of the basal values suggesting ectopic ACTH-dependent CS. Inferior petrosal sinus sampling (IPSS) showed no central-to-peripheral ACTH gradients, and magnetic resonance imaging (MRI) of the pituitary gland showed no abnormality. The serum level of chromogranin A (CgA) was slightly elevated, whereas neuron-specific enolase (NSE), calcitonin, and synaptophysin were within the normal reference range. Screening for other peptides showed normal levels of urinary-fractionated metanephrines and 5-hydroxyindoleacetic acid.

Extensive imaging work-up was initiated in search for a neuroendocrine tumor ectopically secreting ACTH [25–29]. A computed tomography (CT) scan of the chest showed a small lesion in the dorsal lower lobe most likely according to

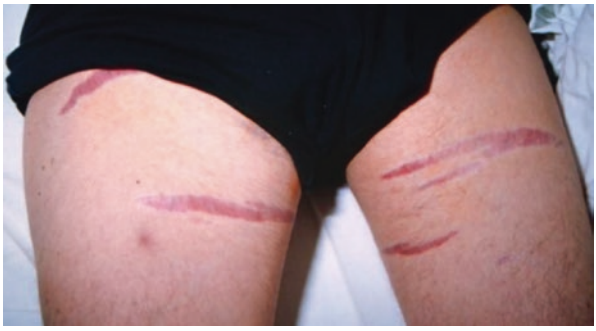


**Fig. 28.3** Purple striae at initial presentation

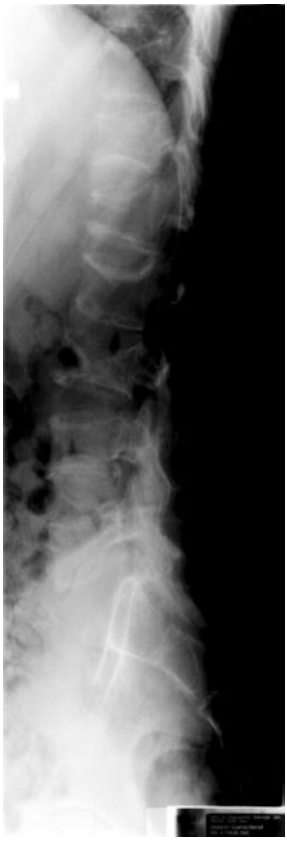


**Fig. 28.4** Radiograph of the vertebral column showing vertebral compression fractures

segment 9 and a lesion in the ventrolateral lower lobe most likely localized in segment 8; both were interpreted as nonspecific rather than possible tumor. Furthermore, a 10-mm-sized lesion in the peripheral left lower lobe close to the costodiaphragmatic recessus was revealed. However, CT-guided biopsy of the left peripheral lesion could not detect any tumor tissue. The patient underwent a whole-body scintigraphy (octreoscan). Images were obtained 4 and 24 h after injection of 170 MBq indium 111-labeled octreotide. The octreoscan yielded three spots of radiotracer enrichment in the right hilar region (Fig. 28.5a, b).

A whole-body positron emission tomography (PET) with $^{18}$F-fluorodeoxyglucose (FDG) and bronchoscopy did not show any suspicious lesions. Medical treatment was initiated in order to suppress the excessive hypercortisolism/glucocorticoid excess. A sufficient cortisol suppression was achieved through a combination of ketoconazole (600 mg/day) and metyrapone (2.5 g/day) with hydrocortisone replacement therapy (10 mg/day). Morning serum cortisol was temporarily reduced (80–300 nmol/L) and the patient improved clinically. According to Trainer and colleagues, the aim of drug therapy for CS should be to lower the mean serum cortisol through the day into the range of 150–300 nmol/L, recognizing that there is high

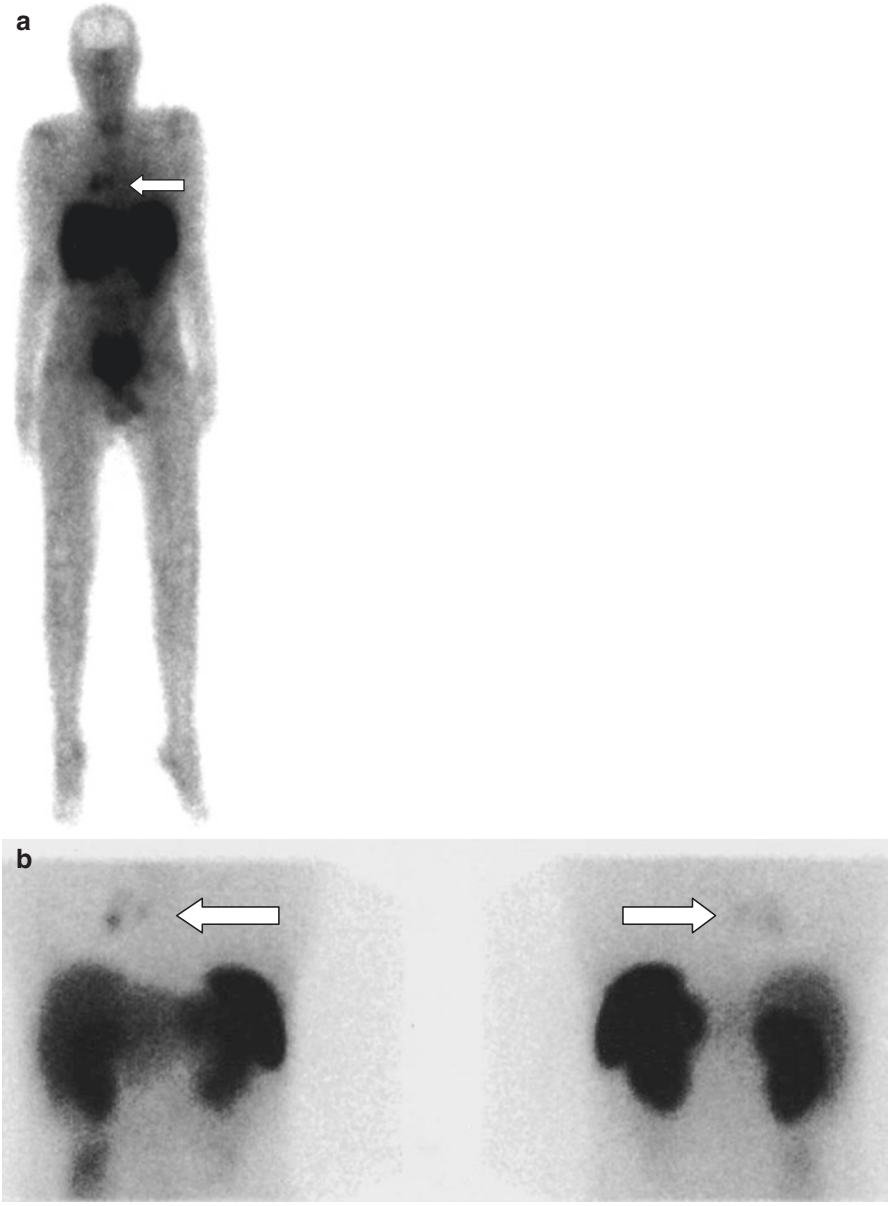



**Fig. 28.5** Whole-body scintigraphy (octreoscan) showing three hilar spots at the right lung

cross-reactivity of 11-deoxycortisol in cortisol immunoassays leading potentially to erroneously high cortisol measurements in patients treated with metyrapone [30, 31]. The latter issue can be avoided by utilizing liquid chromatography/tandem mass spectrometry in measuring cortisol. In the course of treatment of our patient,

liver enzymes became mildly elevated but returned back to normal range after dose reduction of ketoconazole. Osteoporosis treatment was initiated with cholecalciferol, calcium, and a bisphosphonate infusion. Another round of diagnostics 6 months after initial presentation included chest radiograph, thoracic and abdominal CT scans, bronchoscopy, and an octreoscan. The diagnostic findings remained largely unchanged. Thus, an exploratory thoracotomy was performed. The patient underwent localized lymph node dissection along the bronchi of the middle and lower lobe and a wedge resection of a palpable node within the dorsal right lower lobe. Histopathologic examination demonstrated intrapulmonary lymph node metastases of a low-grade neuroendocrine tumor at the right hilar region, the central middle lobe, and the right lower lobe. Immunohistochemical analysis of the metastatic tissue showed strong expression of ACTH. Postoperatively, there was no remission of hypercortisolism. Thus, medical treatment with steroidogenesis inhibitors (ketoconazole + metyrapone) was resumed. Since the primary tumor was not yet identified, further investigations were performed.

Three months after metastasis resection, a CT scan of the chest showed the same lesion in the ventrolateral right lower lobe already revealed by preoperative CT scan. Additionally, a new dorsal lesion in the lower lobe measuring 20 mm in maximal diameter could be identified (Fig. 28.6). An octreoscan confirmed the ventrolateral lesion in the lower lobe (Figs. 28.7 and 28.8) and demonstrated again two right-sided hilar focuses (Figs. 28.9 and 28.10). An FDG-PET scan showed multiple lesions with high glucose accumulation in the dorsal right lower lobe, the right middle lobe, and a focal tracer uptake in the right hilar region (Fig. 28.11).

In accordance with these findings, a right lower bilobectomy was performed, supposing that the primary tumor would be located within the right lower or middle lobe. Radical lymph node dissection was undertaken. Histological examination

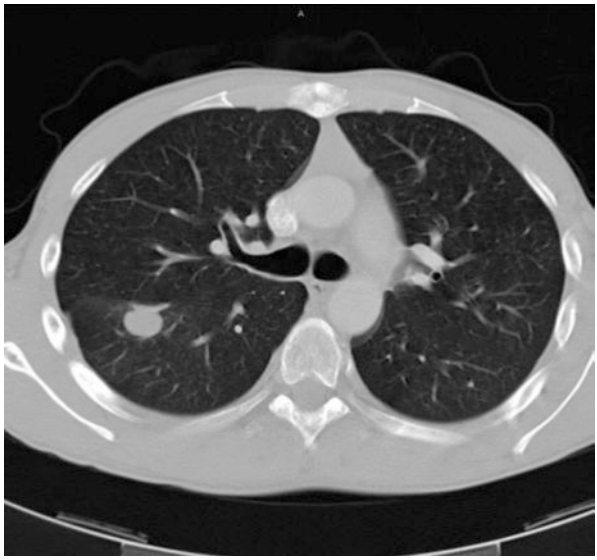


**Fig. 28.6** CT scan of the chest: intrapulmonary 2-cm lesion in the dorsal lower lobe

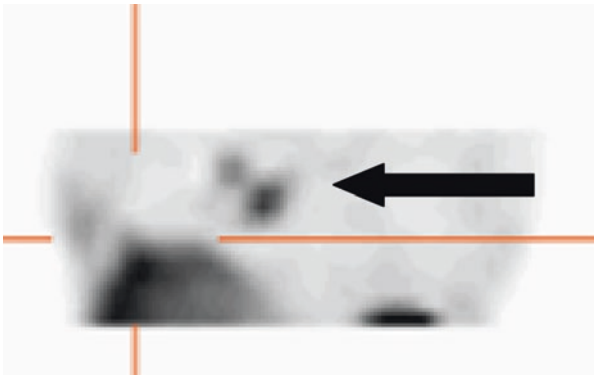


**Fig. 28.7** Octreoscan showing ventrolateral pulmonary tracer enrichment

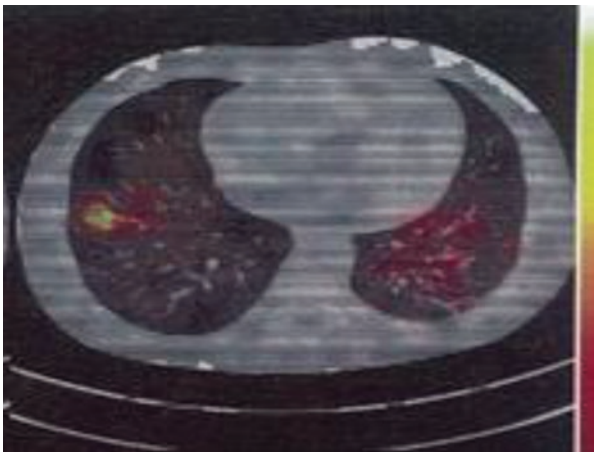


**Fig. 28.8** Fusion of CT imaging and octreoscan showing a ventrolateral focus

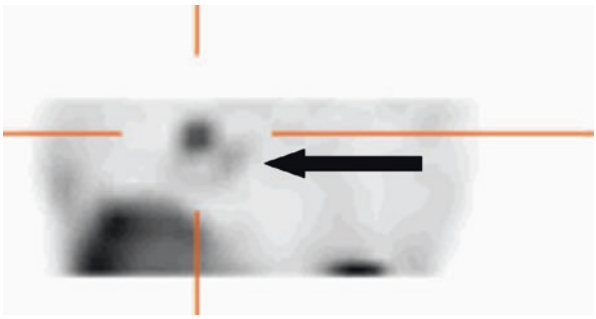


**Fig. 28.9** Octreoscan showing two hilar foci

demonstrated metastases of a highly differentiated neuroendocrine tumor in 9 of 18 resected lymph nodes. Within the lung parenchyma submitted for histopathological evaluation, tumor cells could not be identified. However, postoperatively eightfold elevated ACTH dropped to the midnormal range, and tenfold elevated 24 h-UFC also decreased to the upper normal range. Since no primary tumor was identified by

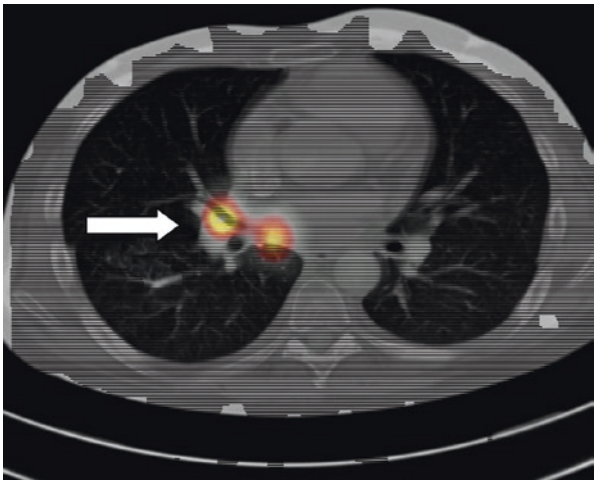


**Fig. 28.10** Fusion of CT imaging and octreoscan of the chest showing two hilar foci

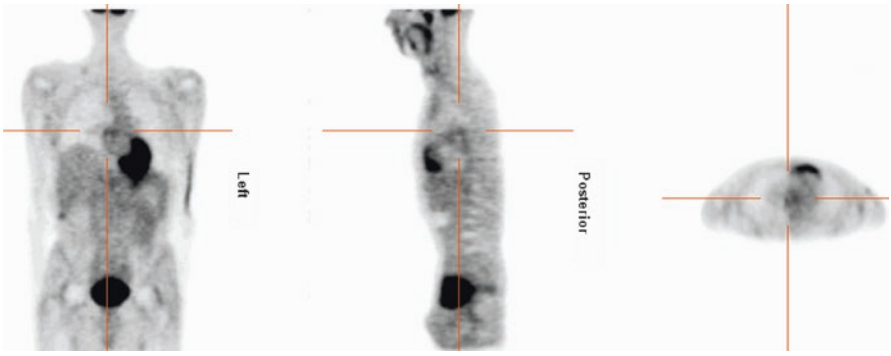



**Fig. 28.11** FDG-PET scan: tracer uptake in the dorsal lower and middle lobe and the right hilar region

histopathologic examination, we decided to perform adjuvant radiation of the mediastinum and the right hilus with a dose of 63.2 Gy over 3 months. Over the course of the following months, the patient experienced remission of cushingoid features. Dexamethasone suppression test showed a significant decline in serum cortisol from 470 to 63 nmol/L (reference aim, <80 nmol/L), and ACTH was suppressed from 7.55 to 1.73 pmol/L. One year after surgical resection, a radiograph of the spine demonstrated unchanged multiple vertebral fractures including end plate deformity and wedge-shaped malformation. Nevertheless, the patient reported having complete relief of back pain. Eight years after the detection of the primary tumor, another follow-up screening was performed. The patient reported well-being and showed no cushingoid features. Bone mineral density measurement of the lumbar spine showed a normal bone density (*T*-score, 0.7), whereas density measurement of the femur indicated increased fracture risk (*T*-score, −1.3). A 1-mg overnight dexamethasone suppression test showed an adequate cortisol suppression,

24-h UFC was within the normal range, and chromogranin A, NSE, and calcitonin in serum were undetectable. Imaging work-up, including $^{68}$Ga-DOTA-D Phe$^{1}$-Tyr$^{3}$-octreotide (DOTATOC)-PET/CT and MRI of the chest and abdomen, showed no evidence of tumor tissue. The now 28-year-old patient did not develop avascular necrosis of the hip which can occur in patients with glucocorticoid excess [32].

### 28.2.3 Case 3

The third illustrative patient, a 48-year-old black woman, had been referred to the clinic for severely elevated parathyroid hormone levels, tingling in her fingertips, and hypertension [33]. On exam, she had no cushingoid features and a body mass index of 35 kg/m2. She was diagnosed with pseudohypoparathyroidism/parathyroid hormone resistance and bilateral adrenal tumors. Bone density measurements showed positive T-scores at the femur and spine but a T-score of minus 0.6 at the left forearm. Serum cortisol at 8 AM after 1 mg of dexamethasone overnight was 5 μg/dL. Her BP was controlled with amlodipine and spironolactone. At present, she did not have diabetes mellitus which can occur in patients with CS [34] but is at risk for that, considering that she is obese and recent studies on "nonfunctional" adrenal tumors with an estimated 10% of such tumors secreting excess cortisol without the classic signs or symptoms of CS [35]. Follow-up of this patient is undertaken according to the recent guidelines for adrenal incidentaloma, considering comorbidities (such as hypertension and diabetes mellitus) and their treatment [36].

In patients with CS caused by an adrenal tumor, ACTH independence exists, that is, cortisol secretion and excess occur without stimulation by ACTH [17, 37]. This usually leads to hypoactivity and atrophy of the contralateral adrenal gland (Fig. 28.12). Rarely, ACTH can be secreted ectopically by adrenal medullary lesions [38–40].

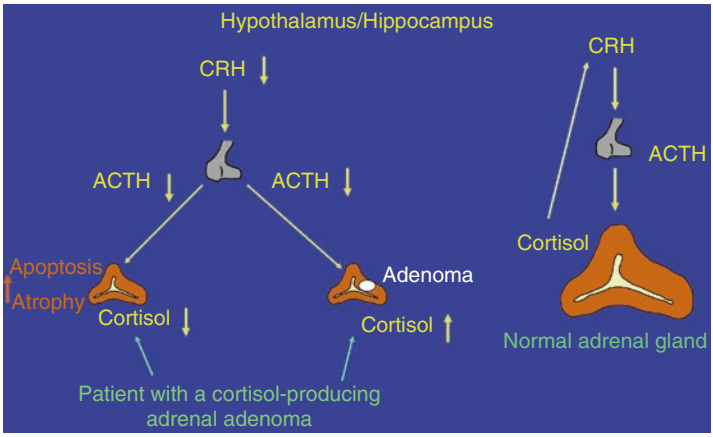



**Fig. 28.12** Hypothalamic-pituitary-adrenal axis

## 28.3 Causes and Diagnosis of Cushing's Syndrome

CS can result from several possible causes:

(a) Iatrogenic (exogenous) use of glucocorticoids
(b) Pituitary tumor secreting ACTH (approx. 70% of endogenous CS cases in adults and 90% in children)
(c) Any neuroendocrine tumor that secretes either ACTH or CRH (approx. 10%)
(d) Adrenal nodule, adenoma, and carcinoma secreting cortisol (4%, 10%, and 5%, respectively)

The incidence of endogenous CS is ~2–3 cases per one million inhabitants per year (6). Approximately 75–90% of ACTH-independent causes of CS are due to unilateral and benign cortisol-producing adenomas, with the remaining majority due to bilateral adrenocortical hyperplasias (BAH) [41]. BAH are divided into micronodular (<1 cm in diameter), macronodular (>1 cm in diameter), or non-nodular. Briefly, the micronodular subtypes are usually diagnosed in children and young adults and are either pigmented (primary pigmented nodular adrenocortical disease [c-PPNAD]) as seen in familial cases in the context of Carney complex, or isolated (i-PPNAD) when nonsyndromic, and not pigmented (iMAD, isolated massive adrenocortical disease). The macronodular subtypes, which are usually diagnosed in adults >50 years old, may be sporadic or familial. Primary bilateral macronodular adrenocortical hyperplasia (PBMAH) was first described in 1964 [42] and was previously called massive macronodular adrenocortical disease (MMAD), bilateral macronodular adrenal hyperplasia (BMAH), or ACTH-independent macronodular adrenocortical hyperplasia (AIMAH) [43]. PBMAH may be syndromic, as seen with mutations in *ARMC5*, *APC*, *MEN1*, *FH*, and the Carney triad, Carney-Stratakis syndrome, and hereditary nonpolyposis colorectal cancer [44–46]. Other subtypes of macronodular PBMAH include primary bimorphic adrenocortical disease (PBAD), as seen in McCune-Albright syndrome, and lesions with G-protein-coupled receptors that produce excess cortisol only in response to certain endogenous factors (e.g., gastrointestinal inhibitory polypeptide, GIP), as seen with food-dependent Cushing's syndrome (FDCS).

If CS is clinically suspected, the following work-up (Fig. 28.13) should be pursued [4, 8].

## 28.4 Diagnostic Considerations

In general, biochemical and other investigations should follow the clinical suspicion for CS based on signs and symptoms. Diagnostically even more challenging are scenarios as demonstrated in case 3 when biochemical evidence of glucocorticoid excess is present without any or very little clinical features of CS. In this regard, one should consider "pseudo-Cushing" states or physiologic hypercortisolism (Table 28.2 in ref. [7], Nieman 2015, with permission).

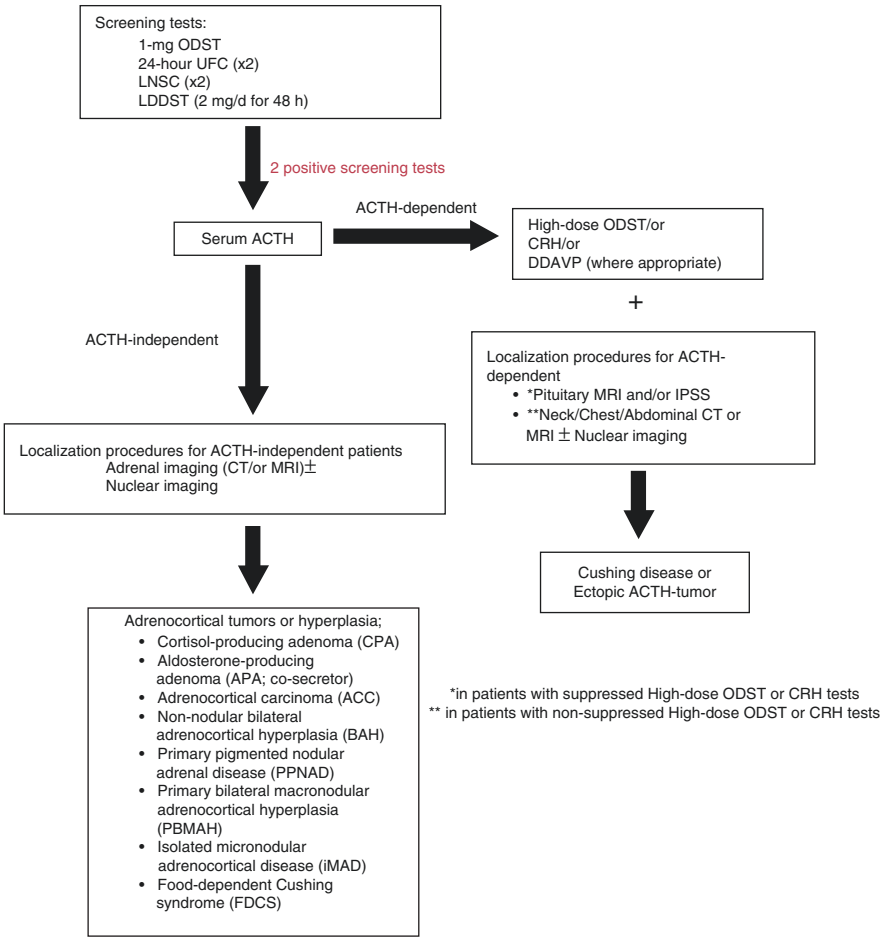



**Fig. 28.13** Diagnostic work-up for patients with Cushing's syndrome. Modified with permission from Hannah-Shmouni, Melcescu, & Koch. Testing for Endocrine Hypertension, Chap. 7, in Leslie De Groot (editor), online www.endotext.org, 2016 (ref. [4])

**Table 28.2** Physiologic hypercortisolism, with permission from ref. [7], Nieman 2015

| |
|---|
| *Some clinical features of CS may be present* |
| Pregnancy |
| Depression and other psychiatric conditions |
| Alcohol dependence |
| Glucocorticoid resistance |
| Morbid obesity |
| Poorly controlled diabetes mellitus |
| *Unlikely to have any clinical features of CS* |
| Physical stress (hospitalization, surgery, pain) |
| Malnutrition, anorexia nervosa |
| Intense chronic exercise |
| Hypothalamic amenorrhea |
| Cortisol-binding globulin excess (increased serum cortisol but not urinary free cortisol) |

## 28.5 Diagnostic Considerations: Biochemical Evaluation

The initial screening test for CS should be based on the suitability for a given patient (see Table 28.1). The tests recommended by the Clinical Practice Guidelines of the Endocrine Society [8] are late-night salivary cortisol (LNSC, two measurements), 1-mg overnight dexamethasone suppression test (ODST), urine free cortisol (UFC, at least two measurements), and the longer low-dose DST (LLDST, 2 mg/day for 48 h).

A random serum cortisol or plasma ACTH levels, 8-mg DST, urinary 17-ketosteroids, or the insulin tolerance test should not be used to screen for CS. The clinician should be aware of any current or recent use of oral, skin creams, rectal, inhaled, topical, herbal, or injected glucocorticoids before biochemical testing to avoid false positives.

Assays differ widely in their accuracy and should be chosen on the basis of their performance. Thus, knowledge of assay variability, functional limit of detection, precision, and normal ranges should be carefully assessed to assist in the interpretation of the test results. Antibody-based immunoassays (RIA and ELISA) can cross-react with cortisol metabolites and synthetic glucocorticoids, while structurally based assays (HPLC and LC-MS/MS) do not pose this problem and are the method of choice for detection of cortisol and/or other metabolites [4].

*Late-night salivary cortisol (LNSC)*: Patients with CS have an impaired diurnal variation of cortisol. The loss of circadian rhythm with absence of a late-night cortisol nadir is a consistent biochemical abnormality in patients with CS [8]. Since biologically active free cortisol in the blood is in equilibrium with cortisol in the saliva, then measurement of a late-night salivary cortisol (LNSC) level by liquid chromatography-tandem mass spectrometry (LC-MS/MS) can be employed as a screening test for CS. 0.5 mL (minimum 0.2 mL) of saliva is necessary for the test. Basic instructions for collection include no food, smoking (ideally avoided on the day of testing), chewing tobacco/licorice (contains the 11β-hydroxysteroid dehydrogenase type 2 inhibitor glycyrrhizic acid), or fluids for 30 min–1 h prior to collection; avoid any activity that can cause gums to bleed, including brushing and flossing of teeth, or stress; the saliva should be collected 10 min after rinsing the mouth with water; the swab is placed under the tongue until well saturated approximately 1 min; the specimen can be placed in room air for up to 5 days and refrigerated for 7 days. Two saliva samples on two separate evenings between 2300 and 2400 ho should be collected because the hypercortisolism of CS can be variable, and this strategy increases confidence in the test results. Levels at midnight ≤0.09 μg/dL (see questdiagnostics.com) are considered normal (cave: cutoff is assay dependent, for instance, the electrochemiluminescence immunoassay). The timing of the collection should be adjusted to the time of sleeping for shift workers or those with variable bedtimes. One study found that in men ≥60 years, 20% of all participants and 40% of diabetic hypertensive subjects had at least one elevated LNSC [47], which questions its utility as a screening test in this age group. LNSC is useful in detection of early recurrence from CS in the postoperative period where urinary free cortisol and morning cortisol levels may be normal. If there is a normal diurnal rhythm (i.e., an appropriately low LNSC), then remission is likely [8]. LNSC yields a 92–100% sensitivity and a 93–100% specificity for the diagnosis of CS.

*1-mg overnight dexamethasone suppression test (ODST)*: Patients with CS fail to suppress ACTH secretion from the pituitary gland when low doses of the synthetic glucocorticoid dexamethasone are given. This test entails administration of 1 mg of dexamethasone at 2300 h the night before a morning (0800 h) blood sample for serum cortisol is drawn, simultaneously with a dexamethasone level (if feasible) to ensure adequate plasma concentrations [>5.6 nmol/L (0.22 μg/dL)] [48]. Variable absorption and metabolism of dexamethasone may influence the result of both the 1-mg ODST and the longer low-dose DST (LDDST, 2 mg/day for 48 h). Patients should avoid eating or drinking for 12 h before the morning blood test. Drugs such as phenytoin, phenobarbital, carbamazepine, rifampicin, and alcohol induce hepatic enzymatic clearance of dexamethasone, mediated through CYP3A4, thereby reducing the plasma dexamethasone concentrations leading to false positives [8]. Dexamethasone clearance may be reduced in patients with liver and/or kidney failure. Interpretation of the serum cortisol has many caveats. The serum cortisol assay measures total cortisol, which is not an adequate representation of the biologically relevant free cortisol levels in conditions that cause cortisol-binding globulin (CBG) deficiency (e.g., nephrotic syndrome, cirrhosis, critical illness, postoperative period, CBG deficiency, or malnourished states) or excess (e.g., obesity, pregnancy, oral contraceptives, and estrogen therapy). False positives for ODST are seen in 50% of women taking oral contraceptives and should be withdrawn for 6 weeks before testing or retesting. Certain conditions associated with abnormal cortisol levels need to be excluded: alcoholism, major depression, stress, thyrotoxicosis, poorly controlled diabetes mellitus, pregnancy, or kidney failure. Morning cortisol levels >1.8 μg/dL (50 nmol/L) are considered positive [8]. If an increased specificity (95–100%) is sought, the longer LDDST (2 mg/day for 48 h) could be employed or a higher serum cortisol threshold for the 1-mg ODST is used. This is particularly useful in the evaluation of adrenal incidentalomas where a cutoff of >5 μg/dL (137.95 nmol/L) increases specificity for the detection of autonomous cortisol secretion [36]. Fast acetylators of dexamethasone may have a false positive test with the 1-mg ODST, which can be overcome with the longer LDDST. DST is not the screening test of choice in pregnancy, epilepsy, and cyclic CS. DST is the test of choice in renal failure and in the evaluation of an adrenal incidentaloma for autonomous cortisol secretion (so-called mild or subclinical CS).

*Urine free cortisol (UFC)*: Unlike serum cortisol, UFC provides an integrated assessment of cortisol secretion that is not bound to CBG over a 24-h period. Therefore, UFC is not affected by conditions and medications that alter CBG. Two UFC samples should be collected, with the first morning void discarded so that the collection begins with an empty bladder, up to and including the first morning void on the second day [8]. Patients should not drink excessive amounts of fluid and to avoid the use of any glucocorticoid preparations. Because the hypercortisolism of CS can be variable, at least two collections should be performed, which increases confidence in the test results [8]. Values above the upper limit of normal for the particular assay are considered positive, provided the creatinine shows that the collection is complete and that the urine volume is not excessive (>5 L). Pseudo-Cushing's syndrome is associated with false positive UFCs and should be

considered on the differential. UFC appears to be less sensitive than the 1-mg DST or LNSC for the identification of autonomous cortisol secretion in the setting of an adrenal incidentaloma. Upper limits of normal are much lower with HPLC or LC-MS/MS than in antibody-based assays (as low as 40% of the value measured by RIA).

*Plasma ACTH:* A serum ACTH level could help narrow the differential diagnosis of hypercortisolemia (ACTH-dependent vs. ACTH-independent) after the diagnosis has been established. Immunochemiluminometric assays detect intact ACTH; 1.5-mL frozen EDTA plasma (0.3 mL minimum) is collected between 7:00 and 10:00 AM, transferred on ice and centrifuged immediately after collection to separate plasma from cells. The reference range for ages 3–17 years is 9–57 pg/mL and age ≥18 years is 6–50 pg/mL (see questdiagnostics.com). Elevated levels are seen in ectopic ACTH and Cushing's disease, unless cyclicity is present, while suppressed levels are seen in ACTH-independent causes, such as CS due to adrenocortical tumors and hyperplasia. An ectopic ACTH-secreting pheochromocytoma from the adrenal glands is an exception to the rule. False positives are not uncommon and could be from errors in sample transfer and processing, assay interference (e.g., 5 mg/day of biotin or presence of monoclonal mouse antibodies), and stress.

*Corticotropin-releasing hormone (CRH) stimulation test*: This test is useful for differentiating between ACTH-dependent and ACTH-independent CS. Human and ovine CRH are commercially available and are given intravenously (bolus) at a dose of 1 μg/kg body weight. ACTH and cortisol levels are measured before (−5, 0 min) and after (15, 30, 45, 60, 90, and 120 min) the administration of CRH. Some studies suggested that the measurements of ACTH and cortisol before and after 15 min, 30 min and 45 min, 60 min, respectively, are sufficient to diagnose patients with ACTH-dependent CS [49]. A rise in cortisol >20% and ACTH >35% in comparison with baseline levels is diagnostic for Cushing's disease, with a sensitivity of 93% and a specificity of 100% [49].

The diagnostic value of the (1 mg) dexamethasone suppression test in the diagnosis of CS has been questioned, especially in borderline cases [50]. There is tremendous interpatient/interindividual variability in plasma levels of dexamethasone during dexamethasone suppression testing [48].

There is also a long list of medications and circumstances that might interfere with the interpretation of results of the dexamethasone suppression test. For instance, there are various drugs that impact CYP450 enzymes including CYP3A which can be induced or inhibited (http://medicine.iupui.edu/clinpharm/ddis/main-table/).

Among medications that accelerate dexamethasone metabolism by inducing CYP3A are phenobarbital, rifampin, mitotane, pioglitazone, and carbamazepine, and among those that impair dexamethasone metabolism by inhibiting CYP3A are diltiazem, fluoxetine, and ritonavir. Cortisol-binding globulin can be raised by estrogens and mitotane which may lead to "falsely" elevated cortisol concentrations. Rather than measuring total serum cortisol, it may be more useful to reliably (for instance, by equilibrium dialysis with liquid chromatography/tandem mass spectrometry) determine the amount of free cortisol analogous to measuring free thyroid hormone, given that the test is validated [51]. As saliva represents an

ultrafiltrate of plasma, more reflecting the serum free cortisol concentration, it is very useful in the diagnosis of CS. Midnight salivary cortisol has a very high sensitivity and specificity (both greater than 97%) in this regard with specificity remaining high at 95% in women taking oral contraceptive pills [52]. Similarly, measuring urinary free cortisol by liquid chromatography tandem mass spectrometry appears to have an excellent accuracy in diagnosing CS [53]. The Endocrine Society guideline and the adrenal incidentaloma guideline consider an 8 AM serum cortisol value of less than 1.8 μg/dL (50 nmol/L) after 1 mg of dexamethasone overnight as cutoff to exclude CS. For patients with adrenal incidentaloma, an 8 AM serum cortisol value of greater than 5 μg/dL is considered positive, while serum cortisol concentrations between 1.8 and 5 μg/dL are considered being suggestive for possible CS [8, 36].

For late-night salivary cortisol, the cutoff to exclude CS is less than 145 ng/dL (4 nmol/L) [8]. In special populations, one should be more selective in utilizing the appropriate test to screen for and diagnose CS. In pregnant women who are suspected to have CS, measuring urinary free cortisol with trimester specific "cutoffs" is helpful [54, 55]. A systematic review of published cases of CS during pregnancy revealed that adrenal adenoma was the most frequent etiology (44% of cases) and women with active CS more often suffered from gestational diabetes, gestational hypertension, and preeclampsia [54]. In patients with cyclic/intermittent CS, urinary free cortisol and late-night salivary cortisol can assist in making the diagnosis besides watching for progressive clinical signs and symptoms of CS [37, 56].

*Patients with chronic kidney impairment*: Plasma-binding protein concentrations and dexamethasone clearance can be significantly altered with decreased renal function, and normal suppression of cortisol after 1 mg of overnight dexamethasone is uncommon [3, 57–59]. Workman and colleagues [60] investigated seven uremic patients and concluded that normal suppression of plasma cortisol can be achieved in uremia if the duration of dexamethasone administration is prolonged sufficiently to compensate for the prolongation of cortisol half-life in patients with chronic renal failure. In patients with end-stage renal disease, the circadian cortisol rhythm is disrupted [58, 61]. Analyzing 100 urine samples, Chan and colleagues [62] found that patients with moderate or severe renal impairment (CrCl less than 60 mL/min) had lower urinary free cortisol excretion rates than those with no or mild renal impairment. A recent study including 80 outpatients with early stages of renal disease and 40 healthy subjects evaluated the diurnal variation of salivary cortisol and suppressibility of cortisol in saliva and serum after 1 mg of overnight dexamethasone with simultaneous measurement of circulating dexamethasone and concluded that false-positive responses to 1 mg dexamethasone testing were associated with glomerular filtration rates lower than 90 mL/min/1.73 $m^2$ with higher dexamethasone doses being necessary to achieve adequate hypothalamic-pituitary-adrenal axis suppression, whereas salivary cortisol measurements were useful in assessing circadian cortisol profiles and feedback regulation in individuals with chronic kidney impairment [63]. Raff and Trivedi [64] measured late-night salivary cortisol concentrations as high as 15 nmol/L in

end-stage renal disease patients (reference range, less than 4 nmol/L or 145 ng/dL) and concluded that a normal late-night salivary cortisol value rules out CS in patients with end-stage renal disease. In patients on hemodialysis, the cortisol-to-cortisone ratio is increased due to reduced activity of 11-beta-hydroxysteroid dehydrogenase [57].

Severe hypokalemia and obesity in an anuric hemodialysis patient can be related to CS from an adrenal adenoma [65].

*Postoperative assessment*: As recently assessed by the pituitary scientific committee of the American College of Endocrinology, recurrence of glucocorticoid excess after initial treatment of Cushing's disease occurs in one third of patients over their lifetime. Therefore, long-term surveillance and monitoring should be conducted [66]. Although the consensus is that a postoperative serum cortisol value of less than 2 μg/dL predicts a higher chance of long-term remission after transsphenoidal surgery in patients with CD, it is acknowledged that there is no single serum cortisol or ACTH cutoff value able to exclude all patients with recurrence. Table 28.1 in that AACE paper reviews caveats of tests that are used to detect remission and/or recurrence in patients with CD, many of which have already been mentioned above in this chapter, including drugs that alter metabolism of dexamethasone, cyclical CS, salivary, and urinary free cortisol. One simple point to consider when evaluating any given individual for the presence of CS is their work schedule and sleep cycle (? shift work). Late-night salivary cortisol assessments appear to be more sensitive than urinary free cortisol or dexamethasone testing for detecting recurrence of CD [67]. Serum cortisol should be measured in the morning of postoperative day 1 after pituitary surgery with perioperative and postoperative glucocorticoids be held [68]. This may prove difficult as many intensive care doctors, neurosurgeons, and anesthesiologists prefer to administer hydrocortisone 50–100 mg intra- or perioperatively. To assess the integrity of the hypothalamic-pituitary-adrenal axis, some colleagues regard a postoperative day 3 serum cortisol value of 10 μg/dL or greater sufficient to decide against adrenal hormone replacement or for low-dose replacement postoperatively [69].

*Nelson syndrome*: Typically, transsphenoidal surgery for removing an ACTHoma smaller than 10 mm has been reported to lead to remission rates between 65 and 90%, whereas such rates are reported lower than 65% for macroadenomas [70]. Don Nelson in 1958 reported a woman who underwent bilateral adrenalectomy for refractory CD and then developed skin hyperpigmentation, visual field defects, elevated plasma ACTH levels, and a large sellar mass. The diagnosis of Nelson syndrome can be established by documenting expansion of the pituitary tumor compared to tumor size before bilateral adrenalectomy and plasma concentrations of ACTH more than 200 ng/mL in addition to progressive elevation of ACTH (with an increase of more than 30%) on at least three consecutive occasions. Based on symptoms and tumor location, repeat surgery (transsphenoidal or transcranial) could be performed. Gamma knife radiosurgery can control tumor growth and lead to a reduction in plasma ACTH. Linear accelerator stereotactic radiosurgery and particle radiation therapy have also been utilized in such patients. Medical therapies include somatostatin analogues including pasireotide, temozolomide, and cabergoline.

In general, ectopic ACTH secretion usually causes higher glucocorticoid excess than ectopic ACTH oversecretion by an ACTHoma in the pituitary gland. This explains in part why patients with ectopic ACTH syndrome usually have a higher prevalence of hypertension and diabetes mellitus than those patients with Cushing's disease [10, 19]. CS is well known to associate with significant morbidity, as well as increase mortality rate. The last, assessed as standardized mortality ratio, ranges between 1.7 and 4.1 [6, 71–73], and is driven by associated morbidities which include hypertension, cardio- and cerebrovascular disease, hypercoagulability, diabetes mellitus, and depression. Of significant concern is the fact that mortality remains increased even after patients with CS have been treated. Although hypertension is seen more frequently in patients with Cushing's disease than in those with adrenal CS, the survival rates are better for the first group of patients [71–74].

## 28.6 Diagnostic Considerations: Imaging

### 28.6.1 Pituitary MRI Pre- and Post-gadolinium Enhancement

As demonstrated in case study 1 (Cushing's disease) of this chapter, MRI is the modality of choice in the evaluation of the pituitary gland and surrounding tissues. In young patients in whom the likelihood of an "incidentaloma" is low compared to older adults, inferior petrosal sinus sampling (IPSS) may not have to be performed. Sagittal and coronal planes are considered the most accurate in evaluating the anatomy of the pituitary gland and other CNS structures. When Cushing's disease is suspected, contrast-enhanced magnetic resonance imaging (MRI) is recommended unless the patient is pregnant. $T_1$-weighted ($T_1$W) sequences and/or spoiled gradient recalled acquisition (SPGR) techniques provide the best images of the sella. 95% of microadenomas appear hypointense with no post-gadolinium enhancement in relation to normal surrounding tissues on $T_1$W sequences [75]. Only ~60–80% of pituitary adenomas are detected, and ~10% of healthy individuals have abnormal findings (incidentalomas) on MRI [76]. Diffuse hyperplasia of ACTH-producing cells and small microadenomas may not be seen on conventional or enhanced MRIs. Other techniques (IPSS or integrated 18F-FDG PET/CT) may be employed to increase the odds of disease detection. Dynamic MRI may further increase the detection rate of pituitary microadenomas at the expense of specificity.

If biochemical testing is suggestive of an ACTH-dependent source, the distinction should be made whether ACTH comes from the pituitary or ectopically from a neuroendocrine tumor. Inferior petrosal sinus sampling can assist in this regard and should be performed when the patient is hypercortisolemic. It usually takes 4–6 weeks of hypercortisolism to suppress normal corticotropin function. Adrenal suppressive medications should be stopped approximately 4 weeks prior to inferior petrosal sinus sampling [9]. During inferior petrosal sinus sampling, ACTH is measured from samples drawn simultaneously from the right and left petrosal sinuses

and a peripheral vein, at 5 and 1 min before and 3, 5, and 10 min after administration of CRH (1 μg per kg body weight), intravenously. At each time point then, the fold increase of each petrosal value compared to the peripheral value is calculated with a central to peripheral step-up greater than 2 before CRH administration being suggestive of CD and a central to peripheral step-up of greater than 3 also being suggestive of CD, whereas lesser increases being more suggestive of an ectopic ACTH source. Caveats in this setting include abnormal venous drainage and anatomy and lack of expertise which may reduce petrosal ACTH values, thereby leading to a false negative test. Anatomical oddities causing difficulties in interpreting results of inferior petrosal sinus sampling include cyclic CS caused by an ectopic pituitary adenoma in the midline sphenoid sinus and ACTH-secreting tumors originating in the maxillary sinus [77, 78]. In patients with CD who fail to demonstrate a peak inferior petrosal sinus to peripheral ACTH ratio greater than 3 after CRH administration, measuring prolactin as an index of pituitary venous effluent during IPSS can assist in accuracy [79, 80].

## 28.7 High-Resolution Chest, Neck, and/or Abdominal CT

This technique may detect tumors in ectopic or adrenocortical areas. Small lesions (<1 cm) could be missed (bronchial carcinoids, pancreatic neuroendocrine tumors). The sensitivity is lower than MRI (~50%) [81].

*Ultrasonography*: Although simple and economic, this imaging modality has a lower sensitivity in detecting adrenocortical masses than CT or MRI [82].

*CT and MRI of the adrenal glands*: CT of the adrenal glands analyzes contiguous 2–5-mm-thick CT slices on multiple sections using multidetector row protocols [83]. CT and MRI can help determine whether an adrenocortical mass is an adrenocortical carcinoma and can also assess for local tumor invasion and metastatic disease [84–86]. A CT cutoff at 4.0 cm has a sensitivity of 93%, while an unenhanced CT density of ≤10 HU has a sensitivity of 96–100% and a specificity of 50–100% in differentiating benign from malignant tumors [87, 88]. Enhanced CT assists in distinguishing between lesions that are lipid-rich (aldosterone-producing adenoma, cortisol-producing adenoma) and lipid-poor (e.g., pheochromocytoma, adrenocortical carcinoma). Lipid-rich adenomas "wash out" contrast faster. They can be differentiated by attenuation values or the percentage or relative percentage of washout as early as 5–15 min after enhancement if the unenhanced CT density is >10 HU [89]. Lipid-rich and lipid-poor lesions have a relative percentage washout on delayed scans of >50% and <50%, respectively [90]. One study demonstrated a washout value of 51% at 5 min and 70% at 15 min in benign lesions, with a sensitivity and specificity for the diagnosis of adrenocortical adenoma of ~96% at a threshold attenuation value of 37 HU on the 15-min delayed enhanced scan [89]. MRI is as accurate in distinguishing lesions that are lipid-rich from lipid-poor. Chemical shift imaging MRI can sort out lipid-rich lesions with a sensitivity of 84–100% and a specificity of 92–100%.

## 28.8 Nuclear Imaging

As shown in case study 2 of this chapter, these techniques include $^{111}$In-pentetreotide (OCT), $^{131}$I/$^{123}$I-metaiodobenzylguanidine, $^{18}$F-fluoro-2-deoxyglucose-positron emission tomography (FDG-PET), $^{18}$F-fluorodopa-PET (F-DOPA-PET), $^{68}$Ga-DOTATATE-PET/CT, or $^{68}$Ga-DOTATOC-PET/CT scan (68Gallium-SSTR-PET/CT), which may be used in select cases, primarily for the detection of ectopic ACTH tumors, which express surface receptors for somatostatin. These scans improve the sensitivity of conventional radiology when tumor site identification is difficult [20]. 68Gallium-SSTR-PET/CT likely offers the highest sensitivity [20]. A study conducted at the National Institutes of Health found that high sensitivity and positive predictive value suggest to perform thoracic CT/MRI plus octreoscan for initial imaging in searching for an ectopic ACTH source, with lesion confirmation by two imaging modalities [25].

With respect to adrenal tumors, one study found that cortisol-producing adenomas had a higher average FDG-PET SUVmax of 5.9 compared to nonfunctioning masses (average SUVmax 4.2) and aldosterone-producing adenoma (SUVmax 3.2), and an SUVmax cutoff of 5.33 had 50.0% sensitivity and 81.8% specificity in localizing a cortisol-producing adenoma [91]. Thus, FDG-PET may aid in the characterization and prioritization of adrenocortical nodules for surgery, particularly in the setting of bilateral adrenocortical masses.

*$^{18}$F-FDG PET*: This modality has a sensitivity of 93–100% and specificity of 80–100% in identifying malignant masses in the adrenal glands or elsewhere [92].

*PET-CT*: This modality has a sensitivity of 98.5–100% and specificity of 92–93.8% in detecting and differentiating between the various types of adrenocortical masses. When enhanced CT is added, the specificity is reached to 100% [83].

## 28.9 Treatment

For all patients with endogenous glucocorticoid excess, the ideal therapy consists of tumor removal with establishment of eucortisolemia. Patients with CS should be treated according to the Endocrine Society guidelines [93]. For patients with CD, ideally transsphenoidal surgery (TSS) with resection of the ACTHoma should be performed. In some instances, preoperative inhibition of steroidogenesis is indicated. If CS persists after TSS and incomplete tumor removal is suspected, a second neurosurgical operation should be done. If evidence for tumor invasion of the cavernous sinus or other inoperable structures is evident, radiation therapy may have to be considered [94, 95]. Remission of CD occurred in 70% of patients treated with a mean tumor margin dose of 22 Gy and a median follow-up time of 48 months. New loss of pituitary function was evident in 36% of patients treated with gamma knife surgery in that study [94]. As the effect on hypercortisolism with declining glucocorticoid excess will take several months, patients treated with this approach may require overlapping medical therapy to help reduce glucocorticoid excess and its detrimental sequelae. Interestingly, in a study of 29 patients with CD and no histological confirmation of ACTHoma after removal of a "typically appearing adenoma"

by a very experienced neurosurgeon, 66% (19 pts) were cured within an average follow-up period of 38 months [96]. Furthermore, it is possible that multiple pituitary adenomas are present in patients with CD, for instance, prolactin secreting, growth hormone secreting, or nonfunctional adenomas [97]. Crooke's changes occur in approximately 80% of patients with CS (81% of cases with histologically confirmed ACTHoma; 74% of 213 patients diagnosed with CS who had undergone pituitary surgery) and depend on the degree of glucocorticoid excess and individual susceptibility [98].

For patients with ectopic ACTH syndrome, the ideal therapy also consists of tumor removal. However, it can take years to identify and localize the primary tumor causing ACTH and glucocorticoid excess [27, 28]. Goal here then also is to achieve eucortisolemia, as demonstrated in case study 2 of this chapter.

For patients with adrenal tumors secreting excessively cortisol, the goal is to remove the respective adrenal tumor. If this requires bilateral adrenalectomy, patients will have primary adrenal insufficiency in need for replacing gluco- and mineralocorticoids in dosages that will prevent exogenous glucocorticoid excess in the individual patient, depending on the individual tissue sensitivity to the type of glucocorticoid used and its affinity to the respective glucocorticoid receptor [99, 100]. Typically, the amount of hydrocortisone 10–15 mg in the morning and 5–10 mg in late afternoon is administered depending on body weight, plus fludrocortisone 50–150 μg daily, depending on blood pressure and plasma renin activity. In a systematic review on the outcome of bilateral adrenalectomy in CS, 82% had CD, 13% ectopic CS, and 5% primary adrenal hyperplasia [101–103]. The surgical mortality was less than 1% in patients with CD, and less than 2% had a relapse of CS (considering also accessory adrenal tissue or remnants). Hypertension, obesity, and depression improved in the majority of patients undergoing bilateral adrenalectomy. Nelson syndrome occurred in 21% of patients and 46% of patients died in the first year after adrenalectomy. The risk of Nelson syndrome is higher in children than in adults after bilateral adrenalectomy, and the best predictor of developing this syndrome seems to be the baseline plasma ACTH value before glucocorticoid administration during the first year after bilateral adrenalectomy [101].

Medical therapy for patients with CD and CS has been systematically reviewed, concluding that pasireotide is the only treatment assessed in a randomized trial with a moderate level of evidence. The response rates with pasireotide in three prospective studies ranged from 17 to 29% [104]. Late-night salivary cortisol can be used to assess the early response to pasireotide in patients with CD [105]. All other medications including metyrapone, mitotane, cabergoline, ketoconazole, and mifepristone are supported by a low level of evidence in the treatment of CD or CS. The prospective cohort SEISMIC study of CS patients with diabetes mellitus, glucose intolerance, or hypertension showed a response rate of 38–60% [106]. Insulin sensitivity can clearly be improved with mifepristone during treatment of CS [107]. Retrospective case series of CD patients treated with ketoconazole demonstrated a response rate of 45%, whereas the response rate in CS patients is 53–88% [104]. For metyrapone the CD response rate is 75% and the CS response rate 57%. For mitotane, the CD response rate is 72% and the CS response rate 39–70%. Retrospective

case series and a prospective cohort study demonstrated a CD response rate of 25–50% for cabergoline. Ketoconazole has been used before transsphenoidal surgery for several months and was able to control urinary free cortisol in 49% of patients with partial control in 36% and no control in 15% [108]. Aggressive corticotroph pituitary tumors can be treated with capecitabine and temozolomide [109]. Some patients with neuroendocrine tumors which ectopically secrete ACTH respond to octreotide [110]. For patients requiring intravenous therapy, etomidate can be used [111].

Combining various medications with an additive or synergistic effect on treating patients with CD seems attractive and possible [112]. Ketoconazole can lead to elevation of liver enzymes in up to 10% of patients that is completely reversible and not dose-dependent. Metyrapone inhibits 11-beta-hydroxylase and aldosterone synthase and has been used as monotherapy or in combination with ketoconazole with normalization of cortisol levels in approx. 80% of patients. Because of generating a potent mineralocorticoid byproduct, deoxycorticosterone (DOC), metyrapone may exacerbate hypertension in addition to increased adrenal androgen synthesis which might lead to virilism in women. Both steroidogenesis inhibitors demonstrate an escape phenomenon related to ACTH secretion which limits their use in long-term treatment. A brief sketchy overview of treating hypertension in patients with CS is provided in Fig. 28.14, with permission from ref. [2].

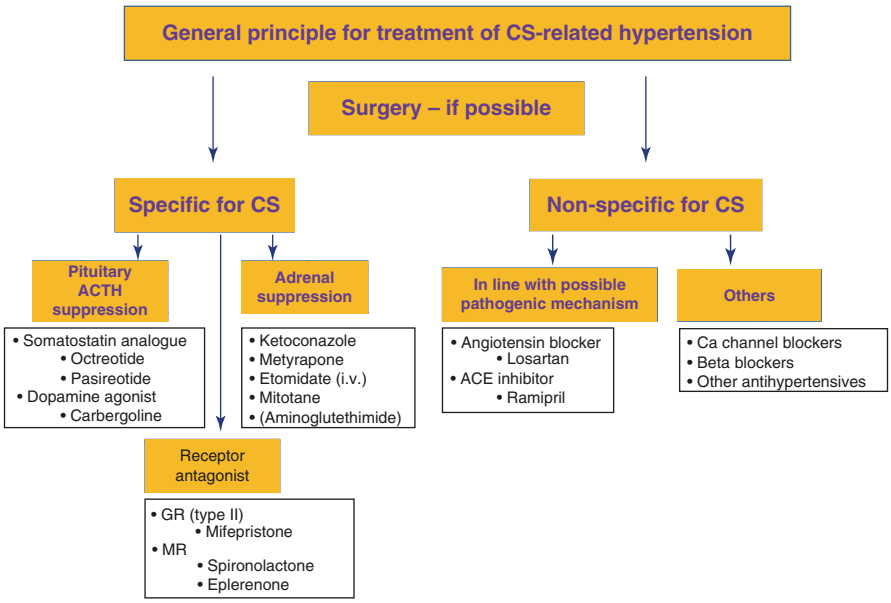



**Fig. 28.14** General principles of treating hypertension in CS. *GR* glucocorticoid receptor. *MR* mineralocorticoid receptor

## 28.10 Molecular Pathogenesis

For this chapter, a review on this topic with regard to corticotroph pituitary tumors, ectopic ACTH-secreting neuroendocrine tumors, and cortisol-secreting adrenal tumors would exceed the frame of this chapter. Therefore, suffice it to provide some references for further reading. Given the current pace of whole genomic sequencing and the collection of precise clinical and pathological data, the elucidation of molecular pathways for any of these tumor entities is closer than it has ever been for the last 20 years [113]. Although the knowledge of the genetic basis of McCune-Albright syndrome, multiple endocrine neoplasia type 1, Carney complex, and other pituitary adenoma predisposition syndromes has increased, the pathogenesis of sporadic pituitary ACTHomas remains widely unknown [114, 115, 122]. With respect to cortisol-secreting adrenal tumors, recent studies have broadened our horizon on their pathogenesis [116–121].

## 28.11 Hypertension in Patients with CS

Hypertension is a major cardiovascular risk factor, and recent study results of SPRINT and ACCORD started major discussions on BP targets and the "right" (safe) amount of sodium intake [5, 123, 124]. To identify patients at risk, screening and subsequent therapy are important and resources to do so in low-resource settings [125]. As discussed in detail in ref. [2], hypertension also is a common clinical feature of CS (sensitivity 74–90%, specificity 83%) but is neither universal nor predictable to the degree of other clinical features of the disease [9]. Approximately 80% of adults and up to 60% of children with CS have been reported to have high BP [10, 126]. After achieving eucortisolemia in such patients, hypertension still persists in adults in as many as 30% and in children and adolescents in around 3–4% [127, 128]. Hypertension will relate mostly to obesity and increased peripheral resistance. In patients with ectopic ACTH production by neuroendocrine tumors, marked hyperplasia of the adrenals and a severe increase in various steroids can occur with high risk for mineralocorticoid excess by overloading the functional capacity of 11-beta-hydroxysteroid dehydrogenase. In ectopic ACTH syndrome, hypertension is seen in up to 95% of cases, while with exogenous glucocorticoids, hypertension is of significantly lower frequency of 20% and correlates with the dose of steroid used [126]. Administration of exogenous glucocorticoids can increase both systolic and, to lesser degree, diastolic blood pressure for hydrocortisone, dexamethasone, or ACTH [129, 130]. Prolonged exposure to dexamethasone 1 mg daily (>1 week) reduced postganglionic muscle sympathetic nerve activity in obese subjects [131].

Causes of hypertension in CS are numerous (Fig. 28.15, with permission from ref. [2]) and relate to different pathogenesis pathways [132]:

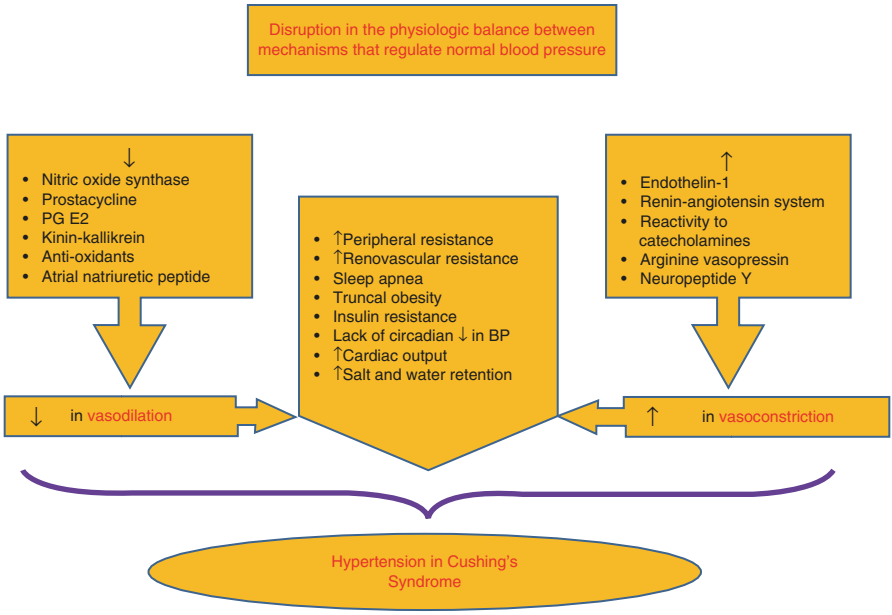



**Fig. 28.15** Pathogenic pathways of hypertension development in CS, with permission from ref. [2]

**Compliance with ethical standards**

*Conflict of Interest* The author declares that he has no conflict of interest related to this work.

## References

1. Koch CA, Chrousos GP (2003) Cushing' disease. In: Powell MP, Lightman SL, Laws ER (eds) Management of pituitary tumors: the clinician's practical guide. Springer, New York, pp 51–75
2. Kantorovich V, Koch CA, Chrousos GP (2013) Hypertension in patients with Cushing's syndrome. In: Koch CA, Chrousos GP (eds) Endocrine hypertension. Springer, New York
3. Koch CA, Pamporaki C, Kantorovich V (2015) Endocrine hypertension in patients with chronic kidney disease. In: Weir MR, Lerma EV (eds) Chronic kidney disease and hypertension. Springer, New York
4. Hannah-Shmouni F, Melcescu E, Koch CA (2016) Testing for Endocrine Hypertension. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, Koch C, Korbonits M, McLachlan R, New M, Purnell J, Rebar R, Singer F, Vinik A (eds) Endotext [Internet]. South Dartmouth: MDText.com; 2000–2016 Dec 30
5. Koch CA, Chrousos GP (2016) Overview of endocrine hypertension. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, Koch C, Korbonits M, McLachlan R, New M, Purnell J, Rebar R, Singer F, Vinik A (eds) Endotext [Internet]. South Dartmouth: MDText.com.; 2000–2016 Oct 26.
6. Lindholm J, Juul S, Jorgensen JO et al (2001) Incidence and late prognosis of Cushing's syndrome: a population-based study. J Clin Endocrinol Metab 86(1):117–123
7. Nieman LK (2015) Cushing's syndrome: update on signs, symptoms and biochemical screening. Eur J Endocrinol 173(4):M33–M38

8. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, Montori VM (2008) The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 93(5):1526–1540
9. Hall JE, Nieman LK (eds) (2003) Handbook of diagnostic endocrinology. Humana, Totowa
10. Magiakou MA, Smyrnaki P, Chrousos GP (2006) Hypertension in Cushing's syndrome. Best Pract Res Clin Endocrinol Metab 20:467–482
11. León-Justel A, Madrazo-Atutxa A, Alvarez-Rios AI et al; Spanish CRISALIDA Study Group (2016) A probabilistic model for Cushing's syndrome screening in at-risk populations: a prospective multicenter study. J Clin Endocrinol Metab 101(10):3747–3754
12. Lanfranco F, Motta G, Minetto MA et al (2010) Neuroendocrine alterations in obese patients with sleep apnea syndrome. Int J Endocrinol 2010:474518
13. Reinehr T, Kulle A, Wolters B et al (2014) Relationships between 24-hour urinary free cortisol concentrations and metabolic syndrome in obese children. J Clin Endocrinol Metab 99(7):2391–2399
14. Storr HL, Savage MO (2015) Management of endocrine disease: paediatric Cushing's disease. Eur J Endocrinol 173(1):R35–R45
15. Stratakis CA (2016) Diagnosis and clinical genetics of Cushing syndrome in pediatrics. Endocrinol Metab Clin North Am 45(2):311–328
16. Magiakou MA, Mastorakos G, Chrousos GP (1994) Final stature in patients with endogenous Cushing's syndrome. J Clin Endocrinol Metab 79(4):1082–1085
17. Robyn JA, Koch CA, Montalto J et al (1997) Cushing's syndrome in childhood and adolescence. J Paediatr Child Health 33(6):522–527
18. Güemes M, Murray PG, Brain CE et al (2016) Management of Cushing syndrome in children and adolescents: experience of a single tertiary centre. Eur J Pediatr 175(7):967–976
19. Sharma ST, Nieman LN (2011) Cushing's syndrome: all variants, detection, and treatment. Endocrinol Metab Clin North Am 40(2):379–391
20. Isidori AM, Graziadio C, Paragliola RM et al; ABC Study Group (2015) The hypertension of Cushing's syndrome: controversies in the pathophysiology and focus on cardiovascular complications. J Hypertens 33(1):44–60
21. Stratakis CA (2016) Skin manifestation of Cushing syndrome. Rev Endocr Metab Disord 17(3):283–286
22. Hannah-Shmouni F, Stratakis CA, Koch CA (2016) Flushing in (neuro)endocrinology. Rev Endocr Metab Disord 17(3):373–380
23. Rahman SH, Papadakis GZ, Keil MF et al (2016) Kidney stones as an underrecognized clinical sign in pediatric Cushing disease. J Pediatr 170:273–277
24. Lodish M, Dunn SV, Sinaii N et al (2012) Recovery of the hypothalamic-pituitary-adrenal axis in children and adolescents after surgical cure of Cushing's disease. J Clin Endocrinol Metab 97(5):1483–1491
25. Zemskova MS, Gundabolu B, Sinaii N et al (2010) Utility of various functional and anatomic imaging modalities for detection of ectopic adrenocorticotropin-secreting tumors. J Clin Endocrinol Metab 95(3):1207–1219
26. Karageorgiadis AS, Papadakis GZ, Biro J et al (2015) Ectopic adrenocorticotropic hormone and corticotropin-releasing hormone co-secreting tumors in children and adolescents causing cushing syndrome: a diagnostic dilemma and how to solve it. J Clin Endocrinol Metab 100(1):141–148
27. Singer J, Werner F, Koch CA et al (2010) Ectopic Cushing's syndrome caused by a well differentiated ACTH-secreting neuroendocrine carcinoma of the ileum. Exp Clin Endocrinol Diabetes 118(8):524–529
28. Fasshauer M, Lincke T, Witzigmann H et al (2006) Ectopic Cushing' syndrome caused by a neuroendocrine carcinoma of the mesentery. BMC Cancer 6:108
29. Miehle K, Tannapfel A, Lamesch P et al (2004) Pancreatic neuroendocrine tumor with ectopic adrenocorticotropin production upon second recurrence. J Clin Endocrinol Metab 89(8):3731–3736

30. Trainer PJ, Eastment C, Grossman AB et al (1993) The relationship between cortisol production rate and serial cortisol estimation in patients on medical therapy for Cushing syndrome. Clin Endocrinol (Oxf) 39(4):441–443
31. Monaghan PJ, Owen LJ, Trainer PJ et al (2011) Comparison of serum cortisol measurement by immunoassay and liquid chromatography-tandem mass spectrometry in patients receiving the 11beta-hydroxylase inhibitor metyrapone. Ann Clin Biochem 48(Pt 5): 441–446
32. Koch CA, Tsigos C, Patronas NJ, Papanicolaou DA (1999) Cushing's disease presenting with avascular necrosis of the hip: an orthopedic emergency. J Clin Endocrinol Metab 84(9):3010–3012
33. Koch CA (2017) Parathyroid hormone resistance and bilateral Macronodular adrenocortical disease: does partial loss of methylation at the GNAS exon 1 differentially methylated region (DMR) play a role? Horm Metab Res. 2017;49(7):558–560
34. East HE, Subauste JS, Gandhi A, Koch CA (2012) About secondary causes of diabetes mellitus. J Miss State Med Assoc 53(11):380–383
35. Lopez D, Luque-Fernandez MA, Steele A et al (2016) "Nonfunctional" adrenal tumors and the risk for incident diabetes and cardiovascular outcomes: a cohort study. Ann Intern Med 165(8):533–542
36. Fassnacht M, Arlt W, Bancos I et al (2016) Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol 175(2):G1–G34
37. Koch CA, Bornstein SR, Chrousos GP, Stratakis CA (2000) Primary pigmented nodular adrenocortical dysplasia (PPNAD) within the scope of Carney complex as the etiology of Cushing's syndrome. Med Klin (Munich) 95(4):224–230
38. Kirkby-Bott J, Brunaud L, Mathonet M et al (2012) Ectopic hormone-secreting pheochromocytoma: a Francophone observational study. World J Surg 36(6):1382–1388
39. Falhammar H, Calissendorff J, Höybye C (2017) Frequency of Cushing's syndrome due to ACTH-secreting adrenal medullary lesions: a retrospective study over 10 years from a single center. Endocrine 55(1):296–302
40. Bancos I, Alahdab F, Crowley RK et al (2016) Therapy of endocrine disease: improvement of cardiovascular risk factors after adrenalectomy in patients with adrenal tumors and subclinical Cushing syndrome: a systematic review and meta-analysis. Eur J Endocrinol 175(6):R283–R295
41. Lodish M, Stratakis CA (2016) A genetic and molecular update on adrenocortical causes of Cushing syndrome. Nat Rev Endocrinol 12(5):255–262
42. Kirschner MA, Powell RD Jr, Lipsett MB (1964) Cushing's syndrome: nodular cortical hyperplasia of adrenal glands with clinical and pathological features suggesting adrenocortical tumor. J Clin Endocrinol Metab 24:947–955
43. Fragoso MC, Alencar GA, Lerario AM et al (2015) Genetics of primary macronodular adrenal hyperplasia. J Endocrinol 224(1):R31–R43
44. Alencar GA, Lerario AM, Nishi MY et al (2014) ARMC5 mutations are a frequent cause of primary macronodular adrenal hyperplasia. J Clin Endocrinol Metab 99(8):E1501–E1509
45. Assie G, Libe R, Espiard S et al (2013) ARMC5 mutations in macronodular adrenal hyperplasia with Cushing's syndrome. N Engl J Med 369(22):2105–2114
46. Faucz FR, Zilbermint M, Lodish MB et al (2014) Macronodular adrenal hyperplasia due to mutations in an armadillo repeat containing 5 (ARMC5) gene: a clinical and genetic investigation. J Clin Endocrinol Metab 99(6):E1113–E1119
47. Liu H, Bravata DM, Cabaccan J et al (2005) Elevated late-night salivary cortisol levels in elderly male type 2 diabetic veterans. Clin Endocrinol (Oxf) 63(6):642–649
48. Meikle AW (1982) Dexamethasone suppression tests: usefulness of simultaneous measurement of plasma cortisol and dexamethasone. Clin Endocrinol (Oxf) 16(4):401–408
49. Nieman LK, Oldfield EH, Wesley R et al (1993) A simplified morning ovine corticotropin-releasing hormone stimulation test for the differential diagnosis of adrenocorticotropin-dependent Cushing's syndrome. J Clin Endocrinol Metab 77(5):1308–1312

50. Lindholm J (2014) Cushing disease, pseudo-Cushing states, and the dexamethasone test: a historical and critical review. Pituitary 17(4):374–380
51. Auchus RJ (2015) Is it time to emancipate plasma cortisol? Endocr Pract 21(12): 1445–1447
52. Manetti L, Rossi G, Grasso L et al (2013) Usefulness of salivary cortisol in the diagnosis of hypercortisolism: comparison with serum and urinary cortisol. Eur J Endocrinol 168(3):315–321
53. Ceccato F, Barbot M, Zilio M et al (2015) Screening tests for Cushing's syndrome: urinary free cortisol role measured by LC-MS/MS. J Clin Endocrinol Metab 100(10): 3856–3861
54. Caimari F, Valassi E, Garbayo P et al (2016) Cushing's syndrome and pregnancy outcomes: a systematic review of published cases. Endocrine 55(2):555–563
55. Lindsay JR, Jonklaas J, Oldfield EH, Nieman LK (2005) Cushing's syndrome during pregnancy: personal experience and review of the literature. J Clin Endocrinol Metab 90(5):3077–3083
56. Velez DA, Mayberg MR, Ludlam WH (2007) Cyclic Cushing syndrome: definitions and treatment implications. Neurosurg Focus 23(3):E4; discussion E4a
57. N'Gankam V, Uehlinger D, Dick B et al (2002) Increased cortisol metabolites and reduced activity of 11beta-hydroxysteroid dehydrogenase in patients on hemodialysis. Kidney Int 61(5):1859–1866
58. Wallace EZ, Rosman P, Toshav N et al (1980) Pituitary-adrenocortical function in chronic renal failure: studies of episodic secretion of cortisol and dexamethasone suppressibility. J Clin Endocrinol Metab 50(1):46–51
59. Ramirez G, Gomez-Sanchez C, Meikle WA, Jubiz W (1982) Evaluation of the hypothalamic hypophyseal adrenal axis in patients receiving long-term hemodialysis. Arch Intern Med 142(8):1448–1452
60. Workman RJ, Vaughn WK, Stone WJ (1986) Dexamethasone suppression testing in chronic renal failure: pharmacokinetics of dexamethasone and demonstration of a normal hypothalamic-pituitary-adrenal axis. J Clin Endocrinol Metab 63(3):741–746
61. Cooke CR, Whelton PK, Moore MA et al (1979) Dissociation of the diurnal variation of aldosterone and cortisol in anephric subjects. Kidney Int 15(6):669–675
62. Chan KC, Lit LC, Law EL et al (2004) Diminished urinary free cortisol excretion in patients with moderate and severe renal impairment. Clin Chem 50(4):757–759
63. Cardoso EM, Arregger AL, Budd D et al (2016) Dynamics of salivary cortisol in chronic kidney disease patients at stages 1 through 4. Clin Endocrinol (Oxf) 85(2):313–319
64. Raff H, Trivedi H (2012) Circadian rhythm of salivary cortisol, plasma cortisol, and plasma ACTH in end-stage renal disease. Endocr Connect 2(1):23–31
65. Mise K, Ubara Y, Sumida K et al (2013) Cushing's syndrome after hemodialysis for 21 years. J Clin Endocrinol Metab 98(1):13–19
66. Fleseriu M, Hamrahian AH, Hoffman AR, Kelly DF, Katznelson L; AACE Neuroendocrine and Pituitary Scientific Committee (2016) American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical Review: Diagnosis Of Recurrence In Cushing Disease Endocr Pract 22(12):1436–1448
67. Carroll TB, Javorsky BR, Findling JW (2016) Postsurgical recurrent cushing disease: clinical benefit of early intervention in patients with normal urinary free cortisol. Endocr Pract 22(10):1216–1223
68. Abdelmannan D, Chaiban J, Selman WR, Arafah BM (2013) Recurrences of ACTH-secreting adenomas after pituitary adenomectomy can be accurately predicted by perioperative measurements of plasma ACTH levels. J Clin Endocrinol Metab 98(4):1458–1465
69. Khan MI, Habra MA, McCutcheon IE et al (2011) Random postoperative day-3 cortisol concentration as a predictor of hypothalamic-pituitary-adrenal axis integrity after transsphenoidal surgery. Endocr Pract 17(5):717–726
70. Azad TD, Veeravagu A, Kumar S, Katznelson L (2015) Nelson syndrome: update on therapeutic approaches. World Neurosurg 83(6):1135–1134

71. Clayton RN, Jones PW, Reulen RC et al (2016) Mortality in patients with Cushing's disease more than 10 years after remission: a multicentre, multinational, retrospective cohort study. Lancet Diabetes Endocrinol 4(7):569–576
72. Clayton RN, Raskauskiene D, Reulen RC, Jones PW (2011) Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. J Clin Endocrinol Metab 96:632–642
73. Bolland MJ, Holdaway IM, Berkeley JE et al (2011) Mortality and morbidity in Cushing's syndrome in New Zealand. Clin Endocrinol (Oxf) 75:436–442
74. Yaneva M, Kalinov K, Zacharieva S (2013) Mortality in Cushing's syndrome: data from 386 patients from a single tertiary referral center. Eur J Endocrinol 169(5):621–627
75. Patronas N, Bulakbasi N, Stratakis CA et al (2003) Spoiled gradient recalled acquisition in the steady state technique is superior to conventional postcontrast spin echo technique for magnetic resonance imaging detection of adrenocorticotropin-secreting pituitary tumors. J Clin Endocrinol Metab 88(4):1565–1569
76. Hall WA, Luciano MG, Doppman JL et al (1994) Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. Ann Intern Med 120(10):817–820
77. Hodish I, Giordano TJ, Starkman MN, Schteingart DE (2009) Location of ectopic adrenocortical hormone-secreting tumors causing Cushing's syndrome in the paranasal sinuses. Head Neck 31(5):699–706
78. Zerikly RK, Eray E, Faiman C et al (2009) Cyclic Cushing syndrome due to an ectopic pituitary adenoma. Nat Clin Pract Endocrinol Metab 5(3):174–179
79. Findling JW, Kehoe ME, Raff H (2004) Identification of patients with Cushing's disease with negative pituitary adrenocorticotropin gradients during inferior petrosal sinus sampling: prolactin as an index of pituitary venous effluent. J Clin Endocrinol Metab 89(12):6005–6009
80. Sharma ST, Nieman LK (2013) Is prolactin measurement of value during inferior petrosal sinus sampling in patients with adrenocorticotropic hormone-dependent Cushing's syndrome? J Endocrinol Invest 36(11):1112–1116
81. Escourolle H, Abecassis JP, Bertagna X et al (1993) Comparison of computerized tomography and magnetic resonance imaging for the examination of the pituitary gland in patients with Cushing's disease. Clin Endocrinol (Oxf) 39(3):307–313
82. Suzuki Y, Sasagawa SH et al (2001) The role of ultrasonography in the detection of adrenal masses: comparison with computed tomography and magnetic resonance imaging. Int Urol Nephrol 32(3):303–306
83. Blake MA, Kalra MK, Sweeney AT et al (2006) Distinguishing benign from malignant adrenal masses: multi-detector row CT protocol with 10-minute delay. Radiology 238(2):578–585
84. Young WF Jr (2011) Conventional imaging in adrenocortical carcinoma: update and perspectives. Horm Cancer 2(6):341–347
85. Rockall AG, Babar SA, Sohaib SA et al (2004) CT and MR imaging of the adrenal glands in ACTH-independent cushing syndrome. Radiographics 24(2):435–452
86. Lumachi F, Marchesi P, Miotto D, Motta R (2011) CT and MR imaging of the adrenal glands in cortisol-secreting tumors. Anticancer Res 31(9):2923–2926
87. Hamrahian AH, Ioachimescu AG, Remer EM et al (2005) Clinical utility of noncontrast computed tomography attenuation value (Hounsfield units) to differentiate adrenal adenomas/hyperplasias from nonadenomas: Cleveland Clinic experience. J Clin Endocrinol Metab 90(2):871–877
88. Caoili EM, Korobkin M, Francis IR et al (2002) Adrenal masses: characterization with combined unenhanced and delayed enhanced CT. Radiology 222(3):629–633
89. Korobkin M, Brodeur FJ, Francis IR et al (1998) CT time-attenuation washout curves of adrenal adenomas and nonadenomas. AJR Am J Roentgenol 170(3):747–752
90. Pena CS, Boland GW, Hahn PF et al (2000) Characterization of indeterminate (lipid-poor) adrenal masses: use of washout characteristics at contrast-enhanced CT. Radiology 217(3):798–802

91. Patel D, Gara SK, Ellis RJ et al (2016) FDG PET/CT scan and functional adrenal tumors: a pilot study for lateralization. World J Surg 40(3):683–689
92. Tenenbaum F, Groussin L, Foehrenbach H et al (2004) 18F-fluorodeoxyglucose positron emission tomography as a diagnostic tool for malignancy of adrenocortical tumours? Preliminary results in 13 consecutive patients. Eur J Endocrinol 150(6):789–792
93. Nieman LK, Biller BM, Findling JW et al; Endocrine Society (2015) Treatment of Cushing's syndrome: An Endocrine Society Clinical Practice Guideline J Clin Endocrinol Metab 100(8):2807–2831
94. Sheehan JP, Xu Z, Salvetti DJ et al (2013) Results of gamma knife surgery for Cushing's disease. J Neurosurg 119(6):1486–1492
95. Budyal S, Lila AR, Jalali R et al (2014) Encouraging efficacy of modern conformal fractionated radiotherapy in patients with uncured Cushing's disease. Pituitary 17(1):60–67
96. Sheehan JM, Lopes MB, Sheehan JP et al (2000) Results of transsphenoidal surgery for Cushing's disease in patients with no histologically confirmed tumor. Neurosurgery 47(1):33–36
97. Ratliff JK, Oldfield EH (2000) Multiple pituitary adenomas in Cushing's disease. J Neurosurg 93(5):753–761
98. Oldfield EH, Vance ML, Louis RG et al (2015) Crooke's changes in Cushing's syndrome depends on degree of hypercortisolism and individual susceptibility. J Clin Endocrinol Metab 100(8):3165–3171
99. Mallappa A, Debono M (2016) Recent advances in hydrocortisone replacement treatment. Endocr Dev 30:42–53
100. Bornstein SR, Allolio B, Arlt W et al (2016) Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 101(2):364–389
101. Ritzel K, Beuschlein F, Mickisch A et al (2013) Clinical review: outcome of bilateral adrenalectomy in Cushing's syndrome: a systematic review. J Clin Endocrinol Metab 98(10):3939–3948
102. Reincke M, Ritzel K, Oßwald A et al (2015) A critical reappraisal of bilateral adrenalectomy for ACTH-dependent Cushing's syndrome. Eur J Endocrinol 173(4):M23–M32
103. Oßwald A, Plomer E, Dimopoulou C et al (2014) Favorable long-term outcomes of bilateral adrenalectomy in Cushing's disease. Eur J Endocrinol 171(2):209–215
104. Gadelha MR, Vieira Neto L (2014) Efficacy of medical treatment in Cushing's disease: a systematic review. Clin Endocrinol (Oxf) 80(1):1–12
105. Trementino L, Cardinaletti M, Concettoni C et al (2015) Salivary cortisol is a useful tool to assess the early response to pasireotide in patients with Cushing's disease. Pituitary 18(1):60–67
106. Fleseriu M, Biller BM, Findling JW, Molitch ME, Schteingart DE, Gross C; SEISMIC Study Investigators (2012) Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. J Clin Endocrinol Metab 97(6):2039–2049
107. Wallia A, Colleran K, Purnell JQ et al (2013) Improvement in insulin sensitivity during mifepristone treatment of Cushing syndrome: early and late effects. Diabetes Care 36(9):e147–e148
108. Newell-Price J (2014) Ketoconazole as an adrenal steroidogenesis inhibitor: effectiveness and risks in the treatment of Cushing's disease. J Clin Endocrinol Metab 99(5):1586–1588
109. Zacharia BE, Gulati AP, Bruce JN et al (2014) High response rates and prolonged survival in patients with corticotroph pituitary tumors and refractory Cushing disease from capecitabine and temozolomide (CAPTEM): a case series. Neurosurgery 74(4):E447–E455
110. Uwaifo GI, Koch CA, Hirshberg B et al (2003) Is there a therapeutic role for octreotide in patients with ectopic Cushing's syndrome? J Endocrinol Invest 26(8):710–717
111. Krakoff J, Koch CA, Calis KA et al (2001) Use of a parenteral propylene glycol-containing etomidate preparation for the long-term management of ectopic Cushing's syndrome. J Clin Endocrinol Metab 86(9):4104–4108

112. Vilar L, Naves LA, Machado MC, Bronstein MD (2015) Medical combination therapies in Cushing's disease. Pituitary 18(2):253–262
113. Koch CA, Pacak K, Chrousos GP (2002) The molecular pathogenesis of hereditary and sporadic adrenocortical and adrenomedullary tumors. J Clin Endocrinol Metab 87(12):5367–5384
114. Dworakowska D, Grossman AB (2012) The molecular pathogenesis of corticotroph tumours. Eur J Clin Invest 42(6):665–676
115. Perez-Rivas LG, Reincke M (2016) Genetics of Cushing's disease: an update. J Endocrinol Invest 39(1):29–35
116. Beuschlein F, Fassnacht M, Assié G et al (2014) Constitutive activation of PKA catalytic subunit in adrenal Cushing's syndrome. N Engl J Med 370(11):1019–1028
117. Goh G, Scholl UI, Healy JM et al (2014) Recurrent activating mutation in PRKACA in cortisol-producing adrenal tumors. Nat Genet 46(6):613–617
118. Bourdeau I, Oble S, Magne F et al (2016) ARMC5 mutations in a large French-Canadian family with cortisol-secreting β-adrenergic/vasopressin responsive bilateral macronodular adrenal hyperplasia. Eur J Endocrinol 174(1):85–96
119. Zilbermint M, Stratakis CA (2015) Protein kinase A defects and cortisol-producing adrenal tumors. Curr Opin Endocrinol Diabetes Obes 22(3):157–162
120. Thiel A, Reis AC, Haase M et al (2015) PRKACA mutations in cortisol-producing adenomas and adrenal hyperplasia: a single-center study of 60 cases. Eur J Endocrinol 172(6):677–685
121. Nakamura Y, Yamazaki Y, Felizola SJ et al (2015) Adrenocortical carcinoma: review of the pathologic features, production of adrenal steroids, and molecular pathogenesis. Endocrinol Metab Clin North Am 44(2):399–410
122. Reincke M, Sbiera S, Hayakawa A et al (2015) Mutations in the deubiquitinase gene USP8 cause Cushing's disease. Nat Genet 47(1):31–38
123. Mancia G, Oparil S, Whelton PK et al (2017) The technical report on sodium intake and cardiovascular disease in low- and middle-income countries by the joint working group of the World Heart Federation, the European Society of Hypertension and the European Public Health Association. Eur Heart J 38(10):712–719
124. Mariampillai JE, Eskås PA, Heimark S et al (2016) A case for less intensive blood pressure control: it matters to achieve target blood pressure early and sustained below 140/90mmHg. Prog Cardiovasc Dis 59(3):209–218
125. Mangat BK, Campbell N, Mohan S et al (2015) Resources for blood pressure screening programs in low resource settings: a guide from the World Hypertension League. J Clin Hypertens (Greenwich) 17(6):418–420
126. Baid S, Nieman LK (2004) Glucocorticoid excess and hypertension. Curr Hypertens Rep 6:493–499
127. Magiakou MA, Mastorakos G, Zachman K, Chrousos GP (1997) Blood pressure in children and adolescents with Cushing's syndrome before and after surgical cure. J Clin Endocrinol Metab 82:1734–1737
128. Lodish MB, Sinaii N, Patronas N et al (2009) Blood pressure in pediatric patients with Cushing's syndrome. J Clin Endocrinol Metab 94:2002–2008
129. Pirpiris M, Yeung S, Dewar E et al (1993) Hydrocortisone-induced hypertension in men. The role of cardiac output. Am J Hypertens 6:287–294
130. Connell JM, Whitworth JA, Davies DL et al (1987) Effects of ACTH and cortisol administration on blood pressure, electrolyte metabolism, atrial natriuretic peptide and renal function in normal man. J Hypertens 5:425–433
131. Grassi G, Seravalle G, Dell'Oro R et al (2001) Participation of the hypothalamus-hypophysis axis in the sympathetic activation of human obesity. Hypertension 38(6):1316–1320
132. Cicala MV, Mantero F (2010) Hypertension in Cushing's syndrome: from pathogenesis to treatment. Neuroendocrinology 92:44–49

# Primary Aldosteronism and Its Various Scenarios

# 29

Nieves Martell-Claros, María Abad-Cardiel,
Beatriz Alvarez-Alvarez, and José A. García-Donaire

Primary hyperaldosteronism (PA), caused by an excessive secretion of aldosterone, renin-independent and non-suppressible by sodium loading, is the most frequent endocrine aetiology of secondary hypertension, recurrently underdiagnosed [1]. The excess of aldosterone exerts a progressive damage on the cardiovascular (CV) system and confers a high CV risk to the patient [1–4]. Since specific treatment offers an optimal blood pressure (BP) control and a decrease in CV risk, its early recognition might even resolve the clinical problem. Furthermore, identifying and appropriately treating patients with PA can improve outcomes in a large number of patients who have resistant hypertension [5]. Nowadays, prevalence of PA is recognized as much higher (>10%) than previously reported (<1%) amongst hypertensive [6, 7].

The presence of primary mineralocorticoid excess (aldosterone and, to a much lesser degree, deoxycorticosterone) should be suspected in any patient with the triad of hypertension, unexplained hypokalaemia and metabolic alkalosis [8]. However, there are patients with primary mineralocorticoid excess who are normokalaemic and, although uncommon, others who are hypokalaemic but normotensive. The PA is known to be expressed according to different anatomic alterations (adenoma, hyperplasia, etc.) [9].

## 29.1 Aldosterone Pathophysiology

Aldosterone is a steroid hormone mostly produced in the glomerulus zone of the adrenal gland. Mechanisms that regulate aldosterone secretion are complex. Synthesis and secretion depend on renin-angiotensin system and serum potassium

N. Martell-Claros (✉) • M. Abad-Cardiel • B. Alvarez-Alvarez • J.A. García-Donaire
Unidad de Hipertensión, Servicio de Medicina Interna, Hospital Clinico San Carlos, Madrid, Spain

Instituto de Investigación Sanitaria, Hospital Clinico San Carlos, Madrid, Spain
e-mail: nmartell.hcsc@salud.madrid.org



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_29

plasmatic concentration. Angiotensin II is one of the main stimulating factors, even though it can be supressed by hypervolaemia and hypokalaemia and, in a lesser degree, by sodium and ACTH [9]. Circulating atrial natriuretic peptide (ANP) and dopamine are inhibitors of aldosterone release in the zona glomerulosa [10]. In the case of imbalance of the inhibition/secretion balance, the deleterious effects on vascular system are prevailing, leading to an organic dysfunction [11].

Aldosterone has genomic and non-genomic effects. Biosynthetic pathway is originated in the cholesterol molecule, and the enzyme that catalyses this process is the aldosterone synthetase, along with the 11β-hydroxylase, 18-hydroxylase and 18-hydroxydehydrogenase; all of them are codified by the CYP11B2 gene. Aldosterone has been shown to display rapid non-genomic effects that do not require signalling through the classic pathways of gene activation, transcription and protein synthesis and non-inhibited by mineralocorticoid antagonists [9, 11, 12]. These actions substantially contribute to the pathophysiology of congestive heart failure and progressive renal dysfunction.

This hormone acts on its target organs via specific mineralocorticoid receptors, located at epithelial cells (distal tubular renal cells, sweat glands, salivary glands, colon, smooth muscle cells, cardiomyocytes and endothelial stem cells) [13, 14]. Aldosterone regulates sodium epithelial channel activity in the apical membrane by this mechanism. Likewise, activity of sodium/potassium pump in the basolateral membrane of the distal tubular cells also appears to be enhanced. Therefore, aldosterone is the main regulator hormone responsible of renal electrolytic balance by regulating sodium retention and potassium excretion [9].

Aldosterone excess induces endothelial dysfunction via vascular inflammation and early tissue remodelling and oxidative stress depending on mineralocorticoid mechanisms [15]. Aldosteronism has also been implied in collagen synthesis, vascular remodelling and myocardial fibrosis in an independent process of its effect on BP and mineralocorticoids [16]. In addition, aldosterone plays an outstanding role in general metabolism, with direct effects on the β-pancreatic cells [17] and insulin signalling [18]. An excess of aldosterone has unfavourable effects that contribute to the appearance of the metabolic syndrome that leads to the development of resistant hypertension [19].

## 29.2 Classification: Anatomical Types and Mutations

Initially, there is an anatomical classification that facilitates the identification of surgically curable patients. The cases of PA are due either to an aldosterone-secreting adenoma (APA) (40%) or due to idiopathic hyperaldosteronism (IHA) (60%, almost all of which are bilateral). Aldosterone-secreting carcinomas are diagnosed in about 1% of patients, while both familial hyperaldosteronism (FH) and ectopic aldosterone-producing adenoma or carcinomas are reported in 1% [20, 21]. Some authors conclude that a pathological continuum is present between the true adrenal adenoma and the micronodular bilateral hyperplasia, including a number of intermediate clinical entities [22]. Unilateral adrenal hyperplasia accounts for 14–17% of all cases of unilateral PA. The prevalence of cortical adenoma within cortical hyperplasia is estimated to be 6–24% [23].

APAs are usually benign encapsulated adenomas with a size smaller than 2 cm. Most cases are solitary, although in as many as one third of cases, evidence exists of nodularity in the same adrenal gland, suggesting that the condition has arisen in a previously hyperplasic gland. The histology is likely to demonstrate cells from the zona fasciculata and mixed and compact cells. An irregular cellular architecture with pleomorphism, enhanced nuclei and chromatin must suggest an APA.

Bilateral hyperplasia is often described as an extension of the zona glomerulosa on the zona fasciculata as a subcapsular band [24]. Patients with IHA have bilateral thickening and variable nodularity of their adrenal cortex. A wide spectrum of severity exists for this disorder, which might be undetected for long periods with no hypokalaemia and only mild hypertension.

These dichotomic descriptions usually share descriptions with unilateral nodular hyperplasia. There are differences between benign and malignant lesions but rarely amongst adenomas, although adenoma has a higher percentage of monoclonality and cellular proliferation versus hyperplasia, in which polyclonality is usual. Otherwise, heterogeneity is likely present in both diagnoses [25].

Correlation in diagnosis between anatomopathological findings and image tests is poor. In a published study regarding sensitivity of adrenal biopsies, diagnostic accuracy was lower than 40% for hyperplasia and 76% for APA [26].

Inherited forms of PA account for only 1%. These forms include FH types I (glucocorticoid-remediable aldosteronism (GRA)), II and III. All forms are inherited in an autosomal dominant manner [27, 28].

In FH-I, bilateral hyperplasia of the zona fasciculata is the most frequent finding, and a significant increase in incidence of cerebrovascular aneurysms is observed. FH-II exhibits a high rate of adenoma formation [29]. FH-III is rare and characterized by early-onset hypertension and hypokalaemia. Mutations of the KCNJ5 gene have been identified as a cause of FH-III [30].

Different studies report somatic KCNJ5 mutations in APAs, ranging from 30 to 65% [31]. These mutations result in increased sodium conductance and membrane depolarization, triggering calcium entry into the zona glomerulosa cells, with activation of the calcium-signalling pathway, the major mediator of aldosterone production. These mutations are more prevalent in females and in younger patients and are related with higher aldosterone levels and lower K+ concentrations [32].

Also, somatic mutations in ATP1A1 (encoding the alpha-1 subunit of the Na+/K+ ATPase), in ATP2B3 (encoding the plasma membrane calcium transporting ATPase 3) and in CACNA1D (encoding a voltage-gated calcium channel) have been identified. These mutations showed male dominance, increased plasma aldosterone concentrations, lower potassium concentrations and smaller tumours [33–35].

## 29.3 Clinical Features as the Consequence of Hyperaldosteronism

Hypertension: the elevation of BP is dependent upon the mild volume expansion that occurs. Persistent hypervolaemia also leads to an increase in systemic vascular resistance that helps to perpetuate the hypertension [6]. PA may be associated with resistant hypertension [5].

Hypokalaemia is an inconsistent finding. The plasma potassium levels tend to be relatively stable at least over the short term. Progressive hypokalaemia does not occur unless some other factor is added, such as very important increased aldosterone production or the use of diuretic therapy. In the case of plasma potassium concentration below 2.5 mEq/L, muscle weakness can appear.

Metabolic alkalosis is largely due to increased urinary hydrogen excretion mediated both by hypokalaemia and by the direct stimulatory effect of aldosterone on distal acidification.

Mild hypernatremia and hypomagnesaemia can also exist.

A long-lasting exposure to inadequately high plasmatic concentrations of aldosterone is associated with a higher oxidative stress, endothelial dysfunction, CV remodelling, hypertrophy and fibrosis. These effects determine the higher CV mortality (significantly higher rates of prior stroke, nonfatal myocardial infarction and atrial fibrillation) of PA patients with regard to essential hypertensive, matched for age and gender, with a similar BP level [2]. Dietary salt may affect the impact of PA on cardiac damage: 24 h urinary sodium excretion was an independent predictor for left ventricular wall thickness and mass in patients with PA [36].

PA is related to cardiac alterations, both in left ventricle filling and diastolic function and in PQ interval increase, although systolic function is preserved [6]. A higher prevalence of left ventricle concentric hypertrophy has been described in PA patients as compared to vascular-renal or essential hypertensive [37, 38].

Excess of aldosterone favours a higher vascular stiffness, especially in great arteries, generalized tissue fibrosis and remodelling of resistance arteries. This can be observed through a higher pulse wave velocity and augmentation index when compared to essential hypertensive patients, even after adjustment of confounding bias [39–41].

Regarding kidney damage, the excess of aldosterone may increase urinary albumin excretion higher than in patients with essential hypertension [42]. Also, it exerts a rise in the glomerular filtration rate (GFR) and renal perfusion pressure independent of systemic hypertension and is reversible after specific treatment [43, 44].

Likewise, a higher frequency of metabolic syndrome [45] leading to resistant hypertension [19] has been observed. Adipose tissue in obese individuals can release molecules that stimulate adrenal aldosterone in an independent manner of the saline volume. This can explain the higher salt sensitivity that obese metabolic syndrome patients have [46].

Also, aldosteronism increases the risk of bone loss, possibly at least in part due to increased calciuria and magnesiuria [47].

Generalized anxiety disorders and other psychiatric illnesses occurred more often in patients with PA than in those with essential hypertension [48].

## 29.4 Difficulties on the PA Diagnosis

In spite of the previous description and classification, the most accurate detection, diagnosis and therapeutic approach to PA is still a big challenge. An active clinical search must be performed amongst individuals at risk [21]. Similarly, the

widespread diagnosis of PA is also a hard task itself due to the multiple faces that this pathology can express. However, the PA correct diagnosis has been shown to be cost-effective [49].

In a large percentage of patients, the clinical findings are not enough to correctly diagnose PA, even in the genetic forms. The phenotype might differ from a mild hypertension to a resistant form of severe high BP that eventually may require bilateral adrenalectomy, since mild or moderate hypertension can be responsive to a pharmacological approach.

FH-I patients usually have a significant increase in incidence of cerebrovascular aneurysms. FH-II exhibits a high rate of adenoma formation [29]. FH-III is a rare condition characterized by early-onset hypertension and hypokalaemia. Different somatic KCNJ5 mutations in APA are more prevalent in females and in younger patients, and they are associated with higher aldosterone levels and lower K+ concentrations [32].

### 29.4.1 Significance of Hypokalaemia

Diverse clinical presentations of PA have been described [42], not considering low potassium levels as indispensable diagnostic criteria. Only a minority of patients with PA (9–37%) has hypokalaemia [50]. Normokalaemic hypertension constitutes the most common presentation of the disease. Our group in a single centre and in a state German cohort [52] has described two types of presentation for the disease, according to the presence/absence of hypokalaemia. The German Conn's registry found a nearly equal distribution of hypokalaemia (45–65%) in all age decades with the exception of patients between the ages of 20 and 29 years, in whom normokalaemia was present more often. In the Martell-Claros et al. study [51], no differences were observed in the biochemical profile or in target organ damage, according to the type of presentation, whether normo- or hypokalaemia. Prevalence of metabolic syndrome did not show differences either.

With respect to clinical characteristics, no statistical differences were observed between groups regarding age. Otherwise, time of evolution of hypertension is directly and significantly related to a higher prevalence of hypokalaemic presentation of PA [51].

### 29.4.2 Comorbidities

In the German Conn's registry, there was no significant difference between hypokalaemic and normokalaemic patients in terms of body mass index (BMI). Similarly, no significant differences in the prevalence of cerebrovascular and peripheral vascular events, sleep apnoea and chronic renal failure were reported between normokalaemic and hypokalaemic PA.

The overall prevalence of comorbidities was significantly higher in hypokalaemic than normokalaemic PA. The prevalence rate for cardiac events was

significantly higher in hypokalaemic PA (OR = 2.2; 95% CI 1.5–3.2). Further analysis of cardiac events revealed significantly higher prevalence rates of angina pectoris (OR = 4.7; 95% CI 1.8–12.4) and chronic cardiac insufficiency (OR = 2.8; 95% CI 1.0–7.6) in hypokalaemic compared with normokalaemic PA patients. Atrial arrhythmias showed a trend towards higher prevalence in hypokalaemic PA [52].

### 29.4.3 BP Levels/Hypertension

It must be highlighted that mean systolic and diastolic blood pressures are often higher in patients with hypokalaemic than normokalaemic aldosteronism. Hypokalaemic patients often have Grade 2 systolic hypertension at baseline [26, 51–53].

A correlation between duration of hypertension and the probability of hypokalaemic presentation has been demonstrated [51]. The duration of hypertension has been reported as a negative predictor of outcome. Delays in diagnosis may result in a poorer response to specific treatment once PA is finally diagnosed. Patients treated for PA, during a median follow-up of 12 years, had a higher rate of events than essential hypertensives, and in particular, arrhythmias and stroke were more frequent in patients with PA. Age, the duration of the hypertension and systolic BP were independently associated with the occurrence of all events [54].

### 29.4.4 Aldosterone Excess

Even serum aldosterone levels in the high-normal range may be associated with increased BP. In a report from the Framingham Offspring study [55], the highest quartile in serum aldosterone was associated with an increased risk of elevated BP and hypertension.

Also, independently of the anatomic variation in PA patients, aldosterone levels show a progressive increase throughout the follow-up period (years) until their stabilization, at very high levels, while potassium levels fall to lowest values [51].

Mean aldosterone concentrations at diagnosis differed between normokalaemic and hypokalaemic PA, with significantly higher levels in the hypokalaemia variant [51, 52].

As shown in Fig. 29.1, both presentations have similar clinical manifestation and heterogeneity. Two rather different evolutions of data are observed in the mathematic model between groups on their association with aldosterone levels and time of evolution of hypertension. In patients with hypokalaemia, baseline aldosterone levels are elevated and maintained for a long time. Conversely, aldosterone levels are lower on the normokalaemic group, but increase throughout the follow-up. Therefore, it seems that aldosterone level determines the form of presentation of PA, regardless of the adrenal morphology and its unilateral or bilateral location.

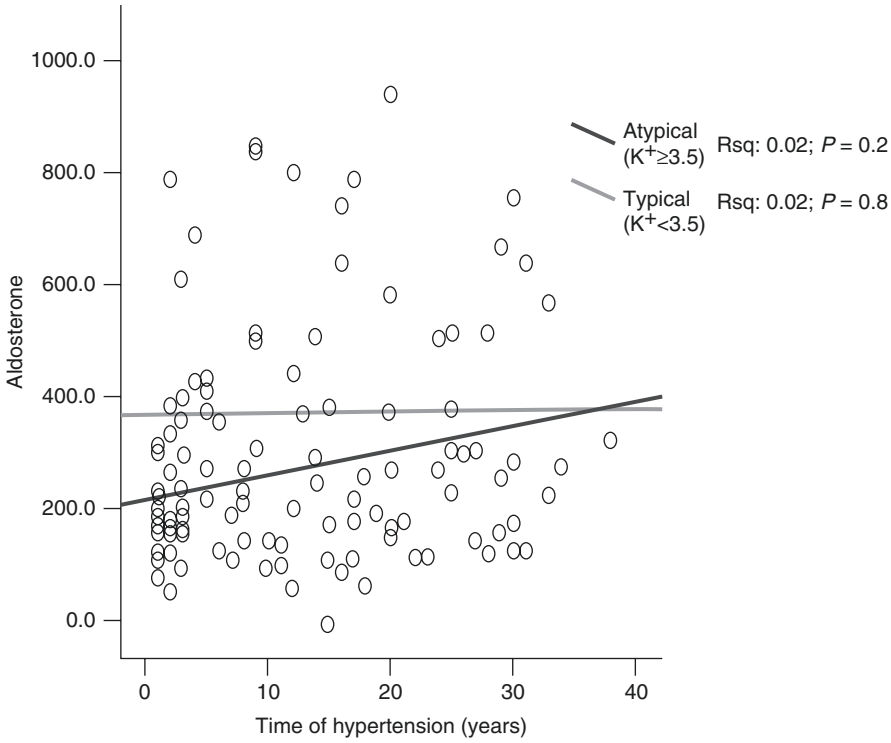



**Fig. 29.1** Evolution of serum aldosterone levels (ng/dl). Patients with primary aldosteronism and typical presentation were more likely to have a higher and stable (light grey line) plasmatic aldosterone levels throughout the follow-up. Typical, serum K+ less than 3.5 mEq/L; atypical, serum K+ of at least 3.5 mEq/L

### 29.4.5 Difficulties in the Analysis of Image Tests

Adrenal CT, a common image test used for the diagnosis of PA, has several limitations. Radiologists might interpret small APAs incorrectly as "IAH" on the basis of CT findings according to bilateral modularity or normal-appearing adrenals. Moreover, apparent adrenal microadenomas may actually represent areas of hyperplasia or non-functioning nodularity. In addition, non-functioning unilateral adrenal macroadenomas are not uncommon, especially in older patients [56], and are indistinguishable from APAs on CT. Likewise, unilateral adrenal hyperplasia (UAH) may be visible on CT, or the UAH adrenal may appear normal on CT. All these potential errors should be taken into account in order for accuracy in diagnosis.

Half of the patients with an APA and 17% of those with idiopathic hyperaldosteronism (IHA) may have serum potassium concentrations <3.5 mmol/L [42]. Thus, the presence of hypokalaemia has low sensitivity, and the absence of hypokalaemia has a low negative predictive value for the diagnosis of PA.

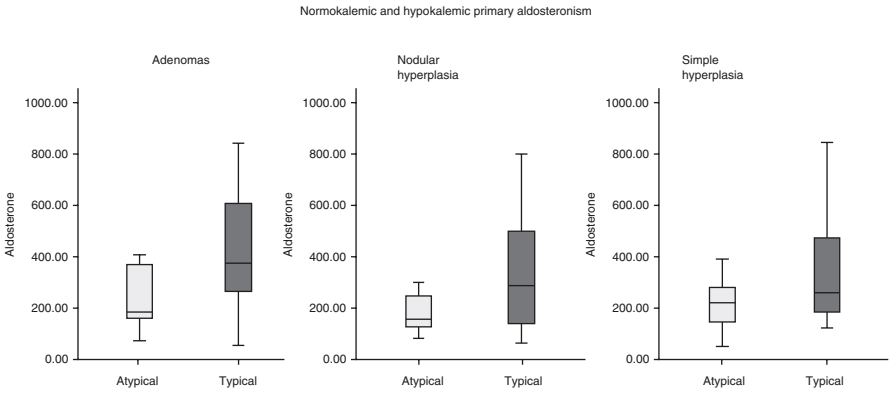



**Fig. 29.2** Aldosterone levels in the three morphological types (adenomas and simple or nodular hyperplasia) and both clinical presentations. In spite of overlapping aldosterone levels, patients with atypical presentation and primary aldosteronism always showed a lower plasmatic aldosterone concentration (light grey bar). Conversely, patients with typical presentation and primary aldosteronism exhibited higher aldosterone levels (black bar). Aldosterone, ng/dl; typical, serum potassium less than 3.5 mEq/L; atypical, serum potassium of at least 3.5 mEq/L. HBP, high blood pressure

In patients with hypokalaemia (K < 3.5), the circulating aldosterone levels are higher than in normokaliemic patients, irrespective of anatomical image: adenoma, nodular hyperplasia or simple hyperplasia (Fig. 29.2) [51].

Furthermore, CT scanning does not provide any functional characterization of the adrenal nodule(s). In a recent meta-analysis, 37.8% discrepancy was observed between adrenal venous sampling (AVS) and adrenal imaging [57].

We believe that lateralization of the source of the excessive aldosterone secretion is critical to guide the management of PA. The sensitivity and specificity of AVS (95 and 100%, respectively) for detecting unilateral aldosterone excess are superior to that of adrenal CT (78 and 75%, respectively). AVS is the gold standard test to distinguish unilateral (APA or UAH) from bilateral disease (IHA) [58, 59].

Notwithstanding the consensus in medical management, interpretation of diagnostic procedures in patients with suspicion of PA, both normokalaemia and hypokalaemia is a challenge nowadays [60]. The accurate distinction between unilateral and bilateral adrenal diseases in patients with PA guides surgical management. Hence, the AVS has been advocated as a required step to demonstrate the lateralization of aldosterone excess [21].

The anatomy of adrenal venous drainage adds difficulty to the procedure to the interpretation of the interventional radiologist: the left adrenal vein (LAV) flows in the left renal vein, whereas the right adrenal vein (RAV) drains directly into the inferior vena cava (IVC); furthermore, LAV blood may be diluted by the inferior phrenic vein and RAV blood by hepatic accessory branches and renal accessory veins [61, 62]. In addition different branches of adrenal veins drain different regions within a gland: in this case super-selective sampling with micro-catheters can be useful in identifying the site of the secreting nodule(s), thereby allowing partial adrenalectomy or enucleation [63].

A solitary cortical adenoma, previously believed to account for the vast majority of histologic diagnoses of surgical primary hyperaldosteronism, was not as prevalent in our series [51]. This is likely due to the use of AVS, rather than image results, to prove a unilateral disease. In conclusion, as AVS is becoming widely used to select patients with primary hyperaldosteronism for adrenalectomy, there is a higher likelihood that these patients will have histologic findings showing higher rates of non-solitary cortical adenoma [23]. We observed that 16% of patients with primary hyperaldosteronism had unilateral adrenal cortical hyperplasia without cortical adenoma [51]. As such, subtotal adrenalectomy may not be appropriate in patients with primary hyperaldosteronism, since cortical hyperplasia may account for increased hormone production in patients with adenoma.

Adrenal anatomic findings have been questioned due to their poor ability to differentiate both entities [22]. PA must be considered as a pathological continuum with a number of intermediate clinical forms [23].

Weisbrod et al. [23] demonstrated that in unilateral PA patients, with a diagnosis of solitary cortical adenoma, cortical hyperplasia or a multinodular hyperplasia (included cortical adenoma plus cortical hyperplasia), no significant difference in age, gender, body mass index, duration of hypertension, number of antihypertensive medications, serum aldosterone level, serum renin level or adrenal vein sampling ratios amongst the three histologic categories was obtained in the analysis. Our group did not find any significant difference amongst the three categories in postoperative cure rate. It can be also suggested that subtotal adrenalectomy might not be appropriate in patients with primary aldosteronism.

Monticone et al. indicate that the combination of genotyping and immunohistochemistry improves the final histopathological diagnosis between single nodule and multinodular hyperplasia of the assessed adrenals [64].

## References

1. Young WF (2007) Primary aldosteronism: renaissance of a syndrome. Clin Endocrinol 66:607–618
2. Milliez P, Girerd X, Plouin PF et al (2005) Evidence for an increased rate of cardiovascular events in patients with primary Aldosteronism. J Am Coll Cardiol 45:1243–1248
3. Savard S, Amar L, Plouin PF, Steichen O (2013) Cardiovascular complications associated with primary aldosteronism: a controlled cross-sectional study. Hypertension 62:331–336
4. Prejbisz A, Warchoł-Celińska E, Lenders JWM, Januszewicz A (2015) Cardiovascular risk in primary hyperaldosteronism. Horm Metab Res 47:973–980
5. Douma S, Petidis K, Doumas M et al (2008) Prevalence of primary aldosteronism in resistant hypertension: a retrospective observational study. Lancet 371:1921–1926
6. Rossi GP, Pessinaa AC, Heagerty AM (2008) Primary aldosteronism: an update on screening, diagnosis and treatment. J Hypertens 26:613–621
7. Piaditis G, Markou A, Papanastasiou L et al (2015) Progress in aldosteronism: a review of the prevalence of primary aldosteronism in pre-hypertension and hypertension. Eur J Endocrinol 172:R191–R203
8. Conn JW (1955) Primary aldosteronism: a new clinical syndrome. J Lab Clin Med 45:3–17
9. Foo R, O'Shaughnessy KM, Brown MJ (2001) Hyperaldosteronism: recent concepts, diagnosis, and management. Postgrad Med J 77:639–644

10. Chang HW, Chu TS, Huang HY et al (2007) Down-regulation of D2 dopamine receptor and increased protein kinase Cmu phosphorylation in aldosterone-producing adenoma play roles in aldosterone overproduction. J Clin Endocrinol Metab 92:1863–1870
11. Adler GK, Williams GH (2007) Aldosterone: villain or protector? Hypertension 50:31–32
12. Funder JW (2010) Aldosterone and mineralocorticoid receptors: past, present and future. Endocrinology 151:5098–5102
13. Basti CP, Hayslett JP (1992) The cellular action of aldosterone in target epithelia. Kidney Int 42:250–264
14. Wu VC, Lo SC, Chen YL et al; TAIPAI Study Group (2011) Endothelial progenitor cells in primary aldosteronism: a biomarker of severity for aldosterone vasculopathy and prognosis. J Clin Endocrinol Metab 96:3175–3183
15. Young MJ (2008) Mechanisms of mineralocorticoid receptor-mediated cardiac fibrosis and vascular inflammation. Curr Opin Nephrol Hypertens 17:174–180
16. Brown NJ (2013) Contribution of aldosterone to cardiovascular and renal inflammation and fibrosis. Nat Rev Nephrol 9:459–469
17. Rayner B (2008) Primary aldosteronism and aldosterone-associated hypertension. J Clin Pathol 61:825–831
18. Whaley-Connell A, Johnson MS, Sowers JR (2010) Aldosterone: role in the cardiometabolic syndrome and resistant hypertension. Prog Cardiovasc Dis 52:401–409
19. Sowers JR, Whaley-Connell A, Epstein M (2009) Narrative review: the emerging clinical implications of the role of aldosterone in the metabolic syndrome and resistant hypertension. Ann Intern Med 150:776–783
20. Aronova A, Fahey TJ III, Zarnegar R (2014) Management of hypertension in primary aldosteronism. World J Cardiol 6:227–233
21. Funder JW, Carey RM, Mantero F et al (2016) The Management of Primary Aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 101(5):1889–1916
22. Rossi GP, Sacchetto A, Chiesura-Corona M et al (2001) Identification of the Etiology of primary Aldosteronism with adrenal vein sampling in patients with equivocal computed tomography and magnetic resonance findings: results in 104 consecutive cases. J Clin Endocrinol Metab 86:1083–1090
23. Weisbrod AB, Webb RC, Mathur A et al (2013) Adrenal histologic findings show no difference in clinical presentation and outcome in primary hyperaldosteronism. Ann Surg Oncol 20:753–758
24. McNicol AM (2008) Lesions of the adrenal cortex. Arch Pathol Lab Med 132:1263–1271
25. Diaz-Cano SJ, de Miguel M, Blanes A et al (2001) Contribution of the Microvessel Network to the clonal and kinetic profiles of adrenal cortical proliferative lesions. Hum Pathol 32:1232–1239
26. Saeger W, Fassnacht M, Chita R et al; For The German And Austrian Adrenal Network (2003) High diagnostic accuracy of adrenal Core biopsy: results of the German and Austrian adrenal Network Multicenter trial in 220 consecutive patients. Hum Pathol 34:180–186
27. Lifton RP, Dluhy RG, Powers M et al (1992) 11 beta-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. Nature 355:262–265
28. Funder JW (2012) The genetic basis of primary aldosteronism. Curr Hypertens Rep 14:120–124
29. Lafferty AR, Torpy DJ, Stowasser M et al (2000) A novel genetic locus for low rennin hypertension: familial hyperaldosteronism type maps to chromosovme 7 (7p22). J Med Genet 37(11):831–835
30. Choi M, Scholl UI, Yue P et al (2011) K+ channel mutations in adrenal aldosterone-producing adenomas and hereditary hypertension. Science 331:768–772
31. Boulkroun S, Beuschlein F, Rossi GP et al (2012) Prevalence, clinical, and molecular correlates of KCNJ5 mutations in primary aldosteronism. Hypertension 59:592–598
32. Azizan EA, Lam BY, Newhouse SJ et al (2012) Microarray, qPCR, and KCNJ5 sequencing of aldosterone-producing adenomas reveal differences in genotype and phenotype between zona glomerulosa- and zona fasciculata-like tumors. J Clin Endocrinol Metab 97:819–829

33. Beuschlein F, Boulkroun S, Osswald A et al (2013) Somatic mutations in ATP1A1 and ATP2B3 lead to aldosterone-producing adenomas and secondary hypertension. Nat Genet 45:440–444
34. Azizan EA, Poulsen H, Tuluc P et al (2013) Somatic mutations in ATP1A1 and CACNA1D underlie a common subtype of adrenal hypertension. Nat Genet 45:1055–1060
35. Williams TA, Monticone S, Schack VR et al (2014) Somatic ATP1A1, ATP2B3 and KCNJ5 mutations in aldosterone-producing adenomas. Hypertension 63:188–195
36. Pimenta E, Gordon RD, Ahmed AH et al (2011) Cardiac dimensions are largely determined by dietary salt in patients with primary aldosteronism: results of a case-control study. J Clin Endocrinol Metab 96:2813–2820
37. Matsumura K, Fujii K, Oniki H et al (2006) Role of aldosterone in left ventricular hypertrophy in hypertension. Am J Hypertens 19:13–18
38. Abad-Cardiel M, Alvarez-Alvarez B, Luque-Garcıa L et al (2013) Hypertension caused by primary hyperaldosteronism: increased heart damage and cardiovascular risk. Rev Esp Cardiol (Engl Ed) 66:47–52
39. Strauch B, Petrák O, Zelinka T et al (2006) Increased Arterial Wall stiffness in primary Aldosteronism in comparison with essential hypertension. Am J Hypertens 19:909–914
40. Rossi GP, Bolognesi M, Rizzoni D et al (2008) Vascular Remodeling and duration of hypertension predict outcome of adrenalectomy in primary Aldosteronism patients. Hypertension 51:1366–1371
41. Bernini G, Galetta F, Franzoni F et al (2008) Arterial stiffness, intima-media thickness and carotid artery fibrosis in patients with primary aldosteronism. J Hypertens 26:2399–2405
42. Rossi GP, Bernini GP (2006) Desideri GB et al; for the PAPY study participants. Renal Damage in Primary Aldosteronism Results of the PAPY Study Hypertension 48:232–238
43. Sechi LA, Novello M, Lapenna R et al (2006) Long-term renal outcomes in patients with primary Aldosteronism. JAMA 295:2638–2645
44. Sechi LA, Di Fabio A, Bazzocchi M et al (2009) Intrarenal hemodynamics in primary aldosteronism before and after treatment. J Clin Endocrinol Metab 94:1191–1197
45. Fallo F, Pilon C, Urbanet R (2012) Primary aldosteronism and metabolic syndrome. Horm Metab Res 44:208–214
46. Fujita T (2010) Mineralocorticoid receptors, salt-sensitive hypertension, and metabolic syndrome. Hypertension 55:813–818
47. Chhokar VS, Sun Y, Bhattacharya SK et al (2005) Hyperparathyroidism and the calcium paradox of aldosteronism. Circulation 111:871–878
48. Sonino N, Tomba E, Genesia ML et al (2011) Psychological assessment of primary aldosteronism: a controlled study. J Clin Endocrinol Metab 96:E878–E883
49. Lubitz CC, Economopoulos KP, Sy S et al (2015) Cost-effectiveness of screening for primary Aldosteronism and subtype diagnosis in the resistant hypertensive patients. Circ Cardiovasc Qual Outcomes 8:621–630
50. Mulatero P, Stowasser M, Loh K et al (2004) Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. J Clin Endocrinol Metab 89:1045–1050
51. Martell-Claros N, Abad-Cardiel M, Alvarez-Alvarez B et al (2015) Primary aldosteronism and its various clinical scenarios. J Hypertens 33:1226–1232
52. Born-Frontsberg E, Reincke M, Rump LC et al (2009) Registry. Participants of the German Conn's cardiovascular and cerebrovascular comorbidities of hypokaliemic and normokalemic primary aldosteronism: results of the German Conn's Registry J Clin Endocrinol Metab 94:1125–1130
53. Calhoun DA (2006) Aldosterone and cardiovascular disease: smoke and fire. Circulation 114:2572–2574
54. Mulatero O, Monticone S, Betello C et al (2013) Long-term cardio- and cerebrovascular events in patients with primary aldosteronism. J Clin Endocrinol Metab 98:4826–4833
55. Vasan RS, Evans JC, Larson MG et al (2004) Serum aldosterone and the incidence of hypertension in nonhypertensive persons. N Engl J Med 351:33–41
56. Kloos RT, Gross MD, Francis IR et al (1995) Incidentally discovered adrenal masses. Endocr Rev 16:460–484

57. Kempers MJ, Lenders JW, van Outheusden L et al (2009) Systematic review: diagnostic procedures to differentiate unilateral from bilateral adrenal abnormality in primary aldosteronism. Ann Intern Med 151:329–337
58. Rossi GP, Barisa M, Allolio B et al (2012) The adrenal vein sampling international study (AVIS) for identifying the major subtypes of primary aldosteronism. J Clin Endocrinol Metab 97:1606–1614
59. Rossi GP, Auchus RJ, Brown M et al (2014) An expert consensus statement on use of adrenal vein sampling for the subtyping of primary aldosteronism. Hypertension 63:151–160
60. Burrello J, Monticone S, Tetti M et al (2015) Subtype diagnosis of primary Aldosteronism: approach to different clinical scenarios. Horm Metab Res 47:959–966
61. Miotto D, De Toni R, Pitter G et al (2009) Impact of accessory hepatic veins on adrenal vein sampling for identification of surgically curable primary aldosteronism. Hypertension 54:885–889
62. Solar M, Ceral J, Krajina A et al (2010) Adrenal venous sampling: where is the aldosterone disappearing to? Cardiovasc Intervent Radiol 33:760–765
63. Satoh F, Morimoto R, Seiji K et al (2015) Progress in primary aldosteronism: is there a role for segmental adrenal venous sampling and adrenal sparing surgery in patients with primary aldosteronism? Eur J Endocrinol 173:465–477
64. Monticone S, Castellano I, Versace K et al (2015) Immunohistochemical, genetic and clinical characterization of sporadic aldosterone-producing adenomas. Mol Cell Endocrinol 411:146–154

# Severe Paroxysmal Hypertension (Pseudopheochromocytoma)

# 30

Samuel J. Mann

Paroxysmal hypertension is a textbook symptom of a catecholamine-secreting pheochromocytoma (pheo) and always arouses suspicion of, and a search for, this tumor. However, fewer than 2% will turn out to have this tumor [1]. This is not surprising given the rarity of pheo [2]. Unfortunately, in the 98 + % who do not have a pheo, the cause and management of the paroxysmal hypertension have remained a mystery and, remarkably, the subject of few papers. Typically, diagnostic evaluation of paroxysmal hypertension reaches a dead end, leaving patients with an unexplained, difficult-to-treat, and often disabling disorder that can be reasonably called pseudopheochromocytoma (pseudopheo). Doctors and researchers simply do not know what to do with these patients.

Recent papers discuss a proposed cause for the disorder and, more importantly, treatment that appears to be effective in most patients. In this chapter, the origin, mechanisms, diagnosis, differential diagnosis, and treatment of this disorder will be reviewed.

## 30.1 Clinical Description of Paroxysmal Hypertension (Pseudopheochromocytoma)

A description of pseudopheo from reported case series is summarized in Tables 30.1 and 30.2 [3, 4]. In this series of 21 patients, 5 were male, 16, female. The mean age was 50 years (range 27-76). The frequency of paroxysms ranged from daily to less

S.J. Mann, M.D.
New York Presbyterian Hospital—Weill/Cornell Medical College,
Hypertension Center, 424 East 70th Street, New York, NY 10021, USA
e-mail: sjmann@med.cornell.edu



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_30

**Table 30.1** Clinical presentation of paroxysmal hypertension in a series of 21 patients [3]

| | *N* (%) | *N* (%) | |
|---|---|---|---|
| *Reported duration of the disorder at time of first visit* | | | |
| <6 months | 9 (43%) | 18–36 months | 5 (24%) |
| 6–18 months | 4 (19%) | >3 years | 3 (14%) |
| Frequency of episodes | | | |
| Daily | 5 (24%) | 1–3/month | 4 (19%) |
| 1–3/week | 10 (48%) | <1/month | 1 (5%) |
| Duration of episodes | | | |
| <10 min | 1 (5%) | 1–3 h | 6 (29%) |
| 10–60 min | 6 (29%) | 3 h–2 days | 6 (29%) |
| | Variable | 2 (10%) | |
| *Peak blood pressure during episodes* | | | |
| 200/≥110 | 16 (76%) | <200/≥110 | 2 (10%) |
| ≥200/<110 | 2 (10%) | <200/<110 | 1 (5%) |
| *Prior hospitalizations because of attacks* | | | |
| | None | 8 (38%) | |
| | One | 5 (24%) | |
| | >Two | 8 (38%) | |

**Table 30.2** Symptoms during episodes: pseudopheo and pheo

| Symptoms (all numbers represent % of patients) | Pseudopheo | Pseudopheo | Pheo | Pheo |
|---|---|---|---|---|
| | Mann [3] ($n$ = 21) | Stein [5] ($n$ = 28) | Stein [5] ($n$ = 30) | Literature review [5] |
| Chest pain | 62 | 25 | 20 | 19–22 |
| Headache | 52 | 39 | 80 | 80–96 |
| Dizziness/lightheadedness | 52 | 46 | 20 | 5–8 |
| Diaphoresis | 48 | 21 | 63 | 67–74 |
| Nausea | 48 | 25 | 23 | 10–42 |
| Palpitations | 43 | 39 | 60 | 62–70 |
| Flushing | 33 | 54 | 7 | 8–18 |
| Dyspnea | 29 | 11 | 13 | 10–19 |
| Weakness | 29 | 25 | 23 | 26–40 |

than once a month. The duration of the paroxysms ranged from <10 min to as long as 2 days. Blood pressure elevation can be extreme, although cases with less severe blood pressure elevation than in the case series are also seen. Multiple emergency room visits are not uncommon, and some patients are hospitalized repeatedly. Many experience some degree of interference with work or day-to-day activity. Further, the fear of recurrent attacks, which typically occur without warning, leads many patients to restrict their activity and in some cases leave their job. Thus, the disorder can have a considerable clinical and financial impact.

## 30.2 Definition of the Syndrome of Pseudopheochromocytoma

Many think of pseudopheo as a diagnosis by default that is made after a pheo and other conditions have been excluded, and no specific cause has been identified. However, the following characteristic features allow a specific diagnosis of pseudopheo to be made with more confidence (Table 30.3):

1. Hypertensive paroxysms are characterized by sudden onset.
   Patients typically describe paroxysms as having an abrupt onset, unassociated with any particular setting or trigger. Patients typically insist that paroxysms occur "out of the blue."
2. Blood pressure elevation is associated with physical symptoms such as headache, flushing, fatigue, dizziness, and others.
   Blood pressure elevation is not asymptomatic; it is almost always accompanied by distressful physical symptoms. Physical symptoms, such as chest pain, lightheadedness, headache, diaphoresis, nausea, palpitations, dyspnea, and weakness, typically accompany the blood pressure surge. The physical symptoms resemble those described among patients with pheo; thus, the symptoms themselves do not distinguish between pheo and pseudopheo [5].
3. Episodes are not triggered by emotional distress or by panic.
   Unlike typical panic attacks, hypertensive paroxysms in patients with pseudopheo are not heralded by panic or emotional distress. However, once an episode has begun, the severe physical symptoms then provoke a consequent fear of dying or stroke.
4. Biochemical tests have been performed and do not support the diagnosis of pheochromocytoma.
   Because of the similarities between pheo and pseudopheo and because of the harm done if a pheo is missed, the possibility of a pheo must be considered in any patient with paroxysmal hypertension. This requires biochemical testing of blood or urine levels for levels of catecholamines or catecholamine metabolites, as discussed below.
5. In most cases, psychosocial inquiry reveals either a past history of severe trauma or abuse or a defensive, very even-keeled personality style.

**Table 30.3** Clinical feature characteristic of pseudopheochromocytoma

| | |
|---|---|
| 1. | Hypertensive paroxysms that are characterized by sudden onset |
| 2. | Blood pressure elevation is associated with physical symptoms such as headache, flushing, fatigue, dizziness, and others |
| 3. | Episodes are not triggered by emotional distress or by panic |
| 4. | Biochemical tests have been performed and do not support the diagnosis of pheochromocytoma |
| 5. | In most cases, psychosocial inquiry reveals either a past history of severe trauma or abuse or a defensive, very even-keeled personality style |

A characteristic psychological background is evident in most patients with pseudopheo, as discussed below. This distinct profile provides a highly important clue of the diagnosis and helps support a confident diagnosis of pseudopheo, rather than a diagnosis by default. Its presence in a patient with normal or near normal catecholamine studies strongly supports the diagnosis of pseudopheo and adds reassurance that a pheo is not being missed.

## 30.3 Pseudopheo and the Sympathetic Nervous System (SNS)

The mechanism underlying pseudopheo differs from that which underlies most cases of essential hypertension. Essential hypertension is usually mediated by either sodium/volume factors or the renin-angiotensin system, as evidenced by the widespread effectiveness of the combination of an ACEI or ARB with a diuretic [6]. Further, essential hypertension, although subject to fluctuation, rarely presents with a pattern of severe, symptomatic, and sudden paroxysms.

The sudden surge of blood pressure in pseudopheo is instead linked to the SNS, which governs instantaneous changes in blood pressure. Evidence of increases in the levels of catecholamines and catecholamine metabolites supports this notion [4, 7–9]. Interestingly, catecholamine levels observed in patients during hypertensive paroxysms suggest that two hemodynamic/hormonal patterns may occur. One is characterized by an increase in heart rate and cardiac output, and associated with elevation in plasma epinephrine level, and is characteristic of stimulation mainly of the adrenal limb of the SNS [4]. This resembles the syndrome of hyperdynamic circulatory state and hyperepinephrinemia described by Streeten and by Frohlich [7, 8]. The other pattern is characterized by an increase in peripheral resistance accompanied by a decrease in heart rate and is associated with elevation in norepinephrine level, with no change in epinephrine level [4].

Different stressors can stimulate one limb of the SNS more than the other. For example, anxiety stimulates mainly the adrenal limb [10]. The observed hemodynamic patterns of pseudopheo suggest that in different patients, for reasons that are not well understood, one limb or the other of the SNS can dominate.

## 30.4 The Psychological Roots of Pseudopheo

Even though the origin of pseudopheo and of the SNS activation underlying it has been a long-standing mystery, and even though it is well known that emotions stimulate the SNS, the possibility that pseudopheo has a psychosomatic etiology has been widely overlooked. This is understandable because paroxysms are dominated by hemodynamic changes and physical symptoms rather than by emotional distress or panic and because patients typically do not report or view stress or emotional distress as a contributory factor.

In this context, a breakthrough in understanding the origin of pseudopheo occurred with the observation that most patients, when asked, acknowledged a past history of unusually severe trauma, such as prior abuse, the Holocaust, or other forms of trauma, often from as long ago as childhood [4]. Remarkably, in most cases, patients claimed they were free of any lingering emotional effects from the trauma, which strongly suggests that they had repressed trauma-related emotion. They had vivid memories of the trauma but did not feel or suffer from the powerful and painful emotions related to it. The clues lay in the story rather than in reported emotional distress.

Repression of painful emotion is a normal and valuable defense mechanism. It is not per se indicative of psychopathology but rather an effective defense protective against overwhelming emotional distress [11]. Such defenses are crucial to emotional health and explain why many victims of severe trauma survive without apparent psychological sequelae.

In this circumstance, patients do not report emotional distress, and usually the remote history of trauma does not arise during history-taking by a physician. Even psychosocially conscious physicians focus on the current and day-to-day stress and emotional distress that a patient reports. The relationship between old trauma and unexplained autonomic surges decades later does not occur to either patient or physician. It was the observation that patient after patient with pseudopheo, upon further history-taking, acknowledged a history of severe trauma that suggested that despite the absence of overt or reported psychological symptoms a psychological basis for the disorder needed to be considered.

This mind/body paradigm in pseudopheo is thus the opposite of the usual mind/body approach to understanding psychosomatic illnesses. It focuses on the absence rather than the presence of emotional distress related to previous major events. Patients might have experienced severe emotional distress immediately following the trauma but eventually repressed emotion related to it.

The concept of repressed emotion, and the possible role of repressed emotion in the hypertensive disorder pseudopheo, is not widely considered, even though no alternative understanding or treatment of pseudopheo has ever emerged. Unfortunately, although there are innumerable convenient tools to measure perceived emotional distress, there are no reliable or validated tools to adequately assess the role of repressed emotion in psychosomatic illness.

## 30.5 Repressed Emotion in Patients with Pseudopheo: Two Patterns

The prominent use of repression can be surmised by examining a patient's life story and personality style. Two patterns of unawareness of emotion appear to be associated with pseudopheo: a past history of severe abuse or trauma and a personality characterized by a repressive coping style [3].

### 30.5.1 Past History of Severe Trauma or Abuse

Roughly two-thirds of patients with pseudopheo acknowledge a history of severe trauma; strikingly most insist that they suffer no lingering effects [3]. A few clinical examples serve to illustrate this pattern.

*A patient with pseudopheo reported that her husband had died in a plane crash two decades earlier, leaving her with two young children and no money. She reported that she had moved on, too busy to grieve. She survived admirably with no emotional breakdown whatsoever, and never grieved the loss, but now has paroxysmal hypertension.*

*A 33-year-old Hispanic male who suffered from hypertensive paroxysms with blood pressure elevation as high as 220/140 reported a childhood history of severe physical abuse by his father. He insisted that he loved his father and bore no anger toward him. Treatment with alprazolam and amitriptyline eliminated hypertensive attacks.*

*A 35-year-old foreign-born physician with debilitating hypertensive paroxysms reported no prior history of trauma, but further questioning revealed that as a college student in her home country, she had been detained as a political prisoner for 30 days. She had been blindfolded, her life had been repeatedly threatened, and she had witnessed the death of several friends. After she was freed she moved on with her life. She insisted there were no emotional aftereffects, had not sought psychotherapy, and had discussed her experiences with no one. Treatment with an antidepressant eliminated the paroxysms.*

In trauma survivors, it is important to recognize repression as a successful psychological defense rather than as psychopathology [11]. Many patients with pseudopheo appear to have dealt with major trauma by repressing and have lived lives marked by considerable achievement. Their resilience can be attributed to successful repression of overwhelming emotion related to severe traumatic events.

### 30.5.2 Personality Characterized by a Repressive Coping Style

A repressive coping style, reported in about a third of patients with pseudopheo, consists of the lifelong tendency to cope unemotionally with stress [3, 12]. Individuals with this coping style tend to be very even-keeled, without experiencing

ups and downs. Since they report little emotional distress, physicians rarely consider their medical condition to be linked to psychological factors.

A repressive coping style is usually a pattern developed in childhood and could be a result of psychosocial experience or inherent personality from birth. Such individuals are not buffeted by emotions, and the experience of depression or anxiety may be foreign to them.

Two cases are illustrative:

*A 66-year-old man suffered from hour-long episodes of blood pressure elevation to 190/110, with diaphoresis and facial reddening. He did not have a history of past trauma but described himself as very independent, never needing or seeking emotional support, and having a very even temperament (the classic description of a repressor). Typical of this, he reported having shed no tears 7 years earlier when his only son was left permanently paraplegic after a car accident. Treatment with atenolol, terazosin, lorazepam, and desipramine eliminated attacks.*

*A 52-year-old well-to-do woman with a pampered lifestyle experienced daily hypertensive attacks for 4 months. She insisted she had no stress or distress and that she was very happy. However, after further discussion, she was able for the first time to acknowledge to herself that she was miserable and ashamed because she had no job or purpose and felt useless. Her attacks ceased quickly, as, ironically, she became depressed for the first time in her life. However, the awareness enabled her to begin to make changes in her life. No medications were necessary.*

## 30.6 Differential Diagnosis of Pseudopheo

Although there is a long list of conditions in which paroxysmal hypertension can occur, usually only a few conditions truly resemble pseudopheo and need to be differentiated from it (Table 30.4). These include pheo, of course, as well as panic disorder and labile hypertension.

### 30.6.1 Pheochromocytoma

Excluding a pheo, which is potentially fatal and is eminently curable, is of course a priority. If catecholamine studies are very abnormal, strongly suggestive of a pheo, radiological studies are indicated.

Plasma metanephrine assay has a high sensitivity and specificity for identifying a pheo and is widely used to screen for pheo [13]. However, mild elevations are frequently encountered and usually represent false positives, perhaps reflecting the 30%

**Table 30.4** Differential diagnosis of pheochromocytoma

| Pheochromocytoma |
|---|
| Common conditions that resemble pseudopheo |
| • Panic disorder |
| • Labile hypertension |
| • Other conditions in which paroxysmal blood pressure elevation can occur |
| • Renovascular hypertension |
| • Vasculitis |
| • Hypertensive encephalopathy |
| • Preeclampsia |
| • Baroreflex failure |
| • Hyperdynamic beta-adrenergic circulatory state |
| • Paroxysmal tachycardia |
| • Ingestion of sympathomimetics |
| • MAO inhibitor + ingestion of tyramine |
| • Clonidine withdrawal |
| • Illicit drugs (e.g., cocaine) |
| • Coronary insufficiency |
| • Migraine |
| • Intracranial mass lesion |
| • Hypoglycemia |
| • Porphyria |
| • Carcinoid |
| • Anxiety |
| • PTSD |

false-positive rate associated with lack of adherence to fasting state, supine position, and rest before sampling [14]. It is also possible that the increased sympathetic tone documented in patients with pseudopheo contributes to a higher false-positive rate, although studies have not compared the false-positive rate of pseudopheo patients with controls [4, 7–9]. Thus, a mildly elevated normetanephrine level should not provoke an endless search for a pheo. Although radiologic imaging is sometimes obtained by physicians suspicious of a pheo in patients with normal or only mildly elevated metanephrines, an unending search for a pheo is unlikely to be of value.

Traditionally, a clonidine suppression test was performed in patients with mild elevation of plasma catecholamines, such as plasma norepinephrine levels in the 1000–2000 pg/ml range [15]. A fall in norepinephrine level to the normal range after administration of 0.3 mg of clonidine would indicate that the origin of an elevated catecholamine level is physiologic rather than tumor-related [15]. Currently however the clonidine suppression test is not widely employed.

Given the rarity of pheo, it is not likely to be the diagnosis in patients with negative or only mildly elevated catecholamine levels. The presence of the classic psychological characteristics of pseudopheo further supports the alternative diagnosis of pseudopheo.

## 30.7 Conditions that Commonly Mimic Pseudopheo

### 30.7.1 Panic Disorder

Both panic disorder and pseudopheo are characterized by sudden episodes of severely distressing physical symptoms such as headache, dyspnea, dizziness, weakness, and diaphoresis. Their presenting symptoms, to a large extent, overlap. Thus, physical symptomatology does not allow differentiation of the two disorders.

The two conditions differ, however, in that panic attacks are dominated by the emotional manifestation of panic, while blood pressure elevation is less prominent, averaging perhaps 20 mmHg [16]. In contrast, pseudopheo is dominated by the autonomic manifestation of the blood pressure surge (40–100 mmHg or more), without panic [3]. Panic does not trigger the paroxysm; it occurs as a result of the frightening physical symptoms.

To a fair extent, the prominence of autonomic versus emotional manifestations is reciprocally related to each other in these two disorders, with autonomic manifestations more prominent in pseudopheo and emotional manifestations in panic attacks. Clinical experience also suggests that some patients have a disorder that is intermediate between the two. It was the perspective of viewing hypertensive paroxysms in pseudopheo as the autonomic equivalent of panic attacks that led to consideration of using antidepressant agents to treat it, in the same way that they are employed in treating panic disorder.

#### 30.7.1.1 Labile Hypertension

Many individuals with essential hypertension experience considerable fluctuation in their blood pressure, often occurring at times of stress or emotional distress. Blood pressure elevation can occur without physical symptoms or can be accompanied by symptoms such as headache or palpitation. The headaches might be tension headaches or might be related to the blood pressure elevation per se.

Labile hypertension differs strongly from pseudopheo in that most patients and their physicians readily attribute blood pressure fluctuation to stress and emotional distress. In many cases, the lability can be related to the patient's obsession about the blood pressure, and frequent measurements, despite their claim that they are not anxious about their blood pressure. Blood pressure increases can be associated with symptoms resulting from anxiety or hyperventilation [17]. Blood pressure lability is a more common phenomenon than pseudopheo and should not be misconstrued as the latter in the absence of the characteristics defined above.

### 30.7.2 Other Diagnoses

Many other conditions, some commonly encountered and others rare, can also cause paroxysmal hypertension (Table 30.3). However, in those conditions, other signs or symptoms more typical of those conditions are almost always present. These conditions provide a differential diagnosis for paroxysmal hypertension and merit consideration, but in the real world rarely provide a diagnosis, whereas pseudopheo is overwhelmingly likely.

The use of illicit drugs such as cocaine or amphetamines must of course be considered. However, patients with pseudopheo are very symptomatic and frightened and are highly unlikely to continue using, and denying their use of, such drugs. The use of drugs such as MAO inhibitors or withdrawal from clonidine should be readily evident from the history.

Baroreceptor failure causes considerable blood pressure lability but is unlikely without a predisposing condition, such as prior neck surgery or irradiation [18, 19]. In addition, the abnormal blood pressure lability is continually present. In patients with pseudopheo, blood pressure surges are seen only during paroxysms without abnormal lability or hypotension at other times. Patients with pseudopheo can become hypotensive following a paroxysm, either because of the acute administration of antihypertensive agents or possibly because of volume depletion due to pressure natriuresis during the paroxysm. However, hypotension does not occur at other times except as an adverse effect of a prescribed antihypertensive regimen.

Post-traumatic stress disorder (PTSD), like pseudopheo, is associated with prior trauma and with elevated plasma norepinephrine levels [20]. However, in contrast to pseudopheo, severe blood pressure elevation is not characteristic. Also differentiating the two conditions, patients with PTSD are very aware of the trauma and its impact.

Are tests to exclude these entities truly needed in the patient who presents with paroxysmal hypertension? Usually not, although each case must be assessed based on the accompanying clinical signs and symptoms. Also, as mentioned above, the presence or absence of the characteristic psychological profile of pseudopheo supports the diagnosis and argues for treatment directed at pseudopheo rather than endless testing for very unlikely causes. A clear response to treatment directed at pseudopheo then provides more evidence that another diagnosis is not being missed.

## 30.8 Approach to Treatment (Table 30.5)

The treatment of paroxysmal hypertension has been a major dilemma. Diuretics, ACEIs, and ARBs would not be expected to prevent hypertensive surges driven by the SNS. Also, it is difficult to prescribe an aggressive antihypertensive regimen in patients whose blood pressure is normal in between paroxysms. A clear limiting factor in treatment recommendations is the paucity of controlled treatment trials, reflecting the widespread lack of understanding of the disorder. Nevertheless, patients need treatment, and successful approaches based on the understanding of

**Table 30.5** Treatment

| **Acute management of paroxysms** |
|---|
| Goal |
| – To reduce blood pressure if severely elevated |
| – To reduce symptoms |
| – To avoid ER visits and hospitalizations |
| Pharmacologic agents |
| – Mild paroxysm: alprazolam |
| – Moderately severe paroxysm: alprazolam +/– clonidine |
| – Severe paroxysm: IV labetalol and alprazolam |
| **Preventive treatment** |
| *Antihypertensive agents are of limited value* |
| *Psychopharmacologic agents* |
| – Antidepressant drugs are highly effective in most patients |
| – Choice of drug class is usually governed by side effects |

pseudopheo presented in this chapter have been reported [3, 21]. With these approaches, paroxysms can be reduced or eliminated in most patients, enabling patients to resume a normal life. The main concerns of treatment include acute management of paroxysms and preventive treatment (Table 30.4), using modalities including antihypertensive drug therapy, psychopharmacologic agents, and psychological interventions.

## 30.9 Acute Management of Hypertensive Paroxysms

Both patients and physicians are concerned about the danger of the sudden and severe elevation of blood pressure during paroxysms, particularly in patients who are normotensive at other times. Fortunately, acute cardiovascular complications seem rare, although outcomes in patients with a long-standing history of severe and/or frequent blood pressure paroxysms are not known. There is a role for antihypertensive agents, psychotropic agents, or both, in the acute management of hypertensive paroxysms.

Selection of treatment depends on the severity of blood pressure elevation and symptoms. There is no specific blood pressure level to define "severe." A value above 220/120 can be considered severe, although the cutoff could be lower or higher depending on factors such as age, symptoms, usual blood pressure, and underlying comorbidities. For paroxysms that are deemed severe, treatment with a rapid-acting intravenous agent such as labetalol or, rarely, nitroprusside may be needed. Concomitant treatment with a quickly effective anxiolytic agent such as alprazolam can be helpful in shortening the duration of the paroxysm and the severity of blood pressure elevation [3, 22].

For milder paroxysms, oral treatment is usually appropriate and effective, consisting of either an oral sympatholytic agent such as clonidine, an anxiolytic agent such as alprazolam, or a combination of the two. In patients with a history of previous uncomplicated paroxysms, and who are known to have responded to these agents, self-treatment at home is a realistic option. Oral labetalol is another alternative, although it might not be effective in patients who are rapid metabolizers of

lipophilic beta-blockers in whom bioavailability of the drug is low [23]. Agents such as ACEIs, ARBs, and diuretics do not appear well suited for acute treatment of SNS-mediated blood pressure surges.

## 30.10 Preventive Management

It is not clear whether a regimen of antihypertensive medication can prevent paroxysms or reduce the magnitude of blood pressure elevation. Clinical experience suggests that an antihypertensive regimen might reduce the magnitude of blood pressure elevation, but does not prevent paroxysms. Regardless, treatment with antihypertensive agents is often limited by the normal blood pressure between paroxysms.

Drugs that antagonize the effects of sympathetically mediated blood pressure elevation would seem most likely to be helpful [24]. The combination of an α- and β-blocker would seem most physiologically appropriate. A central α-agonist, such as clonidine, is another alternative, but chronic use is usually hampered by prominent side effects.

The efficacy of the alternative of prescribing an antidepressant agent was originally suggested by the similarity of pseudopheo to panic disorder. This promise has been borne out in reports indicating that antidepressant drugs are highly effective in preventing paroxysms in most patients, at dosages similar to that given to treat panic disorder, and are the most effective treatment available for preventing paroxysms [3, 4, 21]. The high response rate initially reported in two retrospective case series was recently confirmed in a prospective study in which the antidepressant sertraline, given at a 50 mg dose, was effective in reducing or eliminating paroxysms in 90% of patients and eliminating them in 61% [21]. These reports provide great encouragement in the management of a disorder that generally does not respond to treatment with antihypertensive agents alone and also strongly support the suggested psychosomatic basis of the disorder.

Long-term treatment with an antidepressant agent is not needed in all patients. In patients who have mild or infrequent paroxysms, or who improve with psychological intervention (see below), it is not unreasonable to initially limit treatment to acute management of paroxysms with alprazolam and/or clonidine. However, in patients who continue to experience severe symptoms, severe blood pressure elevation, or frequent paroxysms that interfere with functioning, an antidepressant agent is very likely to be effective and should be strongly considered. Clinical response is usually evident within 2 weeks of initiating an effective dose. There is no evidence that any class of antidepressant agents is more effective than any other.

## 30.11 Psychological Intervention

Finally, psychological intervention plays an important role in the management of patients with pseudopheo. A frequently helpful but underutilized intervention is reassurance. Less commonly, psychological intervention centered on a shift in awareness regarding the role of past events can result in a dramatic reduction or cessation in paroxysms, albeit in a minority of patients, as discussed below.

## 30.12 Reassurance

Three aspects of reassurance play an important role:

1. Reassurance that a hypertensive paroxysm is highly unlikely to cause acute stroke or sudden death
   Symptomatic hypertensive paroxysms are terrifying to patients, regularly provoking fear of suffering a stroke or of dying during a paroxysm. This fear is further stoked by the marked concern of physicians during the patient's hypertensive paroxysm.

   It is a common misconception that a sudden elevation in blood pressure exposes patients to a high risk of acute stroke or cerebral hemorrhage. Certainly there is a remote possibility, although there are no case reports of it happening. A relevant observation is the absence of acute cerebrovascular events during the acute severe blood pressure elevation that occurs during weightlifting, with peak mean arterial pressure averaging 160 mmHg (equivalent to a systolic/diastolic pressure of 220/130) in normotensive weightlifters [25]. Reassurance by a physician that it is very unlikely that the patient will experience such a complication during paroxysms can be extremely helpful in reducing the fear of the patient and the sympathetic stimulation that it aggravates.
2. Reassurance that the patient will be able to resume a normal life
   Many patients have come to view themselves as chronically ill with no hope of improvement or return to a normal life. The reassurance that the disorder can usually be successfully treated and that they will be able to resume a normal life appears to be helpful to patients.
3. Reassurance that the disorder is not indicative of psychopathology
   Many patients will resist an explanation of the psychological roots of the disorder partly because it implies psychological weakness or illness. This concern also pushes patients away from consideration of psychopharmacologic interventions that offer the best chance of clinical improvement.

   The fact that many patients with pseudopheo are successful survivors of severe psychological trauma actually offers testimony not of psychological weakness or psychopathology but of psychological resilience, rooted in successful repression following severe trauma that could have been associated with severe and long-standing psychological sequelae [11]. Reassurance that the disorder is not indicative of psychopathology or psychological weakness increases the likelihood of acceptance of its psychodynamic origin. The effect of this reassurance on acceptance of the treatment with an antidepressant, on the severity and frequency of paroxysms, has not been evaluated.

## 30.13 Awareness

The usual paradigm of psychological intervention in treating physical symptoms caused by psychological distress consists of stress reduction techniques to relieve emotional distress. This paradigm does not fit pseudopheo which is characterized by

the absence of perceived emotional distress. Strikingly, in pseudopheo, it is a shift to conscious awareness of painful emotion that can be helpful in ameliorating the disorder [26].

When the origin of the disorder in repressed emotion, often related to prior, severe trauma, is explored with patients, some will grasp it at an emotional level and might quickly experience a reduction or elimination of paroxysms. Whether there is any role for formal psychotherapy is not known.

However, most patients who are repressing overwhelming emotion related to severe past trauma appear to need to continue repressing and will defend against awareness. In this context, most patients are not interested in, and probably would not benefit from, psychotherapy aimed at awareness of those emotions. And it is probably best that the underlying emotion remains repressed. This is analogous to the lack of benefit, and the risk of harm, documented in studies that have examined the effect of talking about the trauma in recent trauma survivors [11, 27]. The dictum that it is always best to deal with the past is not inherently true. Such patients likely will be resistant to psychological intervention and unlikely to benefit from it.

In the absence of adequate study, the wisest course might be to reassure the patient that the disorder can be successfully managed, and a normal life resumed. If the patient wishes to pursue the psychological origin of the disorder, it can be encouraged. However, if the patient cannot see the connection of the disorder with trauma or repressed emotion or prefers not to pursue psychological intervention, psychological discussion and psychotherapy should not be urged.

## 30.14 Obstacles to Successful Treatment

Barriers to treatment with antihypertensive agents include the ineffectiveness of ACEIs, ARBs, and diuretics and the normal blood pressure between paroxysms that limits the aggressiveness of any prescribed antihypertensive regimen. In addition, even if an effective regimen reduces the magnitude of blood pressure spikes, it is unlikely to prevent future paroxysms.

Barriers to treatment with antidepressants include patients' antipathy to the idea of taking an antidepressant and intolerance to agents that are tried. Some patients will refuse to try an antidepressant no matter how severely symptomatic they are because its use implies a psychological cause. Many such patients however will eventually agree to try one because they are severely symptomatic and no other treatment has helped. The newer SSRIs are well tolerated in most, but in some patients it is difficult to reach an effective dose of any drug.

Finally there are major barriers to acceptance of the psychological origin of the disorder. Because the manifestations of pseudopheo are physical rather than psychological and are not triggered by obvious current stressors, its emotional basis is usually not suspected by either the patient or the physician. In addition, many patients cannot accept that unfelt emotions related to events from decades ago could be affecting them. Further, many trauma survivors need to avoid psychological discussion or awareness. That is why the psychological origin must be broached very

sensitively and not aggressively pursued in the face of patient resistance. Psychological awareness is not an option for most.

Clearly, the treatment of pseudopheo is a challenge and an art. However, fortunately, in most cases, successful treatment is achievable, and a normal quality of life can be restored.

### Conclusion

Despite all the attention given to pheochromocytoma, >98% of patients with paroxysmal hypertension do not have this tumor. Most have pseudopheo, whose origin and treatment have received remarkably little attention. The obscurity of its origin is attributable to its link to repressed emotion, a phenomenon essentially unrecognized by patients, physicians, and even psychologically oriented medical clinicians and researchers. Also, it is a disorder for which patients seek out physicians, not psychologists, and therefore has remained under the radar of psychologists.

The diagnosis of pseudopheo is not a diagnosis by default after exclusion of pheo and other rare entities. If catecholamine studies are normal, the characteristic psychological background usually supports a confident diagnosis and greatly reduces concern that a pheo or other obscure cause is being missed. And, fortunately, with this understanding, the suffering of many patients with this disorder can be addressed and overcome.

Several successful treatment options are available, including treatment at the time of paroxysms with an anxiolytic agent and/or antihypertensive agents directed at the SNS and preventive treatment with an antidepressant agent. Finally, in some patients, understanding of the cause of the disorder and reassurance that a catastrophic event is not likely to occur during a paroxysm appears helpful.

## References

1. Pacak K, Linehan WM, Eisenhofer G, Walther MM, Goldstein DS (2001) recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. Ann Intern Med 134(4):315–329
2. Manger WM (2006) an overview of pheochromocytoma: history, current concepts, vagaries, and diagnostic challenges. Ann N Y Acad Sci 1073:1–20
3. Mann SJ (1999) severe paroxysmal hypertension (pseudopheochromocytoma)—understanding the cause and treatment. Arch Intern Med 159(7):670–674
4. Mann SJ (1996) severe paroxysmal hypertension: an autonomic syndrome and its relationship to repressed emotions. Psychosomatics 37:444–450
5. Stein PP, Black HR (1991) a simplified diagnostic approach to pheochromocytoma. A review of the literature and report of one institution's experience. Medicine (Baltimore) 70(1):46–66
6. Gradman AH, Basile JN, Carter BL, Bakris GL (2011) combination therapy in hypertension. J Clin Hypertens (Greenwich) 13(3):146–154
7. Frohlich ED, Tarazi RC, Dustan HP (1969) Hyperdynamic beta-adrenergic circulatory state. Increased beta-receptor responsiveness. Arch Intern Med 123(1):1–7
8. Streeten DH, Anderson GH, Lebowitz M, Speller PJ (1990) primary hyperepinephrinemia in patients without pheochromocytoma. Arch Intern Med 150(7):1528–1533

9. Sharabi Y, Goldstein DS, Bentho O et al (2007) Sympathoadrenal function in patients with paroxysmal hypertension: pseudopheochromocytoma. J Hypertens 25(11):2286–2295
10. Dimsdale JE, Moss J (1980) plasma catecholamines in stress and exercise. JAMA 243(4):340–342
11. Bonanno GA (2004) loss, trauma, and human resilience: have we underestimated the human capacity to thrive after extremely aversive events? Am Psychol 59(1):20–28
12. Weinberger DA, Schwartz GE, Davidson RJ (1979) low-anxious, high-anxious, and repressive coping styles: psychometric patterns and behavioral and physiological responses to stress. J Abnorm Psychol 88:369–380
13. Lenders JWM, Pacak K, Walther MM et al (2002) biochemical diagnosis of pheochromocytoma: which test is best? JAMA 287(11):1427–1434
14. Eisenhofer G, Peitzsch M (2014) laboratory evaluation of pheochromocytoma and paraganglioma. Clin Chem 60(12):1486–1499
15. Bravo EL, Tarazi RC, Fouad FM et al (1981) clonidine-suppression test: a useful aid in the diagnosis of pheochromocytoma. N Engl J Med 305(11):623–626
16. Balon R, Ortiz A, Pohl R, Yeragani VK (1988) heart rate and blood pressure during placebo-associated panic attacks. Psychosom Med 50(4):434–438
17. Kaplan NM (1997) anxiety-induced hyperventilation. A common cause of symptoms in patients with hypertension. Arch Intern Med 157(9):945–948
18. Kuchel O, Cusson JR, Larochelle P et al (1987) posture- and emotion-induced severe hypertensive paroxysms with baroreceptor dysfunction. J Hypertens 5(3):277–283
19. Aksamit TR, Floras JS, Victor RG, Aylward PE (1987) paroxysmal hypertension due to sino-aortic baroreceptor denervation in humans. Hypertension 9(3):309–314
20. Kosten TR, Mason JW, Giller EL et al (1987) sustained urinary norepinephrine and epinephrine elevation in post-traumatic stress disorder. Psychoneuroendocrinology 12(1):13–20
21. Vaclavik J, Krenkova A, Kocianova E et al (2015) 7B.04: effect of sertraline in paroxysmal hypertension. J Hypertens 33 Suppl 1:e93
22. Mann S (2008) severe paroxysmal hypertension (pseudopheochromocytoma). Curr Hypertens Rep 10(1):12–18
23. Frishman WH, Alwarshetty M (2002) Beta-adrenergic blockers in systemic hypertension: pharmacokinetic considerations related to the current guidelines. Clin Pharmacokinet 41(7):505–516
24. Mann SJ (2003) neurogenic essential hypertension revisited: the case for increased clinical and research attention. Am J Hypertens 16:881–888
25. Sullivan J, Hanson P, Rahko PS, Folts JD (1992) continuous measurement of left ventricular performance during and after maximal isometric deadlift exercise. Circulation 85(4):1406–1413
26. Mann SJ (2008) severe paroxysmal hypertension (pseudopheochromocytoma). Curr Hypertens Rep 10:12–18
27. Rose S, Bisson J, Churchill R, Wessely S (2002) Psychological debriefing for preventing post traumatic stress disorder (PTSD). Cochrane Database Syst Rev (2):CD000560

# Paroxysmal Hypertension: Pheochromocytoma

# 31

Graeme Eisenhofer and Jacques W.M. Lenders

## 31.1 Clinical Presentation

Pheochromocytomas and paragangliomas (PPGLs) are catecholamine-producing neuroendocrine tumors that respectively arise from chromaffin or paraganglial tissue at adrenal and extra-adrenal locations [1]. Paragangliomas usually form from chromaffin cells associated with paravertebral sympathetic ganglia, most usually in the abdomen (e.g., organ of Zuckerkandl), but also in the pelvic areas (e.g., bladder) and less frequently in the thorax (e.g., mediastinum). Paragangliomas may also form at the neck and skull base, but these derive from parasympathetic or carotid body-associated tissue and usually do not produce significant amounts of vasoactive catecholamines.

As a result of tumoral secretion of catecholamines, patients with high blood pressure and symptoms of catecholamine excess are those in whom PPGLs are most frequently suspected. The tumors are also frequently identified among patients who undergo imaging for unrelated purposes and in whom incidental abdominal or adrenal masses (i.e., incidentalomas) are found. Patients with germline mutations of an increasing number of PPGL susceptibility genes represent another group in whom the tumors are now often found in the setting of routine screening due to hereditary risk.

G. Eisenhofer (✉)
Institute of Clinical Chemistry and Laboratory Medicine and Department of Medicine III, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
e-mail: Graeme.Eisenhofer@uniklinikum-dresden.de

J.W.M. Lenders
Department of Internal Medicine, Division of Vascular Medicine, Radboud University Medical Center, Nijmegen, The Netherlands

Department of Medicine III, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
e-mail: Jacques.Lenders@radboudumc.nl



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_31

PPGLs usually occur during middle age, but in 10–20% of cases present during childhood [2], the latter usually associated with a hereditary cause reflecting the younger age of presentation of hereditary than sporadic tumors. The clinical presentation of PPGLs can vary enormously from severe cardiovascular emergencies associated with sustained or paroxysmal hypertension and symptoms of catecholamine excess to a completely normotensive and asymptomatic presentation often found among patients screened due the presence of an incidentalomas or an underlying hereditary predisposition [3, 4].

### 31.1.1 Prevalence

Autopsy studies have indicated prevalences of PPGLs of 0.05–0.13%, mostly reflecting cases that remained undetected during life [5–7]. From reported annual incidences of PPGLs of between two and five cases detected per million per year [8, 9], translating to lifelong prevalences of 0.013–0.033%, it seems clear from the autopsy series that most PPGLs remain undetected throughout life, contributing to premature death. Nevertheless, prevalences at autopsy have dropped from 0.13% in the 50-year period before 1982 [5] to 0.05% in the 20-year period up until the turn of the century [6, 7], suggesting improved diagnosis during life. Presumably there have been further improvements in diagnosis over the subsequent 15 years, so that annual detection rates at some centers might be expected to reach ten or more per million.

Among patients with hypertension, the prevalence of PPGLs has been estimated at 0.6% [10], at least fourfold higher than overall prevalence rates. It can therefore be expected that prevalences are higher, possibly reaching 2% among patients with sustained or paroxysmal hypertension and symptoms of catecholamine excess. This is in agreement with findings that among unselected patients screened for PPGLs, prevalences of PPGLs range from 0.8 to 1.6% [11–13]. Among patients with adrenal incidentalomas, prevalences of pheochromocytoma are higher, between 4 and 9% [14, 15], with an overall prevalence of 7% indicated by review of 29 studies performed between 1982 and 2002 [16]. Depending on the mutation, prevalences can be even higher in patients with a hereditary predisposition to PPGLs, reaching 40% in patients with multiple neoplasia type 2 (MEN 2) [17].

### 31.1.2 Signs and Symptoms

Most patients with PPGLs have classical symptoms due to the effects of excessive circulating concentrations of catecholamines (Table 31.1). Reported frequencies of symptoms depend however on the studied populations and are often biased by the retrospective nature of studies. Some patients have been reported as normotensive and completely asymptomatic, particularly those in whom tumors are diagnosed based on screening because of hereditary predisposition or of findings of an incidentaloma [4]. In rare cases, tumors may synthesize no or little catecholamines or only produce dopamine [18, 19].

**Table 31.1** Frequency (%) of signs and symptoms

| | |
|---|---|
| Headache | 70–90 |
| Palpitations | 50–70 |
| Diaphoresis | 55–75 |
| Hypertension | 85–90 |
| – Sustained | 50–60 |
| – Paroxysmal | 50 |
| Orthostatic hypotension | 10–60 |
| Pallor | 40–60 |
| Hyperglycemia/diabetes | 40–60 |
| Nausea/vomiting | 20–45 |
| Anxiety/panic attacks | 20–40 |
| Fatigue | 20–40 |
| Gastrointestinal: constipation, ileus | 10–15 |
| Weight loss | 15–40% |

Signs and symptoms of PPGLs usually present paroxysmally, consequent to the hemodynamic and metabolic actions of peak levels of catecholamines (Fig. 31.1). Such episodes usually last between a few to 60 min and can occur spontaneously or may be provoked by drugs (e.g., steroids, antiemetics), anesthesia, tyramine-containing foods, or mechanical factors. Adverse reactions to medications can be particularly problematic (Table 31.2). The frequency of such episodes varies from once daily to only a few times per month.

The hallmark that usually triggers clinicians to consider the diagnosis of PPGL is hypertension. At least 50% of patients have chronic but usually labile hypertension with short-lasting episodes of high surges in blood pressure. Specific blood pressure patterns often feature prominent daytime variability, an absent or blunted diurnal blood pressure rhythm, orthostatic hypotension, and more rarely hypotension [20, 21]. A small percent of patients present with shock, which has been suggested to occur particularly in epinephrine- or dopamine-secreting tumors [22].

Apart from hypertension, there is wide constellation of other established signs and symptoms, dominated by the classic triad of paroxysmal headache, palpitations, and diaphoresis (Table 31.1). In addition many other nonspecific symptoms may be encountered, including nausea, tremulousness, anxiety, panic attacks, weight loss, and gastrointestinal symptoms such as constipation and vomiting. Hyperglycemia and even overt diabetes mellitus in young lean hypertensive subjects should arouse suspicion of the tumor. Due to the nonspecific nature of most symptoms, there are many other clinical conditions, mostly associated with increased sympathetic activity, that mimic presence of a catecholamine-producing tumor [3].

In about 10% of patients with PPGLs, elevations in blood pressure may evolve into a hypertensive crisis with subsequent organ damage involving acute coronary syndrome, left ventricular heart failure, Takotsubo cardiomyopathy, arrhythmias, or stroke [21, 23–25]. Occasional patients may also present with multisystem crisis associated with an IL-6-mediated acute inflammatory syndrome, high-grade fever (>40 °C), and leukocytosis [21], evolving into renal failure, pulmonary edema, encephalopathy, and lactic acidosis. Delayed treatment is associated with a high fatality rate [23].

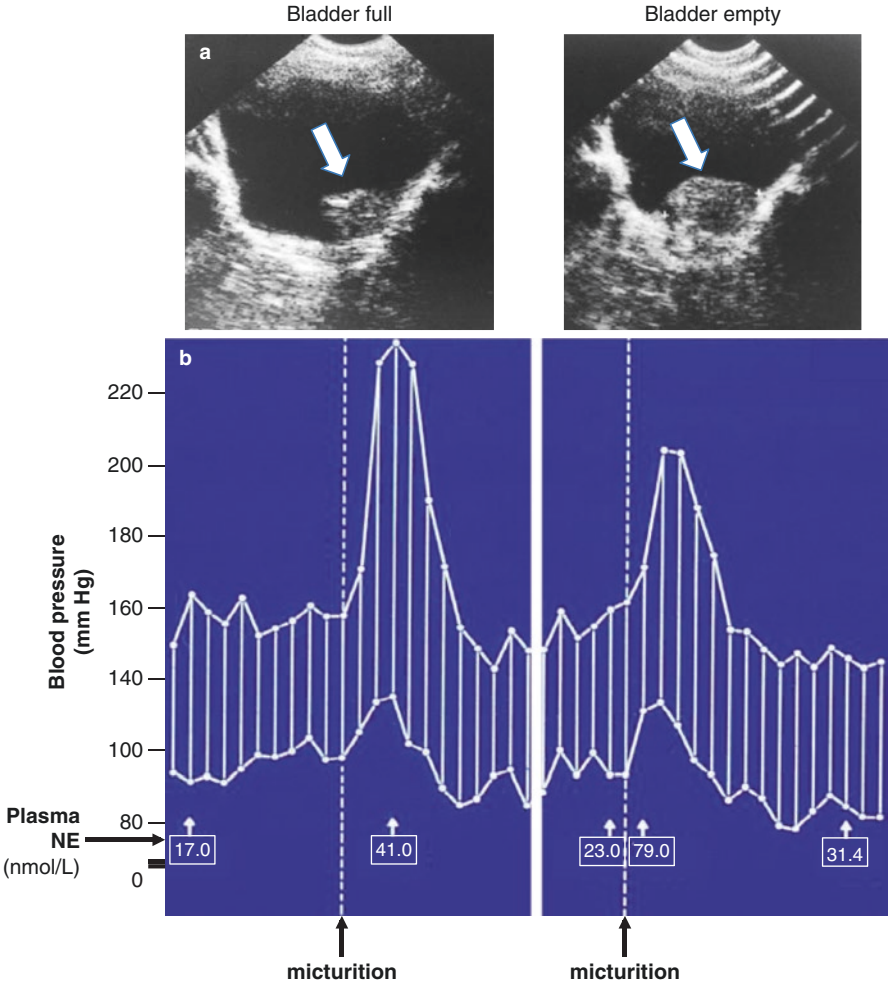



**Fig. 31.1** Paroxysmal hypertension in a patient with a paraganglioma of the urinary bladder. Sonograms of urinary bladder in the patient before and after micturition are shown in *panel A*. Blood pressure profiles recorded before, during, and after micturition on two separate days are shown in *panel B*. Blood samples were taken at intervals and plasma concentrations of norepinephrine (NE) measured as shown for the five time points of collections

Several factors account for the variable clinical picture of PPGLs, including tumor size, biochemical phenotype, co-secreted peptides, and underlying pathogenic mutations. In general, larger tumors are associated with larger elevations in catecholamines and more prominent signs and symptoms, but this association may be lost when the tumors contain substantial hemorrhage or necrosis. Patients with epinephrine-producing tumors are more likely to display paroxysmal symptoms such as palpitations, tremulousness, and anxiety than tumors producing merely norepinephrine [26–28]. This may in part reflect the more prominent

**Table 31.2** Classes of drugs potentially responsible for adverse reactions in patients with PPGLs

| Drug class | Examples |
|---|---|
| β-adrenergic receptor blockers | Propranolol, metoprolol, atenolol, labetalol |
| Hormones (steroids, peptides) | Prednisone, dexamethasone, methylprednisolone, glucagon |
| Dopamine D2 receptor antagonists | Metoclopramide, sulpiride, chlorpromazine, droperidol |
| Antidepressants (tricyclics, SSRIs, MAO inhibitors) | Amitriptyline, imipramine, clomipramine, paroxetine, fluoxetine, phenelzine, moclobemide |
| Sympathomimetics | Ephedrine, phenylpropanolamine, fenfluramine, phentermine (dex)amphetamine, methylphenidate, cocaine |
| Anesthetics (opioid analgesics, neuromuscular blocking agents) | Pethidine, morphine, tubocurarine, succinylcholine, atracurium besilate |

SSRIs: selective serotonin uptake inhibitors
MAO: mono amine oxidase

beta$_2$-adrenergic effects of epinephrine, but as detailed later may also reflect differences in secretory characteristics. Tumors that produce predominantly dopamine are rare, presenting mainly as paragangliomas, particularly in the head and neck. Patients with such tumors are usually normotensive and asymptomatic [18, 29]. Presence of nausea or orthostatic hypotension has been reported in several patients with dopamine-producing PPGLs [18, 30]. Given the widely varying clinical spectrum of signs and symptoms, a meticulously taken detailed medical history and physical examination are essential for timely diagnosis of this treacherous tumor.

### 31.1.3 Incidentalomas

As many as or more than 25% of all pheochromocytomas are now being diagnosed after presentation as an adrenal incidentaloma [31–33]. Many cases of abdominal or thoracic paragangliomas are also being discovered after imaging for nonspecific reasons such as abdominal pain or due to other mass effects of tumors [18, 33]. Due to the high prevalence of PPGLs among such patients, combined with the substantial proportion of normotensive and asymptomatic cases, routine screening for PPGLs is widely recommended for all patients with incidentally discovered masses, regardless of the presence or absence of signs and symptoms [16, 33–35].

As indicated in one study, biochemical phenotypic features and other tumor characteristics differ between patients presenting with normotensive incidentally discovered adrenal pheochromocytomas and those with similarly sized tumors associated with overt signs and symptoms [36]. Specifically tumors from patients who were normotensive showed lesser increases in both urinary metanephrines and catecholamines than in patients who were hypertensive. This suggested that differences in biochemical features might contribute to discovery of such tumors as incidentalomas rather than more classically secondary to hypertension and symptoms of catecholamine excess.

### 31.1.4 Hereditary Disease

At least a third of PPGLs are inherited due to germline mutations of more than 13 tumor susceptibility genes identified to date [37, 38]. The most well-established hereditary causes of PPGLs are those associated with syndromic presentations including neurofibromatosis type 1 (NF 1) due to mutations of the *NF1* gene, multiple endocrine neoplasia type 2 (MEN2) due to mutations of the rearranged during transfection (*RET*) gene, von Hippel-Lindau (VHL) syndrome due to mutations of the *VHL* gene, and familial paraganglioma syndromes caused by mutations of genes encoding succinate dehydrogenase subunits B and D (SDHB and SDHD). Other less frequent forms of hereditary PPGLs can result from mutations of succinate dehydrogenases A and C (*SDHA* and *SDHC*), succinate dehydrogenase complex assembly factor 2 (*SDHAF2*), transmembrane domain protein 127 (*TMEM127*), MYC-associated factor X (*MAX*), prolyl hydroxylase 2 (*PHD2*), fumarate hydratase (*FH*), and malate dehydrogenase 2 (*MDH2*).

Prevalence of PPGLs associated with the above mutations varies according to penetrance of disease and incidence of mutations. For NF1, although relatively common (1:3000), penetrance of pheochromocytoma is low with not more than 5% of patients developing the tumors [39]. In contrast, the penetrance of pheochromocytoma for *RET* mutation carriers reaches 40–50% [17], while for VHL syndrome it averages 20% with variability according to the particular mutation [40]. For some mutations of the SDHD gene penetrance has been reported to reach up to 100% [41]. Among patients with *SDHD*, *SDHAF2*, and *MAX* mutations, disease is transmitted to offspring paternally, skipping a generation with maternal transmission [42–44]. For most of the recently discovered tumor susceptibility genes, penetrance has not yet been precisely established, this requiring long-term follow-up of non-index cases.

Despite the variability and uncertainty of disease risk, it is widely recognized that all patients carrying mutations of PPGL susceptibility genes should undergo periodic screening for the tumors. For patients with VHL syndrome and MEN2, such screening at specialist centers is already well established and clearly results in diagnosis of tumors at an earlier stage when tumors are small and patients are normotensive and asymptomatic [28, 45]. For all there is an emerging need for personalized management according to risk. Patients with *SDHB* mutations, who carry a high risk for metastatic PPGLs [46], provide an example of those who might particularly benefit from earlier detection of disease before metastatic involvement.

Due to the rich hereditary background of PPGLs, it is recommended by Endocrine Society clinical practice guidelines that all patients with PPGLs receive counseling about possible genetic risk and that genetic testing should be particularly encouraged for several groups of patients [47]: (1) those with a positive family history of PPGLs or tumor susceptibility gene mutations, (2) those with syndromic features, (3) those with PPGLs occurring at a young age, (4) those with multifocal or bilateral adrenal tumors, (5) those with paragangliomas in whom

there is high risk of mutations for genes encoding succinate dehydrogenase subunits, and (6) those with metastatic disease in whom there is a high risk of *SDHB* mutations. The underlying rationale for such testing is that identification of a gene mutation provides a context for routine screening programs that can result in earlier detection of PPGLs and other neoplasms, thereby reducing morbidity and mortality. For patients with aggressive disease in whom surgical intervention is not an option, new developments on the horizon also make it likely that establishing the underlying mutation can provide a rationale for therapies that target downstream signaling pathways [48].

For PPGLs, the pathways leading to tumorigenesis are being rapidly elucidated consequent to their rich hereditary background [37, 49, 50]. As originally indicated by gene expression profiling, the various types of hereditary PPGLs fall into one of two main cluster groups according to the mutation and downstream affected signaling pathways [37]. Mutations of *RET*, *NF1*, *TMEM127*, and *MAX*, associated with cluster group 2, all involve activation of RAS and kinase signaling pathways and lead to well-differentiated adrenal pheochromocytomas with low susceptibility to malignancy. In contrast, mutations of *VHL*, *SDHB*, *SDHD*, *SDHC*, *SDHA*, *SDHAF2*, *PHD2*, and *FH*, associated with the cluster group 1, all result in stabilization of hypoxia-inducible factors (HIFs) leading to activation of hypoxia-angiogenic pathways. Apart from increased expression of hypoxia pathway genes, these tumors are also characterized by increased expression of the *HIF2α* itself and occur at an earlier age at both adrenal and extra-adrenal locations compared to the more differentiated cluster 2 tumors [51, 52]; this is suggested to reflect importance of transient expression of *HIF2α* during early differentiation of sympathoadrenal progenitors, with stabilization at the protein level leading to inhibition of both apoptosis and differentiation [53].

Support for involvement of *HIF2α* in development of cluster 1 PPGLs has come from identification of *HIF2α* itself as a tumor susceptibility gene, in almost all cases involving somatic mutations [54]. Importantly, *HIF2α* mutations show mosaicism, indicating occurrence during embryogenesis [55]. Nevertheless, even with the commonality of HIF2α in development of cluster 1 PPGLs, there are additional differences in signaling pathways among cluster 1 PPGLs. For *HIF2α*, *VHL*, and *PHD2* mutations, stabilization of HIFs reflects the direct central tumorigenic mechanism. In contrast, for mutations of genes encoding succinate dehydrogenase subunits and other Krebs cycle enzymes (e.g., fumarate hydratase), stabilization of HIFs occurs secondary to wider actions of the elevated cellular levels of oncometabolites, succinate, or fumarate [48]. These oncometabolites inhibit not only the prolyl-hydroxylases that facilitate HIF degradation but also other alpha-ketoglutarate-dependent hydroxylases, such as histone and DNA demethylases. As a result, PPGLs resulting from mutations of genes encoding Krebs cycle enzymes exhibit a hypermethylator phenotype, turning off expression of numerous genes involved in restricting growth and controlling differentiation [56]. The result is that among cluster 1 PPGLs, those due to mutations of genes encoding Krebs cycle enzymes, and *SDHB* in particular, are the most aggressive and poorly differentiated (Fig. 31.2).

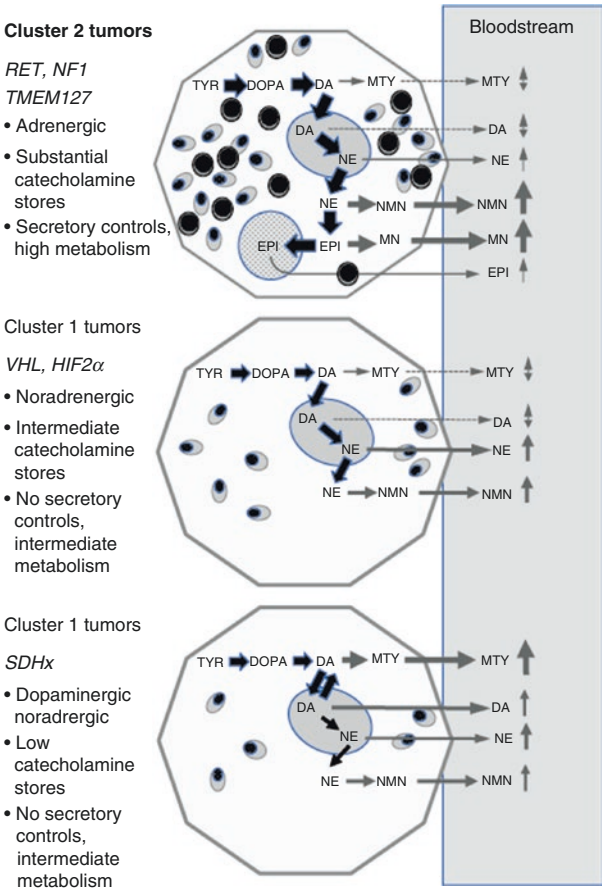



**Fig. 31.2** Catecholamine phenotypic features in PPGLs according to mutation. Cluster 2 tumors due to RET, NF1, and TMEM1 mutations are well differentiated, metabolizing tyrosine (TYR) to L-dopa (DOPA) by tyrosine hydroxylase, then to dopamine (DA) by aromatic amino acid decarboxylase, then to norepinephrine (NE) by dopamine β-hydroxylase after uptake into noradrenergic vesicles, and then to epinephrine (EPI) by phenylethanolamine N-methyltransferase (PNMT) after leakage of NE into the cytoplasm. DA is metabolized to methoxytyramine (MTY), NE is metabolized to normetanephrine (NMN), and EPI is metabolized to metanephrine (MN), all conversions catalyzed in the cytoplasm by catechol-O-methyltransferase. Cluster 1 tumors due to VHL, HIF2α, and SDHx mutations do not express PNMT so that these tumors do not produce EPI or MN. Also, these tumors, although having lower catecholamine stores compared to cluster 2 tumors, have poorer secretory controls than cluster 2 tumors and secrete catecholamines at higher rates. Tumors due to SDHx mutation are particularly poorly differentiated and often produce large amounts of MTY

## 31.2 Biochemistry

### 31.2.1 Catecholamine Synthesis, Storage, Secretion, and Metabolism

Synthesis, storage, secretion, and metabolism of catecholamines in PPGLs vary substantially depending on expression of catecholamine biosynthetic and secretory machinery, this as outlined above determined by underlying gene mutations [57, 58] (Fig. 31.2). The well-differentiated cluster 2 type pheochromocytomas all express phenylethanolamine N-methyltransferase (PNMT), which converts norepinephrine to epinephrine. Norepinephrine and epinephrine are stored in electron microscopically distinct secretory vesicles, the presences of which differ in cluster 1 and 2 mutated tumors [28].

Catecholamine secretion primarily involves exocytosis in which storage vesicles fuse with the plasma membrane and extrude their catecholamine contents into the extracellular space. This secretory process is a highly regulated calcium-dependent process responsive to neuronal input or secretogogues for evoked but controlled release of catecholamines. While PPGLs lack the former control, they can be influenced by secretogogues, but vary considerably in expression of the cellular secretory machinery responsive to regulatory control. Cluster 1 mutated tumors not only lack expression of PNMT, but in contrast to well-differentiated cluster 2 tumors also exhibit poorer expression of other key catecholamine biosynthetic enzymes and components responsible for storage and regulated secretion of catecholamines [57] (Fig. 31.2).

As a consequence of the above differences, cluster 1 tumors lack production of epinephrine and also contain lower overall stores of catecholamines [58] (Fig. 31.2). Furthermore, due to their relative lack of regulated secretory pathway machinery, cluster 1 tumors also secrete the limited amounts of catecholamines they produce in a more continuous or constitutive fashion compared to cluster 2 tumors. Thus, in contrast to cluster 1 PPGLs, cluster 2 epinephrine-producing pheochromocytomas, such as those in patients with MEN 2 or NF1, are characterized by highly concentrated stores of catecholamines and relatively low rates of catecholamine secretion. These tumors can, however, be easily provoked to secrete catecholamines in response to secretogogues and other stimuli, which may provide the basis for why epinephrine-producing tumors have been described as more often producing paroxysmal hypertension compared to norepinephrine-producing tumors.

The above differences along with differences in co-secretion of bioactive peptides are likely responsible for some of the highly variable clinical manifestations of chromaffin cell tumors, but as yet there has been no fully prospective study to firmly establish such a link between underlying mutations to differences in presentation of disease. There are, however, forms of undifferentiated PPGLs for which a link seems clear. These in particular involve patients who have PPGLs due to mutations

of the *SDHB* gene which appears to be associated with further downregulated expression of catecholamine phenotypic features due to epigenetic silencing secondary to actions of elevated succinate to inhibit alpha-ketoglutarate-dependent enzymes involved in regulating DNA methylation [56]. As a consequence, tumors in patients with SDHB mutation contain the lowest amounts of catecholamines, among all PPGLs; catecholamine contents are also characterized by relative high proportions of dopamine [58, 59]. The tumors often reach large sizes before their discovery, which may reflect both relative paucity of signs and symptoms and diversion of energy from maintaining chromaffin-like phenotypic features to enhanced growth. Consequently, these tumors carry a high risk of malignancy.

Most other PPGLs contain large amounts of catecholamines, particularly norepinephrine, in about 50% of cases additional epinephrine and a variable amount of dopamine [58]. Tumor contents and secretion of dopamine are impacted by the efficiency of dopamine beta-hydroxylase in converting the dopamine to norepinephrine after the former amine is translocated into secretory vesicles [60]. Importantly, the catecholamines stored in secretory granules exist in a highly dynamic equilibrium with the surrounding cytoplasm, with passive outward leakage into the cytoplasm counterbalanced by inward active transport under the control of vesicular monoamine transporters [61]. For all catecholamines, whether stored in sympathetic neurons, adrenal chromaffin cells, or tumors derived from adrenal or extra-adrenal chromaffin cells, most initial metabolism takes place within the cells where the catecholamines are synthesized [62].

In sympathetic nerves, the presence of monoamine oxidase (MAO), but absence of catecholamine-O-methyltransferase (COMT), leads to deamination of norepinephrine to dihydroxyphenylglycol (DHPG). This primary norepinephrine metabolite is derived largely from norepinephrine leaking from storage vesicles, but is also derived from reuptake of the transmitter back into nerves [62]. Only a small amount of norepinephrine escapes reuptake; some of this is metabolized extraneuronally to normetanephrine or DHPG, while a remaining small proportion (<5%) reaches the circulation as norepinephrine. In adrenal chromaffin cells and tumors of chromaffin cells, the additional presence of COMT leads to production of metanephrine from epinephrine, normetanephrine from norepinephrine, and methoxytyramine from dopamine [63]. This production again depends on leakage of catecholamines from storage vesicles, a continuous process that is independent of exocytotic release of catecholamines, which makes a relatively minor contribution to production of metanephrine. Thus, over 90% of all circulating metanephrine is normally derived from metabolism of epinephrine within adrenal chromaffin cells [64]. These cells also make the single largest contribution to circulating normetanephrine (at least 24%), with the rest from norepinephrine metabolized to normetanephrine in non-neuronal and non-chromaffin extraneuronal cells. Continuous production of the O-methylated metabolites within chromaffin cells and their tumor derivatives explains why measurements of plasma-free and urine deconjugated metanephrines provide advantages over measurements of catecholamines, which can be released by some tumors intermittently or in low amounts. Other catecholamine metabolites are produced in various organs and tissues of the body and also are not as useful as the metanephrines for diagnosis of PPGLs.

Vanillylmandelic acid, for example, is almost exclusively formed in the liver as the end product of catecholamine metabolism and derived mainly from DHPG produced in sympathetic nerves [65].

### 31.2.2 Biochemical Diagnosis

The superior diagnostic accuracy of measurements of plasma-free metanephrines over other tests has been clearly outlined by several independent studies [66–71], with several others confirming the high diagnostic accuracy of either plasma or urinary fractionated metanephrines for identifying patients with PPGLs [72–74]. With this evidence at hand, it has been a simple matter for Endocrine Society clinical practice guidelines on PPGLs to stipulate that initial testing for PPGLs should always include measurements of plasma-free or urinary fractionated metanephrines [47]. All other available tests, including urinary or plasma catecholamines, urinary vanillylmandelic acid, urinary total metanephrines (measured by spectrophotometric methods), and chromogranin A, are unnecessary and generally inappropriate for initial screening of PPGLs, but may be employed for follow-up confirmation of positive results of plasma-free or urinary fractionated metanephrines or in specific presentations of disease.

If used correctly with appropriate analytical methods and reference intervals, measurements of plasma-free metanephrines in particular provide diagnostic sensitivity approaching 100% with diagnostic specificity of at least 95% [74]. Over 90% of PPGLs show elevations of normetanephrine, about 50% elevations of metanephrine, and 45% elevations of methoxytyramine, with about 70% showing some combination of increases of normetanephrine with metanephrine or methoxytyramine or both. Moreover, increases are usually well in excess of twofold above the upper cutoffs. Such magnitudes of increases and combinations of increases are rare in patients without PPGLs, providing high positive predictive value in over 80% of patients with PPGLs. For these patients it is simply a matter of locating the tumor. For the other minority of patients with PPGLs in whom false positives are difficult to distinguish from true positives, biochemical diagnosis can be made using the clonidine test when elevations involve normetanephrine or by follow-up to establish increasing concentrations over time.

With measurements of plasma metanephrines by mass spectrometry and employing appropriate preanalytical precautions and reference intervals, diagnosis of PPGLs is simple [75]. Common problems, however, occur with the use of inaccurate analytical methods (e.g., immunoassays), incorrect reference intervals, and inappropriate preparation of patients for blood sampling. For the latter, patients should be sampled after 30 min supine rest and should not be under physiological or mental stress that might increase sympathoadrenal activity. Sampling in the seated position or under any form of stress carries a high likelihood of false positive results. When measurements involve plasma methoxytyramine, sampling should be carried out after an overnight fast.

At many centers, however, clinicians have problems following the above recommendations, and there can also be problems with availability or adequacy of

laboratory measurements or reference intervals for plasma-free metanephrines [75]. For this reason, measurements of urinary fractionated metanephrines provide an alternative to plasma-free metanephrines.

### 31.2.3 Interpretation of Positive Biochemical Test Results

In addition to indicating the presence of PPGLs, usually with high positive predictive value, patterns of increases in plasma free metanephrines can also be used to predict tumor size, location, underlying mutations, and metastatic involvement [75]. As outlined earlier, mutations of different genes are associated with differences in expression of catecholamine biosynthetic enzymes and thus differences in patterns of increases of normetanephrine, metanephrine, and methoxytyramine [76]. Patients with cluster 2 types mutations, such as those involving *RET* and *NF1* genes, almost all show increases in plasma metanephrine, with or without increases in normetanephrine. In contrast, PPGLs due to cluster 1 type mutations, such as those involving *VHL*, *SDHD*, and *SDHB* genes, do not express PNMT and do not produce epinephrine. Consequently, cluster 1 type tumors are associated with increases of normetanephrine, but not metanephrine. Furthermore, in patients with *SDHB* and *SDHD* mutations, there are often increases in methoxytyramine, which reflect the more immature nature of these tumors compared to other PPGLs.

Phenotypic immaturity, as indicated by increases in plasma methoxytyramine, is also associated with higher likelihood of metastatic involvement. In this context increases in plasma methoxytyramine provide the only currently available biomarker for metastatic involvement [59]. Although substantial increases of methoxytyramine are present in only about 60–70% of all cases of metastatic PPGLs, when present they are important to consider as an indicator of malignancy.

Since the extent of increase in plasma metanephrines is dependent on size of vesicular stores of catecholamines, the magnitude of increases in the metabolites can be used to roughly indicate mean tumor diameter [77]. Additionally, increased plasma metanephrine almost always indicates an adrenal pheochromocytoma or recurrence of an adrenal pheochromocytoma, whereas large increases in methoxytyramine relative to normetanephrine are indicative of extra-adrenal tumors. Such biochemical information indicating tumor size and location can be useful for subsequent imaging or interpretation of imaging results.

## 31.3 Tumor Localization

### 31.3.1 Anatomical Imaging

In general, imaging studies to locate a PPGL should be ordered once there is clear biochemical evidence for the presence of the tumor [47]. Exceptions to this rule are emergency situations where an immediate diagnosis and treatment are required [78]. Imaging studies without an established biochemical diagnosis are not cost-effective

and entail a risk for diagnostic confusion with incidentaloma, thus complicating the work-up further. The first choice imaging modality for PPGL is computed tomography scanning (CT) before and after contrast administration of the abdominal and pelvic areas [47]. More than 95% of all PPGLs are located in these areas.

CT is in general preferred over magnetic resonance imaging (MRI) because of its superior spatial resolution. The sensitivity of CT for detecting pheochromocytomas is over 90%, but lower for paragangliomas and for recurrent or metastatic tumors [79, 80]. Since CT has no high reliability for elucidating the nature of a mass, the specificity for correct identification of the mass is moderate, even with consideration of imaging features such as density, contrast enhancement, and washout [81].

Although MRI imaging with or without gadolinium enhancement has a superior sensitivity over CT for detecting paragangliomas [79], again as with CT, specificity of MRI falls short due to features that may impair signal intensity such tumor necrosis or hemorrhage [81]. Apart from extra-adrenal paragangliomas, MRI is also indicated in specific patient groups, such as those with metastases, with intracardiac or head and neck PGLs, with postoperative surgical clips, and with iodine allergy. Patients in whom radiation exposure should be kept to a minimum are also candidates for MRI, including children, pregnant women, and others with known germline mutations who are likely to undergo repeated imaging studies [47].

### 31.3.2 Functional Imaging

Since anatomical imaging is insufficient for assessing multifocality or metastatic disease and is not specific for establishing the diagnosis, a complementary functional imaging step is often required after anatomical imaging [82, 83]. The aim of functional imaging is thus to establish the nature of a mass and identify other focal or metastatic lesions. For this purpose several radiolabeled ligands targeting specific cell membrane and/or vesicular catecholamine transport systems are available. Some ligands are employed for single photon emission computed tomography (SPECT), such as $^{123}$I-MIBG, while others are used for positron emission tomography (PET), such as $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) or $^{68}$Ga-DOTATATE.

The most widely available functional imaging ligand is $^{123}$I-MIBG. Sensitivity with $^{123}$I-MIBG SPECT for detection of pheochromocytoma approaches 100%, but is considerably less for extra-adrenal paragangliomas (56–75%) and metastases, particularly when associated with underlying SDHx mutations (<50%) [84–86]. A specific advantage of using $^{123}$I-MIBG is the potential to identify patients with metastatic PPGLs who may benefit from treatment with therapeutic doses of $^{131}$I-MIBG [83].

PET imaging agents used for functional imaging of PGGLs include $^{18}$F-fluorodopamine ($^{18}$F-FDA), $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG), $^{111}$In-DTPA-pentetreotide, $^{68}$Ga-DOTATATE, and $^{68}$Ga-DOTATOC [83, 86]. The diagnostic accuracies of these different compounds vary, depending on specific clinical features, such as tumor location, genetic mutation, and metastatic involvement, requiring personalized considerations for best choice of agent as available. Since many PPGLs overexpress subtype 2 somatostatin receptors, radiolabeled somatostatin

receptor ligands can be particularly useful for localization. Such ligands developed for PET imaging, including $^{68}$Ga-DOTATATE and $^{68}$Ga-DOTATOC, have shown particularly excellent diagnostic accuracy for head and neck paragangliomas and SDHB-related metastatic disease [87–89].

## 31.4 Management

### 31.4.1 Preoperative Management

Surgical outcomes of patients with PPGLs have improved considerably over the last 50 years with a current perisurgical mortality rate of less than 1%. This can be attributed to improved presurgical medical preparation of patients as well as emergence of multidisciplinary teams and sophisticated approaches to anesthesiological management. Although most patients are in the long term cured by tumor removal, postsurgical recurrence rates average 16.5% [90].

Elective surgical removal of a catecholamine-producing tumor should be preceded by preoperative medical preparation to prevent or minimize hazardous complications due to massive release of catecholamines from the tumor, particularly provoked by mechanical manipulation during surgery [47, 91]. Such precautions are indicated in all patients in whom elevations of plasma or urinary metanephrines indicate a catecholamine-producing tumor, regardless of the presence or absence of symptoms or whether patients are hypertensive or normotensive. Although some retrospective small series of patients have questioned the need for medical preparation, there are no randomized trials documenting that refraining from medical pretreatment is safe. Since it is impossible to predict the course during surgery in individual patients, a patient-tailored strategy of preoperative blockade provides the safest approach.

The mainstay for successful medical pretreatment remains α-adrenoceptor antagonist therapy using the noncompetitive inhibitor, phenoxybenzamine, or the competitive inhibitor, doxazosin [91, 92]. Evidence from randomized trials showing benefits of one over the other are lacking [47]. Calcium channel blockers are generally not used as first-line blocking agent but do hold a place as an add-on drug to α-adrenoceptor blockade. Similarly, the catecholamine-synthesis inhibitor α-methylparatyrosine (metyrosine) can be employed as an add-on treatment to α-adrenoceptor blockade when required [91, 93]. A β-adrenoceptor antagonist, such as atenolol or metoprolol, can also be included several days before surgery to prevent tachyarrhythmias, but only after α-adrenoceptor blockade [91].

The recommended duration of pharmacological pretreatment in elective patients is 7–14 days, but this is based mainly on expert opinion. The target blood pressure level is less than 130/80 mm Hg in the sitting position with a systolic blood pressure in the upright position higher than 90 mm Hg [47, 91]. A presurgical high-sodium diet and high fluid intake during preparation are helpful to circumvent postsurgical hypotension [91]. Close postsurgical surveillance for at least 24 h is essential for detection and proper treatment of hypotension and hypoglycemia. In specific patients undergoing bilateral or major unique adrenal surgery, the possibility of adrenal insufficiency is the first and most important consideration in situations of postsurgical hypotension.

### 31.4.2 Surgical Management

Surgical removal of pheochromocytomas by minimal invasive laparoscopic tumor resection is first choice treatment with the posterior retroperitoneal approach preferred in patients with pheochromocytoma [94]. Paragangliomas may also be resected by laparoscopic surgery depending on tumor size, relation to other organs, and on the experience of the surgeon [95]. Retrospective cohort studies have shown that patients operated by laparoscopy experience less blood loss and have a shorter stay in hospital as compared to conventional open surgery [96, 97]. In patients with underlying mutations such as those with MEN2 and VHL, adrenal-sparing surgery is indicated when technically feasible. Leaving some remnant adrenocortical tissue in situ avoids or postpones need for lifelong steroid replacement therapy for adrenal insufficiency, but this benefit should be balanced against the increased risk of tumor recurrence [98–100].

### 31.4.3 Follow-Up

Following surgical removal of PPGLs, all patients should undergo follow-up to ascertain whether the tumor has been removed completely [101]. For patients with presurgically elevated plasma or urine metanephrines, measurements can be repeated at 2–6 weeks after surgery. Persistently elevated test results suggest residual disease that should then be confirmed by additional imaging studies.

Since there is a persistent risk of recurrent disease after apparently complete resection of an initially discovered PPGL, it is important that follow-up is continued in the long term well after surgical resection [102]. Risk of recurrence is higher in young patients (<20 years), in those with syndromic presentations, paragangliomas, and patients with large tumors. However, there is no “safe” tumor size below which the risk is zero. Thus, follow-up is recommended in all operated patients annually for at least 10 years, but continuing thereon in high-risk patients, such as those who are young, carry an underlying germline mutation or who present with an extra-adrenal or large tumor. Follow-up should include an annually taken medical history, physical examination including blood pressure, and measurements of plasma or urinary fractionated metanephrines.

## References

1. Tischler AS (2008) Pheochromocytoma and extra-adrenal paraganglioma: updates. Arch Pathol Lab Med 132(8):1272–1284. doi:2007-0731-RAR [pii]
2. Waguespack SG, Rich T, Grubbs E et al (2010) A current review of the etiology, diagnosis, and treatment of pediatric pheochromocytoma and paraganglioma. J Clin Endocrinol Metab 95(5):2023–2037. doi:10.1210/jc.2009-2830
3. Manger WM (2009) The protean manifestations of pheochromocytoma. Hom Metab Res 41(9):658–663. doi:10.1055/s-0028-1128139
4. Mannelli M, Lenders JW, Pacak K et al (2012) Subclinical phaeochromocytoma. Best Pract Res Clin Endocrinol Metab 26(4):507–515. doi:10.1016/j.beem.2011.10.008

5. Sutton MG, Sheps SG, Lie JT (1981) Prevalence of clinically unsuspected pheochromocytoma. Review of a 50-year autopsy series. Mayo Clin Proc 56(6):354–360
6. McNeil AR, Blok BH, Koelmeyer TD et al (2000) Phaeochromocytomas discovered during coronial autopsies in Sydney, Melbourne and Auckland. Aust NZ J Med 30(6):648–652
7. Lo CY, Lam KY, Wat MS, Lam KS (2000) Adrenal pheochromocytoma remains a frequently overlooked diagnosis. Am J Surg 179(3):212–215
8. Fernandez-Calvet L, Garcia-Mayor RV (1994) Incidence of pheochromocytoma in South Galicia, Spain. J Intern Med 236(6):675–677
9. Ariton M, Juan CS, AvRuskin TW (2000) Pheochromocytoma: clinical observations from a Brooklyn tertiary hospital. Endocr Pract 6(3):249–252
10. Omura M, Saito J, Yamaguchi K et al (2004) Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. Hypertens Res 27(3):193–202
11. Hernandez FC, Sanchez M, Alvarez A et al (2000) A five-year report on experience in the detection of pheochromocytoma. Clin Biochem 33(8):649–655
12. Vaclavik J, Stejskal D, Lacnak B et al (2007) Free plasma metanephrines as a screening test for pheochromocytoma in low-risk patients. J Hypertens 25(7):1427–1431
13. Brain KL, Kay J, Shine B (2006) Measurement of urinary metanephrines to screen for pheochromocytoma in an unselected hospital referral population. Clin Chem 52(11):2060–2064. doi:10.1373/clinchem.2006.070805
14. Mantero F, Terzolo M, Arnaldi G et al (2000) A survey on adrenal incidentaloma in Italy. Study group on adrenal Tumors of the Italian Society of endocrinology. J Clin Endocrinol Metab 85(2):637–644
15. Terzolo M, Bovio S, Pia A et al (2009) Management of adrenal incidentaloma. Best Pract Res Clin Endocrinol Metab 23(2):233–243. doi:10.1016/j.beem.2009.04.001
16. Mansmann G, Lau J, Balk E et al (2004) The clinically inapparent adrenal mass: update in diagnosis and management. Endocrine Rev 25(2):309–340
17. Howe JR, Norton JA, Wells SA Jr (1993) Prevalence of pheochromocytoma and hyperparathyroidism in multiple endocrine neoplasia type 2A: results of long-term follow-up. Surgery 114(6):1070–1077
18. Eisenhofer G, Goldstein DS, Sullivan P et al (2005) Biochemical and clinical manifestations of dopamine-producing paragangliomas: utility of plasma methoxytyramine. J Clin Endocrinol Metab 90:2068–2075
19. Timmers HJ, Pacak K, Huynh TT et al (2008) Biochemically silent abdominal Paragangliomas in patients with mutations in the Sdhb Gene. J Clin Endocrinol Metab 93:4826–4832
20. Zelinka T, Strauch B, Petrak O et al (2005) Increased blood pressure variability in pheochromocytoma compared to essential hypertension patients. J Hypertens 23(11):2033–2039. doi:00004872-200511000-00018 [pii]
21. Prejbisz A, Lenders JW, Eisenhofer G, Januszewicz A (2011) Cardiovascular manifestations of phaeochromocytoma. J Hypertens 29(11):2049–2060. doi:10.1097/HJH.0b013e32834a4ce9
22. Bergland BE (1989) Pheochromocytoma presenting as shock. Am J Emerg Med 7(1):44–48
23. Brouwers FM, Eisenhofer G, Lenders JW, Pacak K (2006) Emergencies caused by pheochromocytoma, neuroblastoma, or ganglioneuroma. Endocrinol Metab Clin N Am 35(4):699–724
24. Giavarini A, Chedid A, Bobrie G et al (2013) Acute catecholamine cardiomyopathy in patients with phaeochromocytoma or functional paraganglioma. Heart ;99(19):1438–1444. doi:10.1136/heartjnl-2013-304073
25. Riester A, Weismann D, Quinkler M et al (2015) Life-threatening events in patients with pheochromocytoma. Eur J Endocrinol 173(6):757–764. doi:10.1530/EJE-15-0483
26. Lance JW, Hinterberger H (1976) Symptoms of pheochromocytoma, with particular reference to headache, correlated with catecholamine production. Arch Neurol 33(4):281–288
27. Ito Y, Fujimoto Y, Obara T (1992) The role of epinephrine, norepinephrine, and dopamine in blood pressure disturbances in patients with pheochromocytoma. World J Surg 16(4):759–763. discussion 763-754

28. Eisenhofer G, Walther MM, Huynh TT et al (2001) Pheochromocytomas in von Hippel-Lindau syndrome and multiple endocrine neoplasia type 2 display distinct biochemical and clinical phenotypes. J Clin Endocrinol Metab 86(5):1999–2008
29. Proye C, Fossati P, Fontaine P et al (1986) Dopamine-secreting pheochromocytoma: an unrecognized entity? Classification of pheochromocytomas according to their type of secretion. Surgery 100(6):1154–1162
30. Awada SH, Grisham A, Woods SE (2003) Large dopamine-secreting pheochromocytoma: case report. South Med J 96(9):914–917
31. Lenders JW, Eisenhofer G, Mannelli M, Pacak K (2005) Phaeochromocytoma. Lancet 366(9486):665–675
32. Amar L, Servais A, Gimenez-Roqueplo AP et al (2005) Year of diagnosis, features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. J Clin Endocrinol Metab 90(4):2110–2116
33. Kopetschke R, Slisko M, Kilisli A et al (2009) Frequent incidental discovery of phaeochromocytoma: data from a German cohort of 201 phaeochromocytoma. Eur J Endocrinol 161(2):355–361. doi:10.1530/EJE-09-0384
34. Terzolo M, Pia A, Ali A et al (2002) Adrenal incidentaloma: a new cause of the metabolic syndrome? J Clin Endocrinol Metab 87(3):998–1003
35. Kirshtein B, Pagliarello G, Yelle JD, Poulin EC (2007) Incidence of pheochromocytoma in trauma patients during the management of unrelated illness: a retrospective review. Int J Surg 5(5):332–335. doi:10.1016/j.ijsu.2007.04.015
36. Haissaguerre M, Courel M, Caron P et al (2013) Normotensive incidentally discovered pheochromocytomas display specific biochemical, cellular, and molecular characteristics. J Clin Endocrinol Metab 98(11):4346–4354. doi:10.1210/jc.2013-1844
37. Dahia PL (2014) Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity. Nat Rev Cancer 14(2):108–119. doi:10.1038/nrc3648
38. Flynn A, Benn D, Clifton-Bligh R et al (2015) The genomic landscape of phaeochromocytoma. J Pathol 236(1):78–89. doi:10.1002/path.4503
39. Walther MM, Herring J, Enquist E et al (1999) von Recklinghausen's disease and pheochromocytomas. J Urol 162(5):1582–1586
40. Walther MM, Keiser HR, Choyke PL et al (1999) Management of hereditary pheochromocytoma in von Hippel-Lindau kindreds with partial adrenalectomy. J Urol 161(2):395–398
41. Peczkowska M, Erlic Z, Hoffmann MM et al (2008) Impact of screening kindreds for SDHD p.Cys11X as a common mutation associated with paraganglioma syndrome type 1. J Clin Endocrinol Metab 93(12):4818–4825. doi:10.1210/jc.2008-1290
42. Baysal BE (2004) Genomic imprinting and environment in hereditary paraganglioma. Am J Med Genet C Semin Med Genet 129C(1):85–90
43. Comino-Méndez I, Gracia-Aznárez FJ, Schiavi F et al (2011) Exome sequencing identifies MAX mutations as a cause of hereditary pheochromocytoma. Nat Genet 43:663–667
44. Hoekstra AS, Devilee P, Bayley JP (2015) Models of parent-of-origin tumorigenesis in hereditary paraganglioma. Semin Cell Dev Biol 43:117–124. doi:10.1016/j.semcdb.2015.05.011
45. van Duinen N, Steenvoorden D, Bonsing BA et al (2010) Pheochromocytomas detected by biochemical screening in predisposed subjects are associated with lower prevalence of clinical and biochemical manifestations and smaller tumors than pheochromocytomas detected by signs and symptoms. Eur J Endocrinol 163(1):121–127. doi:10.1530/EJE-10-0114
46. Amar L, Bertherat J, Baudin E et al (2005) Genetic testing in pheochromocytoma or functional paraganglioma. J Clin Oncol 23(34):8812–8818
47. Lenders JWM, Duh QY, Eisenhofer G et al (2014) Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 99:1915–1942
48. Favier J, Amar L, Gimenez-Roqueplo AP (2015) Paraganglioma and phaeochromocytoma: from genetics to personalized medicine. Nature Rev Endocrinol 11(2):101–111. doi:10.1038/nrendo.2014.188

49. Jochmanova I, Yang C, Zhuang Z, Pacak K (2013) Hypoxia-inducible factor signaling in pheochromocytoma: turning the rudder in the right direction. J Natl Canc Inst 105(17):1270–1283. doi:10.1093/jnci/djt201
50. Qin N, de Cubas AA, Garcia-Martin R et al (2014) Opposing effects of HIF1alpha and HIF2alpha on chromaffin cell phenotypic features and tumor cell proliferation: insights from MYC-associated factor X. Int J Cancer 135(9):2054–2064. doi:10.1002/ijc.28868
51. Eisenhofer G, Huynh TT, Pacak K et al (2004) Distinct gene expression profiles in norepinephrine- and epinephrine-producing hereditary and sporadic pheochromocytomas: activation of hypoxia-driven angiogenic pathways in von Hippel-Lindau syndrome. Endocr Relat Cancer 11:897–911
52. Eisenhofer G, Timmers H, Lenders JW et al (2011) Age at diagnosis of pheochromocytoma differs according to catecholamine phenotype and tumor location. J Clin Endocrinol Metab 96:375–384
53. Richter S, Qin N, Pacak K, Eisenhofer G (2013) Role of hypoxia and HIF2a in development of the sympathoadrenal cell lineage and chromaffin cell tumors with distinct catecholamine phenotypic features. Adv Pharmacol 68:285–317
54. Zhuang Z, Yang C, Lorenzo F et al (2012) Somatic HIF2A gain-of-function mutations in paraganglioma with polycythemia. NEJM 367(10):922–930. doi:10.1056/NEJMoa1205119
55. Buffet A, Smati S, Mansuy L et al (2014) Mosaicism in HIF2A-related polycythemia-paraganglioma syndrome. J Clin Endocrinol Metab 99(2):E369–E373. doi:10.1210/jc.2013-2600
56. Letouze E, Martinelli C, Loriot C et al (2013) SDH mutations establish a hypermethylator phenotype in paraganglioma. Cancer Cell 23(6):739–752. doi:10.1016/j.ccr.2013.04.018
57. Eisenhofer G, Huynh TT, Elkahloun A et al (2008) Differential expression of the regulated catecholamine secretory pathway in different hereditary forms of pheochromocytoma. Am J Physiol Endocrinol Metab 295(5):E1223–E1233
58. Eisenhofer G, Pacak K, Huynh TT et al (2011) Catecholamine metabolomic and secretory phenotypes in phaeochromocytoma. Endocr Relat Cancer 18(1):97–111. doi:ERC-10-0211 [pii]. doi:10.1677/ERC-10-0211
59. Eisenhofer G, Lenders JW, Siegert G et al (2012) Plasma methoxytyramine: a novel biomarker of metastatic pheochromocytoma and paraganglioma in relation to established risk factors of tumour size, location and SDHB mutation status. Eur J Cancer 48:1739–1749
60. Feldman JM (1985) Increased dopamine production in patients with carcinoid tumors. Metab Clin Exp 34(3):255–260
61. Eisenhofer G, Kopin IJ, Goldstein DS (2004) Leaky catecholamine stores: undue waste or a stress response coping mechanism? Ann N Y Acad Sci 1018:224–230
62. Eisenhofer G, Kopin IJ, Goldstein DS (2004) Catecholamine metabolism: a contemporary view with implications for physiology and medicine. Pharmacol Rev 56(3):331–349
63. Eisenhofer G, Keiser H, Friberg P et al (1998) Plasma metanephrines are markers of pheochromocytoma produced by catechol-O-methyltransferase within tumors. J Clin Endocrinol Metab 83(6):2175–2185
64. Eisenhofer G, Rundquist B, Aneman A et al (1995) Regional release and removal of catecholamines and extraneuronal metabolism to metanephrines. J Clin Endocrinol Metab 80(10):3009–3017
65. Eisenhofer G, Aneman A, Hooper D et al (1996) Mesenteric organ production, hepatic metabolism, and renal elimination of norepinephrine and its metabolites in humans. J Neurochem 66(4):1565–1573
66. Lenders JW, Pacak K, Walther MM et al (2002) Biochemical diagnosis of pheochromocytoma: which test is best? JAMA 287(11):1427–1434
67. Raber W, Raffesberg W, Bischof M et al (2000) Diagnostic efficacy of unconjugated plasma metanephrines for the detection of pheochromocytoma. Arch Intern Med 160(19):2957–2963
68. Unger N, Pitt C, Schmidt IL et al (2006) Diagnostic value of various biochemical parameters for the diagnosis of pheochromocytoma in patients with adrenal mass. Eur J Endocrinol 154(3):409–417

69. Hickman PE, Leong M, Chang J et al (2009) Plasma free metanephrines are superior to urine and plasma catecholamines and urine catecholamine metabolites for the investigation of phaeochromocytoma. Pathology 41(2):173–177. doi:907871493 [pii]. doi:10.1080/00313020802579284
70. Grouzmann E, Drouard-Troalen L, Baudin E et al (2010) Diagnostic accuracy of free and total metanephrines in plasma and fractionated metanephrines in urine of patients with pheochromocytoma. Eur J Endocrinol 162(5):951–960. doi:EJE-09-0996 [pii]. doi:10.1530/EJE-09-0996
71. Pussard E, Chaouch A, Said T (2014) Radioimmunoassay of free plasma metanephrines for the diagnosis of catecholamine-producing tumors. Clin Chem Lab Med 52(3):437–444. doi:10.1515/cclm-2013-0406
72. Procopiou M, Finney H, Akker SA et al (2009) Evaluation of an enzyme immunoassay for plasma-free metanephrines in the diagnosis of catecholamine-secreting tumors. Eur J Endocrinol 161(1):131–140. doi:EJE-09-0172 [pii]. doi:10.1530/EJE-09-0172
73. Christensen TT, Frystyk J, Poulsen PL (2011) Comparison of plasma metanephrines measured by a commercial immunoassay and urinary catecholamines in the diagnosis of pheochromocytoma. Scan J Clin Lab Invest 71(8):695–700. doi:10.3109/00365513.2011.622410
74. Darr R, Pamporaki C, Peitzsch M et al (2014) Biochemical diagnosis of phaeochromocytoma using plasma-free normetanephrine, metanephrine and methoxytyramine: importance of supine sampling under fasting conditions. Clin Endocrinol 80(4):478–486. doi:10.1111/cen.12327
75. Eisenhofer G, Peitzsch M (2014) Laboratory evaluation of pheochromocytoma and paraganglioma. Clin Chem 60(12):1486–1499. doi:10.1373/clinchem.2014.224832
76. Eisenhofer G, Lenders JW, Timmers H et al (2011) Measurements of plasma methoxytyramine, normetanephrine, and metanephrine as discriminators of different hereditary forms of pheochromocytoma. Clin Chem 57(3):411–420. doi:clinchem.2010.153320 [pii]. doi:10.1373/clinchem.2010.153320
77. Eisenhofer G, Lenders JW, Goldstein DS et al (2005) Pheochromocytoma catecholamine phenotypes and prediction of tumor size and location by use of plasma free metanephrines. Clin Chem 51(4):735–744
78. Amar L, Eisenhofer G (2015) Diagnosing phaeochromocytoma/paraganglioma in a patient presenting with critical illness: biochemistry versus imaging. Clin Endocrinol 83(3):298–302. doi:10.1111/cen.12745
79. IliasI, SahdevA, ReznekRHet al (2007) The optimal imaging of adrenal tumours: a comparison of different methods. Endocr Relat Cancer 14 (3):587-599. doi:14/3/587[pii]10.1677/ERC-07-0045
80. Sahdev A, Sohaib A, Monson JP et al (2005) CT and MR imaging of unusual locations of extra-adrenal paragangliomas (pheochromocytomas). Eur Radiol 15(1):85–92
81. Leung K, Stamm M, Raja A, Low G (2013) Pheochromocytoma: the range of appearances on ultrasound, CT, MRI, and functional imaging. AJR Am J Roentgenol 200(2):370–378. doi:10.2214/AJR.12.9126
82. Pacak K, Eisenhofer G, Goldstein DS (2004) Functional imaging of endocrine tumors: role of positron emission tomography. Endocr Rev 25(4):568–580
83. Taieb D, Timmers HJ, Hindie E et al (2012) EANM 2012 guidelines for radionuclide imaging of phaeochromocytoma and paraganglioma. Eur J Nucl Med Mol Imaging 39(12):1977–1995. doi:10.1007/s00259-012-2215-8
84. Wiseman GA, Pacak K, O'Dorisio MS et al (2009) Usefulness of 123I-MIBG scintigraphy in the evaluation of patients with known or suspected primary or metastatic pheochromocytoma or paraganglioma: results from a prospective multicenter trial. J Nucl Med 50(9):1448–1454. doi:jnumed.108.058701 [pii]. doi:10.2967/jnumed.108.058701
85. Fiebrich HB, Brouwers AH, Kerstens MN et al (2009) 6-[F-18]Fluoro-L-dihydroxyphenylalanine positron emission tomography is superior to conventional imaging with (123)I-metaiodobenzylguanidine scintigraphy, computer tomography, and magnetic resonance imaging in localizing tumors causing catecholamine excess. J Clin Endocrinol Metab 94(10):3922–3930. doi:10.1210/jc.2009-1054

86. Timmers HJ, Chen CC, Carrasquillo JA et al (2012) Staging and functional characterization of pheochromocytoma and paraganglioma by 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography. J Natl Canc Inst 104(9):700–708. doi:10.1093/jnci/djs188
87. Maurice JB, Troke R, Win Z et al (2012) A comparison of the performance of (6)(8) Ga-DOTATATE PET/CT and (1)(2)(3)I-MIBG SPECT in the diagnosis and follow-up of phaeochromocytoma and paraganglioma. Eur J Nucl Med Mol Imaging 39(8):1266–1270. doi:10.1007/s00259-012-2119-7
88. Janssen I, Blanchet EM, Adams K et al (2015) Superiority of [68Ga]-DOTATATE PET/CT to other functional imaging modalities in the localization of SDHB-associated metastatic Pheochromocytoma and Paraganglioma. Clin Cancer Res 21(17):3888–3895. doi:10.1158/1078-0432.CCR-14-2751
89. Janssen I, Chen CC, Taieb D et al (2016) 68Ga-DOTATATE PET/CT in the localization of head and neck Paragangliomas compared with other functional imaging modalities and CT/MRI. J Nucl Med 57(2):186–191. doi:10.2967/jnumed.115.161018
90. Amar L, Fassnacht M, Gimenez-Roqueplo AP et al (2012) Long-term postoperative follow-up in patients with apparently benign pheochromocytoma and paraganglioma. Hom Metab Res 44(5):385–389
91. Pacak K, Eisenhofer G, Ahlman H et al (2007) Pheochromocytoma: recommendations for clinical practice from the first international symposium. Nat Clin Pract Endocrinol Metab 3(2):92–102
92. Weingarten TN, Cata JP, O'Hara JF et al (2010) Comparison of two preoperative medical management strategies for laparoscopic resection of pheochromocytoma. Urology 76(2):508e506–511. doi: 10.1016/j.urology.2010.03.032
93. Steinsapir J, Carr AA, Prisant LM, Bransome ED Jr (1997) Metyrosine and pheochromocytoma. Arch Int Med 157(8):901–906
94. Walz MK, Alesina PF, Wenger FA et al (2006) Laparoscopic and retroperitoneoscopic treatment of pheochromocytomas and retroperitoneal paragangliomas: results of 161 tumors in 126 patients. World J Surg 30(5):899–908. doi:10.1007/s00268-005-0373-6
95. Goers TA, Abdo M, Moley JF et al (2013) Outcomes of resection of extra-adrenal pheochromocytomas/paragangliomas in the laparoscopic era: a comparison with adrenal pheochromocytoma. Surg Endosc 27(2):428–433. doi:10.1007/s00464-012-2451-9
96. Shen WT, Grogan R, Vriens M et al (2010) One hundred two patients with pheochromocytoma treated at a single institution since the introduction of laparoscopic adrenalectomy. Arch Surg 145(9):893–897. doi:10.1001/archsurg.2010.159
97. Agarwal G, Sadacharan D, Aggarwal V et al (2012) Surgical management of organ-contained unilateral pheochromocytoma: comparative outcomes of laparoscopic and conventional open surgical procedures in a large single-institution series. Langenbeck's Arch Surg 397(7):1109–1116. doi:10.1007/s00423-011-0879-3
98. Asari R, Scheuba C, Kaczirek K, Niederle B (2006) Estimated risk of pheochromocytoma recurrence after adrenal-sparing surgery in patients with multiple endocrine neoplasia type 2A. Arch Surg 141(12):1199–1205.; discussion 1205. doi:10.1001/archsurg.141.12.1199
99. Benhammou JN, Boris RS, Pacak K et al (2010) Functional and oncologic outcomes of partial adrenalectomy for pheochromocytoma in patients with von Hippel-Lindau syndrome after at least 5 years of followup. J Urol 184(5):1855–1859. doi:10.1016/j.juro.2010.06.102
100. Grubbs EG, Rich TA, Ng C et al (2013) Long-term outcomes of surgical treatment for hereditary pheochromocytoma. J Am Coll Surg 216(2):280–289. doi:10.1016/j.jamcollsurg.2012.10.012
101. Plouin PF, Amar L, Dekkers OM et al (2016) European Society of Endocrinology Clinical Practice Guideline for long-term follow-up of patients operated on for a phaeochromocytoma or a paraganglioma. Eur J Endocrinol 174(5):G1–G10. doi:10.1530/EJE-16-0033
102. Amar L, Lussey-Lepoutre C, Lenders J et al (2016) Management of endocrine disease: recurrence or new tumors after complete resection of phaeochromocytomas and paragangliomas. A systematic review and meta-analysis. Eur J Endocrinol. 175(4):R135–R145. doi: 10.1530/EJE-16-0189

# Hypertension in Thyroid Disorders

# 32

V. Kotsis and C. Antza

Hypertension is an important cardiovascular risk factor since deaths, disability-adjusted life years, and years of life lost are increased with high blood pressure [1]. Hypothyroidism has been linked to hypertension. The prevalence of hypertension was found higher in hypothyroid patients, while adequate thyroid hormone replacement therapy normalized thyroid function and reduced blood pressure. Thyrotoxic patients who became hypothyroid after radioiodine therapy had significantly increased diastolic blood pressure [2, 3]. Thyroid abnormalities have been associated with increased cardiovascular risk profile. Even within the normal range, TSH was associated with lipid levels and blood pressure among both men and women. Despite that, subclinical thyroid abnormalities were not associated with increased risk of coronary heart disease or all-cause mortality [4]. Subclinical hypothyroidism was associated with hypertension in most but not in all cross-sectional studies [4–6]. In a population-based study, included 30,728 individuals, a positive and linear association between TSH within the reference range and systolic and diastolic blood pressure was reported. The average increase in systolic blood pressure per multiunit per liter increase in TSH was 2.0 mm Hg in men and 1.8 mm Hg in women, and the average increase in diastolic blood pressure per multiunit per liter increase in TSH was 1.6 mmHg in men and 1.1 mmHg in women [7]. Higher TSH levels were associated with current hypertension but not with a 5-year change in blood pressure and incident hypertension suggesting a short-term effect of thyroid hormone levels on arterial blood pressure that may be altered from thyroid hormone replacement treatment in population studies [8]. The HUNT study showed that higher TSH levels at baseline were associated with higher future BP levels in euthyroid participants (baseline TSH level of 0.45–4.5 mU/L) after 11 years of follow-up, but the association was modest and mainly in women [9].

V. Kotsis (✉) • C. Antza
Aristotle University Thessaloniki, Thessaloniki, Greece
e-mail: vkotsis@auth.gr



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_32

Thyroid hormone actions in the heart and the vessels are important and associated with the physiology of thyroid-induced heart disease and hypertension. The thyroid gland is responsible for the production of thyroid hormone and consists of follicles in which thyroid hormone is synthesized through iodination of tyrosine residues in the glycoprotein thyroglobulin [10]. Thyroid-stimulating hormone (TSH), secreted by the anterior pituitary in response to feedback from circulating thyroid hormone, acts directly on the TSH receptor (TSH-R) expressed on the thyroid follicular cell basolateral membrane [11]. Thyroid hormone holds an important role in normal development, growth, neural differentiation, and metabolic regulation in mammals [12, 13]. Thyroxin (T4) and 3,5,3′-triiodothyronine (T3) are synthesized by the thyroid gland in response to TSH. The thyroid gland secretes T4 which is converted to T3 in the liver, kidney, and skeletal muscle [14, 15]. Hyperthyroidism induces a hyperdynamic cardiovascular state, which is associated with increased heart rate and enhanced left ventricular systolic and diastolic function, whereas hypothyroidism is characterized by the opposite changes. T3 is taken up in neonatal rat cardiomyocytes by an energy-dependent carrier-mediated mechanism. Such a transport mechanism for T4 is not present. The heart is mainly affected by serum T3 because intracellular deiodinase activity does not take place in myocytes [16]. Atrial fibrillation (AF) occurs in 10–25% of patients with hyperthyroidism, more commonly in men and elderly patients [17]. Treatment is directed toward restoring a euthyroid state, which is usually associated with a spontaneous reversion to sinus rhythm.

Thyroid hormones play an important role in BP control by a number of direct and indirect actions on the cardiovascular system [18]. BP changes are observed in both hypo- and hyperthyroid states in humans and animals. Thyroid hormone increases metabolism and oxygen consumption, indirectly increasing the cardiac workload. In addition, thyroid hormone exerts direct inotropic, chronotropic, and dromotropic effects that are similar to those seen with adrenergic stimulation. Hyperthyroidism is characterized by an overload circulation with increased heart rate, cardiac output, pulse pressure, and blood pressure with decreased peripheral vascular resistance, whereas overt hypothyroidism is associated with low heart rate, cardiac output, pulse pressure, and high blood pressure due to increased peripheral vascular resistance [19].

Thyroid hormones act directly on the vascular smooth muscle cells, decreasing the resistance in peripheral arterioles. These changes sensed by the kidneys increase renin synthesis and secretion, activating the renin-angiotensin-aldosterone system (RAAS) to increase renal sodium absorption. T3 also stimulates the synthesis of renin substrate in the liver [20] and increases erythropoietin synthesis, which leads to an increase in red cell mass and blood volume [21]. Therefore, whereas thyroid hormone decreases systematic vascular resistance and afterload, it also activates RAAS, leading to an increase in blood volume and heart preload which contributes to the characteristic increase in cardiac output in hyperthyroidism [21, 22]. T3 also regulates the basal metabolic rate by increasing oxygen consumption in peripheral tissues and tissue thermogenesis. In hypothyroidism, tissue thermogenesis is decreased 5–8%, whereas in hyperthyroidism, tissue thermogenesis is increased

15–20%. The metabolic demands of the peripheral tissues increase heart rate and output [19, 21]. In hypothyroidism, arterial compliance is reduced, which leads to increased systematic vascular resistance (2100–2700 dyn/s/cm$^{-5}$) [23]. In hyperthyroidism, systemic vascular resistance is decreased at 700–1200 dyn/s/cm$^{-5}$, increasing blood volume and perfusion in peripheral tissues [18]. Vascular resistance could be an explanation for increased diastolic blood pressure in hypothyroidism and decreased in hyperthyroidism.

The renin-angiotensin-aldosterone system (RAAS) plays an important role in blood pressure regulation [20]. Several in vivo and in vitro studies have reported that thyroid hormones may modulate the RAAS and have evidenced a relationship between thyroid state and RAAS components [24, 25]. Angiotensin (ANG) II type 2 (AT2)-subtype density is increased both in hyper- and hypothyroidism, whereas ANG II type 1 (AT1)-subtype density is decreased in hyperthyroidism [26]. In thyroidectomized fetal sheep, AT1 RNA expression was decreased in the kidneys and lungs, whereas AT2 mRNA expression was increased in the kidney [27]. A decrease in AT1 receptors was also observed after T3 administration to cultures of vascular rat smooth muscle cells. T3 downregulates AT1R expression both at transcriptional and posttranscriptional levels and attenuates the biological function of Ang II [28].

Atrial natriuretic peptide (ANP) stimulates vasodilatation, fluid excess, and salt and water excretion and blocks the release or actions of several hormones, including angiotensin II, aldosterone, and vasopressin. ANP levels are commonly elevated in situations of excessive fluid volume or hypertension [29]. Furthermore, brain natriuretic peptide (BNP) shows a remarkable sequence homology with ANP and has peripheral and central actions similar to those of ANP. Secretion of BNP is accelerated via hypertrophied ventricles in experimental hypertension [30], and it was found that BNP, which is synergistically increased with aging and left ventricular hypertrophy, may be an important risk marker for hypertensive cardiovascular events [31]. Stretch, glucocorticoids, thyroid hormone(s), mineralocorticoids, and calcium enhance proANP gene expression. Enhanced proANP gene expression is found in congestive heart failure, hypertension, and cirrhosis with ascites [32]. Plasma BNP concentration was increased in patients with hyperthyroidism compared with normal healthy subjects and positively correlated with serum T4 levels [33].

Obesity could also be another possible explanation for hypothyroid-induced increase in BP. Thyroid dysfunction is associated with changes in body weight and composition, body temperature, and total and resting energy expenditure independent of physical activity. Both subclinical hypothyroidism and overt hypothyroidism are frequently associated with weight gain, decreased thermogenesis, and metabolic rate [34].

## 32.1 Hypertension in Hyperthyroidism (Thyrotoxicosis)

Serum TSH measurement has the highest sensitivity and specificity of any single blood test used in the evaluation of suspected hyperthyroidism and should be used as an initial screening test. In overt hyperthyroidism, usually both serum-free T4

**Table 32.1** Studies for hypertension in hyperthyroidism

| | |
|---|---|
| Saito et al. [35] | A higher SBP was found in hyperthyroidism for each decade between 20 and 59 years of age |
| Saito et al. [36] | The prevalence of hypertension was significantly higher in patients younger than 50 years of age |
| Marcisz et al. [37] | (1) In untreated hyperthyroid patients, systolic BP was higher and diastolic BP was lower than in healthy controls<br>(2) The pulse pressure was significantly increased in the hyperthyroid patients and decreased during therapy |
| Iglesias et al. [38] | The 24h systolic blood pressure was found to be statistically significant and increased in hyperthyroid patients compared to the control group |
| Middeke et al. [39] | Patients with hypertension and hyperthyroidism had significantly smaller reductions in nocturnal blood pressure |
| Cai et al. [41] | A rather weak relationship of subclinical hyperthyroidism with increased systolic and diastolic blood pressure |

and T3 estimates are elevated, and serum TSH is undetectable; however, in mild hyperthyroidism, serum T4 and free T4 estimates can be normal, serum T3 may be elevated, and serum TSH is less than 0.01 mU/L. The term thyrotoxicosis refers to the clinical syndrome caused by thyroid hormone excess, while the term hyperthyroidism is limited to those disorders associated with increased thyroid hormone synthesis and secretion [35].

In 1985, Saito I et al. compared blood pressure values of hyperthyroid patients with those of euthyroid subjects according to their age; a higher SBP was found in hyperthyroidism for each age decade. The prevalence of hypertension was significantly higher in patients younger than 50 years of age compared to older patients [36]. In Table 32.1., studies with hyperthyroidism and hypertension are listed. Hyperthyroid patients were investigated before the initiation of treatment, 2 weeks after the initiation of therapy, and after attainment of a euthyroid state. In untreated hyperthyroid patients, systolic BP was higher and diastolic BP was lower than in healthy controls. Short-term treatment was satisfactory for lowering systolic BP, but diastolic BP returned to normal only after long-term treatment. Pulse pressure was significantly increased in the hyperthyroid patients and decreased during therapy [37]. The 24h systolic blood pressure, evaluated by ambulatory blood pressure measurements, was found to be increased in hyperthyroid normotensive patients compared to the control group, and 24 h and daytime SBP significantly decreased after normalizing thyroid function [38]. Patients with hypertension and hyperthyroidism had a significantly lower nocturnal fall in blood pressure (6/8 mmHg) compared to normotensive subjects (14/13 mmHg) [39]. Patients with thyroid cancer were evaluated for blood pressure during hyperthyroid, euthyroid, and hypothyroid states. A non-dipping pattern was found when treated cancer patients were at hyperthyroid and hypothyroid states compared to euthyroid state [40]. Finally, a recent meta-analysis revealed that subclinical hypothyroidism is associated with increased SBP and DBP, whereas subclinical hyperthyroidism is not [41].

**Table 32.2** Hypertension in hypothyroidism

| | |
|---|---|
| Saito I. et al. [2] | Diastolic BP correlated significantly with T4 and T3 in slightly hypothyroid females over 50 years of age |
| Streeten et al. [3] | Diastolic hypertension resulting from hypothyroidism is a relatively common disorder |
| Iqbal et al. [5] | Significant positive association between serum TSH and blood pressure within the normal serum TSH range |
| Liu et al. [6] | The prevalence of hypertension in subclinical hypothyroidism group was significantly higher than in euthyroid group in females |
| Botella-Carretero et al. [40] | The proportion of non-dippers is significantly increased in overt hypothyroidism compared with the control group |
| Endo et al. [44] | The hypothyroid state does not accelerate the development of hypertension |
| Bergus et al. [45] | In the population of postmenopausal women, we did not find hypertension to be associated with hypothyroidism |
| Bergus et al. [46] | In the population of geriatric patients, we did not find hypertension to be associated with the presence of hypothyroidism |
| Saltiki et al. [47] | The "freeT4TSH" product appears to be a strong predictor of DAP |
| Kanbay et al. [48] | A graded independent relation between lower level of FT3 and the risk ofnon-dipping |
| Fommei et al. [49] | Higher systolic and diastolic daytime BP levels, measured by ABPM, were observed in the hypothyroid compared with the euthyroid state |
| Kotsis et al. [50] | (1) Mean 24 h systolic BP, 24 h pulse pressure, and 24 h systolic BP variability were significantly higher among the hypothyroid population compared with subjects with normal thyroid function<br>(2) Lower 24h BP parameters were found in patients with severe hypothyroidism compared with those with mild thyroid dysfunction |

## 32.2 Hypertension in Hypothyroidism

Overt hypothyroidism is defined as the lack of T4 feedback that leads to elevated TSH levels, whereas subclinical hypothyroidism is defined as increased TSH levels with normal free T3 levels [42, 43].

Hypothyroidism has been recognized as a cause of secondary hypertension [2]. Previous studies on the prevalence of hypertension in subjects with hypothyroidism have demonstrated elevated systolic or diastolic BP values, whereas one study has reported no association between hypertension and hypothyroidism (Table 32.2.) [2, 3, 5, 6, 44–48]. Saito et al. found that diastolic BP correlated significantly with T4 and T3 in slightly hypothyroid females over 50 years of age [2]. Fommei et al. studied 12 normotensive subjects with previous total thyroidectomy after 6 weeks of treatment withdrawal and 2 months after resumption of treatment using 24 h ABPM [49]. Higher systolic and diastolic daytime BP levels were observed in the hypothyroid compared with the euthyroid state. Thyroid hormone replacement treatment resulted in a significant decrease in daytime systolic and diastolic BP values. More recently, 24 h BP differences between hypothyroid and euthyroid healthy control subjects matched for gender and age were studied [50]. A mean 24 h systolic BP, 24 h pulse pressure, and 24 h systolic BP variability were significantly higher among

the hypothyroid population compared with subjects with normal thyroid function. The 24 h diastolic BP values did not differ significantly, whereas 24 h daytime and nighttime heart rate variabilities were significantly lower, despite the similar 24 h heart rate levels. A 24 h systolic BP, 24 h pulse pressure [[51], ] and BP variability [52, 53] have been reported to independently associate with end-organ damage and total cardiovascular morbidity and mortality. However, lower 24 h BP parameters were found in patients with severe hypothyroidism compared with those with mild thyroid dysfunction [50]. In severe hypothyroidism, mechanisms reducing BP, such as reduced cardiac output [54], lower sympathetic nervous system activity, decreased sodium reabsorption, or others like adrenal insufficiency, probably have a stronger effect than the mechanisms that increase BP, such as vasoconstriction and increased total peripheral resistance. ABPM studies also demonstrated that the proportion of non-dippers is significantly increased in overt hypothyroidism (50%) compared with 17% in the control group [40, 50].

## References


1. Lim SS, Vos T, Flaxman AD et al (2012) A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the global burden of disease study 2010. Lancet 380(9859):2224–2260
2. Saito I, Ito K, Saruta T (1983) Hypothyroidism as a cause of hypertension. Hypertension 5(1):112–115
3. Streeten DH, Anderson GH Jr, Howland T et al (1988) Effects of thyroid function on blood pressure. Recognition of hypothyroid hypertension. Hypertension 11(1):78–83
4. Boekholdt SM, Titan SM, Wiersinga WM et al (2010) Initial thyroid status and cardiovascular risk factors: the EPIC-Norfolk prospective population study. Clin Endocrinol 72(3):404–410
5. Iqbal A, Figenschau Y, Jorde R (2006) Blood pressure in relation to serum thyrotropin: the Tromso study. J Hum Hypertens 20(12):932–936
6. Liu D, Jiang F, Shan Z et al (2010) A cross-sectional survey of relationship between serum TSH level and blood pressure. J Hum Hypertens 24(2):134–138
7. Asvold BO, Bjøro T, Nilsen TI, Vatten LJ (2007) Association between blood pressure and serum thyroid-stimulating hormone concentration within the reference range: a population-based study. J Clin Endocrinol Metab 92(3):841–845
8. Ittermann T, Tiller D, Meisinger C et al (2013) High serum thyrotropin levels are associated with current but not with incident hypertension. Thyroid 23(8):955–963
9. Asvold BO, Bjoro T, Vatten LJ (2013) Associations of TSH levels within the reference range with future blood pressure and lipid concentrations: 11-year follow-up of the HUNT study. Eur J Endocrinol 169(1):73–82
10. Zimmermann MB (2009) Iodine deficiency. Endocr Rev 30(4):376–408
11. Chiamolera MI, Wondisford FE (2009) Minireview: thyrotropin-releasing hormone and the thyroid hormone feedback mechanism. Endocrinology 150(3):1091–1096
12. Williams GR (2008) Neurodevelopmental and neurophysiological actions of thyroid hormone. J Neuroendocrinol 20(6):784–794
13. Tata JR (2013) The road to nuclear receptors of thyroid hormone. Biochim Biophys Acta 1830(7):3860–3866
14. Maia AL, Kim BW, Huang SA et al (2005) Type 2 iodothyronine deiodinase is the major source of plasma T3 in euthyroid humans. J Clin Invest 115(9):2524–2533
15. Bianco AC, Salvatore D, Gereben B et al (2002) Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev 23(1):38–89
16. Everts ME, Verhoeven FA, Bezstarosti K et al (1996) Uptake of thyroid hormones in neonatal rat cardiac myocytes. Endocrinology 137(10):4235–4242

17. Davidson E, Weinberger I, Rotenberg Z et al (1989) Atrial fibrillation. Cause and time of onset. Arch Intern Med 149(2):457–459
18. Vargas F, Moreno JM, Rodríguez-Gómez I et al (2006) Vascular and renal function in experimental thyroid disorders. Eur J Endocrinol 154(2):197–212
19. Klein I, Ojamaa K (2001) Thyroid hormone and the cardiovascular system. N Engl J Med 344(7):501–509
20. Laragh JH, Sealey JE (2003) Relevance of the plasma renin hormonal control system that regulates blood pressure and sodium balance for correctly treating hypertension and for evaluating ALLHAT. Am J Hypertens 16(5 Pt 1):407–415
21. Danzi S, Klein I (2004) Thyroid hormone and the cardiovascular system. Minerva Endocrinol 29(3):139–150
22. Biondi B, Palmieri EA, Lombardi G, Fazio S (2002) Effects of thyroid hormone on cardiac function: the relative importance of heart rate, loading conditions, and myocardial contractility in the regulation of cardiac performance in human hyperthyroidism. J Clin Endocrinol Metab 87(3):968–974
23. Taddei S, Caraccio N, Virdis A et al (2003) Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy. J Clin Endocrinol Metab 88(8):3731–3737
24. Carneiro-Ramos MS, Silva VB, Santos RA, Barreto-Chaves ML et al (2006) Tissue-specific modulation of angiotensin-converting enzyme (ACE) in hyperthyroidism. Peptides 27(11):2942–2949
25. Montiel M, Ruiz M, Jimenez E, Morell M (1987) Angiotensin converting enzyme in hyper- and hypothyroid rats. Horm Metab Res 19(2):90–92
26. Marchant C, Brown L, Sernia C (1993) Renin-angiotensin system in thyroid dysfunction in rats. J Cardiovasc Pharmacol 22(3):449–455
27. Chen K, Carey LC, Valegoet NK et al (2005) Thyroid hormone modulates renin and ANG II receptor expression in fetal sheep. Am J Physiol Regul Integr Comp Physiol 289(4):R1006–R1014
28. Fukuyama K, Ichiki T, Takeda K et al (2003) Downregulation of vascular angiotensin II type 1 receptor by thyroid hormone. Hypertension 41(3):598–603
29. Wang J, Wang Z, Yu C (2016) Association of polymorphisms in the atrial natriuretic factor gene with the risk of essential hypertension: a systematic review and meta-analysis. Int J Environ Res Public Health 13(5):458
30. Kohno M, Horio T, Yokokawa K et al (1995) Brain natriuretic peptide as a marker for hypertensive left ventricular hypertrophy: changes during 1-year antihypertensive therapy with angiotensin-converting enzyme inhibitor. Am J Med 98(3):257–265
31. Suzuki M, Hamada M, Yamamoto K et al (2002) Brain natriuretic peptide as a risk marker for incident hypertensive cardiovascular events. Hypertens Res 25(5):669–676
32. Vesely DL (2002) Atrial natriuretic peptide prohormone gene expression: hormones and diseases that upregulate its expression. IUBMB Life 53(3):153–159
33. Kohno M, Horio T, Yasunari K et al (1993) Stimulation of brain natriuretic peptide release from the heart by thyroid hormone. Metabolism 42(8):1059–1064
34. Hoogwerf BJ, Nuttall FQ (1984) Long-term weight regulation in treated hyperthyroid and hypothyroid subjects. Am J Med 76(6):963–970
35. de los Santos ET, Starich GH, Mazzaferri EL (1989)Sensitivity, specificity, and cost-effectiveness of the sensitive thyrotropin assay in the diagnosis of thyroid disease in ambulatory patients. Arch Intern Med149(3): 526–532
36. Saito I, Ito K, Saruta T (1985) The effect of age on blood pressure in hyperthyroidism. J Am Geriatr Soc 33(1):19–22
37. MarciszC, JonderkoG, KucharzE (2002)Changes of arterial pressure in patients with hyperthyroidism during therapy. Med Sci Moni t8(7):Cr502–507
38. Iglesias P, Acosta M, Sánchez R et al (2005) Ambulatory blood pressure monitoring in patients with hyperthyroidism before and after control of thyroid function. Clin Endocrinol 63(1):66–72
39. Middeke M, Schrader J (1994) Nocturnal blood pressure in normotensive subjects and those with white coat, primary, and secondary hypertension. BMJ 308(6929):630–632

40. Botella-Carretero JI, Gómez-Bueno M, Barrios V et al (2004) Chronic thyrotropin-suppressive therapy with levothyroxine and short-term overt hypothyroidism after thyroxine withdrawal are associated with undesirable cardiovascular effects in patients with differentiated thyroid carcinoma. Endocr Relat Cancer 11(2):345–356
41. Cai Y, Ren Y, Shi J (2011) Blood pressure levels in patients with subclinical thyroid dysfunction: a meta-analysis of cross-sectional data. Hypertens Res 34(10):1098–1105
42. Demers LM, Spencer CA (2003) Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol (Oxf) 58(2):138–140
43. Surks MI, Ortiz E, Daniels GH et al (2004) Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 291(2):228–238
44. Endo T, Komiya I, Tsukui T et al (1979) Re-evaluation of a possible high incidence of hypertension in hypothyroid patients. Am Heart J 98(6):684–688
45. Bergus GR, Randall C, Van Peursem R (1997) Lack of association between hypertension and hypothyroidism in postmenopausal women seen in a primary care setting. J Am Board Fam Pract 10(3):185–191
46. Bergus GR, Mold JW, Barton ED, Randall CS (1999) The lack of association between hypertension and hypothyroidism in a primary care setting. J Hum Hypertens 13(4):231–235
47. Saltiki K, Voidonikola P, Stamatelopoulos K et al (2008) Association of thyroid function with arterial pressure in normotensive and hypertensive euthyroid individuals: a cross-sectional study. Thyroid Res 1(1):3
48. Kanbay M, Turgut F, Karakurt F et al (2007) Relation between serum thyroid hormone and 'nondipper' circadian blood pressure variability. Kidney Blood Press Res 30(6):416–420
49. FommeiE, Iervasi G (2002) The role of thyroid hormone in blood pressure homeostasis: evidence from short-term hypothyroidism in humans. J Clin Endocrinol Metab 87(5):1996–2000
50. Kotsis V, Alevizaki M, Stabouli S et al (2007) Hypertension and hypothyroidism: results from an ambulatory blood pressure monitoring study. J Hypertens 25(5):993–999
51. Benetos A (1999) Pulse pressure and cardiovascular risk. J Hypertens Suppl 17(5):S21–S24
52. Parati G, Valentini M (2006) Prognostic relevance of blood pressure variability. Hypertension 47(2):137–138
53. Parati G, Mancia G, Di Rienzo M, Castiglioni P (2006) Point: cardiovascular variability is/is not an index of autonomic control of circulation. J Appl Physiol (1985) 101(2):676–678. discussion 681-682
54. Danzi S, Klein I (2003) Thyroid hormone and blood pressure regulation. Curr Hypertens Rep 5(6):513–520

# Primary Hyperparathyroidism

# 33

Gian Paolo Rossi and Paul-Emmanuel Vanderriele

## 33.1 Introduction

Primary hyperparathyroidism (PHP) is a common endocrine disorder featuring excess secretion of parathyroid hormone (PTH) independent of serum calcium levels [1–8]. Over the past decade, the understanding of this disease has substantially advanced, thus leading to improved biochemical, radiological and molecular testing [1, 9, 10]. Because uncontrolled PHP, besides affecting the kidneys and bones, causes arterial hypertension with excess target organ damage and increased cardiovascular morbidity and mortality and furthermore can lead to neurocognitive dysfunction, an early detection of PHP is key to prevent complications [1, 3, 5, 9–15].

PHP is the most common cause of hypercalcaemia with an annual incidence ranging from 0.3 to 1.2 cases per 1000 [3, 5, 11, 16–18]; 95% of the cases are sporadic; the rest occur in hereditary syndromes (Table 33.1) [5, 19–21]. It has, however, to be acknowledged that far more commonly than PHP, hyperparathyroidism results from chronic stimuli increasing PTH secretion, such as vitamin D deficiency and chronic kidney disease, or can be tertiary, as discussed below [1–8].

G.P. Rossi (✉)
Clinica dell'Ipertensione Arteriosa—Department of Medicine—DIMED, University of Padova, Padova, Italy

International PhD Program in Arterial Hypertension and Vascular Biology (ARHYVAB), University of Padova, Padova, Italy

Department of Medicine—DIMED—Internal Medicine 4, University Hospital, via Giustiniani, 2, -31526 Padova, Italy
e-mail: gianpaolo.rossi@unipd.it

P.-E. Vanderriele
International PhD Program in Arterial Hypertension and Vascular Biology (ARHYVAB), University of Padova, Padova, Italy

Department of Medicine—DIMED—Internal Medicine 4, University Hospital, via Giustiniani, 2, -31526 Padova, Italy



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_33

The surgical resection of abnormal 'hyperfunctioning' parathyroid gland(s) remains the only curative treatment for PHP; medical treatment is undertaken when surgery is not indicated [1, 3, 5, 19, 22–32]. The pathology underlying PHP includes parathyroid adenoma (80–85%), hyperplasia (10–15%) and rarely (<1–5%) carcinoma. Secondary hyperparathyroidism is due to diffuse parathyroid hyperplasia [1, 3, 5, 19, 22–32]. Tertiary hyperparathyroidism reflects the emergence of an autonomous PTH-producing adenoma or, much more rarely, of PTH-producing carcinoma from a background of hyperplasia due to long-standing secondary hyperparathyroidism [5, 8, 25, 26, 28, 33]. Subtyping requires a thorough clinical, biochemical and radiological investigation with integration of pathological features. Intraoperative findings, including PTH measurement, are key for the treatment decision-making. This chapter is aimed at providing update information on the evolving knowledge of hyperparathyroidism with emphasis on its impact on the cardiovascular system.

**Table 33.1** Hereditary syndromes

| | Name | Cause | Phenotype |
|---|---|---|---|
| Familial cancer predisposition syndromes | MEN-1 | Germ line inactivating mutations in the *MEN1* gene (11q13)<br>Protein encoded: Menin | Multi-glandular parathyroid adenomas (90%)<br>Gastroenteropancreatic neuroendocrine tumours (60%) and pituitary adenomas (30%)<br>Adrenocortical tumours, facial angiofibromas, collagenomas<br>Lipomas and/or other neuroendocrine tumours of various sites as the thymus, lung or stomach |
| | MEN-2A | Germ line activating mutations in the RET proto-oncogene (10q11.2)<br>Protein encoded: RET (receptor for GDNF – family ligands) | Development of HPT (20–30%)<br>Medullary thyroid carcinoma arising from a background of precursor C-cell hyperplasia (also known as primary or neoplastic C-cell hyperplasia)<br>Pheochromocytoma arising in adrenal medullary hyperplasia |
| | MEN-4 | Inactivating germ line mutation in the *CDKN1B* gene<br>Protein encoded: Cyclin-dependent kinase Inhibitor 1B | Indistinguishable from MEN-1 phenotype |
| | HPT-JT | Germ line inactivating mutations of CDC73<br>Protein encoded: Parafibromin | Primary HPT<br>Fibro-osseous lesions in the mandible and maxilla<br>Uterine and renal cysts, hamartomas, carcinoma and Wilms' tumours |

**Table 33.1** (continued)

| | Name | Cause | Phenotype |
|---|---|---|---|
| Familial hypercalcaemic syndromes | FHH-1 | Germ line heterozygous inactivating mutation of *CaSR*<br>Protein encoded: Calcium-sensing receptor | |
| | Neonatal severe PHP | Germ line homozygous inactivating mutations of the *CaSR* gene<br>Protein encoded: Calcium-sensing receptor | |
| | Familial hypercalciuric hypercalcaemia or autosomal-dominant moderate PHP | Germ line inactivating mutation in the intracytoplasmic tail domain of the *CaSR* gene<br>Protein encoded: Calcium-sensing receptor | |
| | FHH-2 | Germ line inactivating mutations of *GNA11* (19p13.3) gene<br>Protein encoded: α-subunit of G11 (one of the principal G proteins activating CaSR signalling pathway) | |
| | FHH-3 | Germ line inactivating mutations of *AP2S1* (19q13.2) gene<br>Protein encoded: Adaptor protein 2 σ-subunit involved in CaSR endocytosis | |

## 33.2 Physiology of PTH Secretion

The secretion of PTH is physiologically controlled by signalling through the calcium-sensing receptor (CaSR), a G-protein-coupled receptor located on the parathyroid chief cells [5, 21, 34–39]. Circulating ionised $Ca^{2+}$ activates the CaSR with ensuing recruitment of phospholipase C-β (through $G_q$ and $G_{11}$), production of inositol triphosphate, release of $Ca^{2+}$ from intracellular stores, elevation of diacylglycerol concentration and activation of protein kinase C, followed by phosphorylation and internalisation of the CaSR. Ultimately, this signalling pathway suppresses PTH secretion, first, by activating Gq-α and phospholipase A2 and generating arachidonic acid metabolites that directly inhibit PTH secretion and, second, by increasing their sensitivity to the negative feedback exerted by $1,25(OH)_2$-vitamin D [5, 21, 34–39]. In hypocalcaemia, CaSR signalling is downregulated, with ensuing release of the PTH from the parathyroid chief cells, increased PTH gene transcription and PTH synthesis.

PTH binds to PTH/PTH-related peptide receptors stimulating osteoclast-mediated bone resorption, renal $Ca^{2+}$ reabsorption and $1,25(OH)_2$-D synthesis to increase intestinal $Ca^{2+}$ absorption and $Ca^{2+}$ levels. With the rise of circulating $Ca^{2+}$ levels, the CaSRs and its signalling pathway are reactivated, leading to blunting of PTH secretion. Excess PTH secretion in PHP can derive from various alterations inactivating CaSR signalling pathway [5, 21, 34–39]; furthermore, long-standing downregulation of CaSR can lead to aberrant cell growth and proliferation via aberrant Wnt/β-catenin and cyclin D1 signalling [5, 8, 10, 21, 25, 35, 36, 40–45].

## 33.3 Clinical and Biochemical Features of Hyperparathyroidism

The advent of accurate methods for measuring pH-normalised ionised serum calcium and intact PTH has led to incidental identification of most hyperparathyroidism cases, e.g. in the *asymptomatic* form [3, 5, 9, 11]. At this stage, the cardiovascular complications are much less common than in older times. Nonetheless, since even 'asymptomatic' PHP can lead to potential morbidities, including osteoporosis and clinically 'silent' nephrolithiasis/nephrocalcinosis [9, 11, 13–15, 46–50], even incidentally detected hypercalcaemia with raised PTH deserves work-up to clarify its aetiology, e.g. to determine if it is PTH dependent or PTH independent [3, 5]. Nowadays, the classical hypercalcaemia-related symptoms (i.e. weakness, easy fatigability, anxiety and cognitive impairment) and gastrointestinal symptoms (i.e. peptic ulcer and pancreatitis) are almost never seen [3, 5, 9, 11, 12, 46, 51–53]. Sporadic PHP can occur at any age, but most commonly in postmenopausal women [3, 5, 20, 25, 54, 55]. In the rare symptomatic cases, the clinical manifestations depend on the duration and degree of PTH oversecretion and hypercalcaemia [3, 5, 9, 11, 56].

In sporadic PHP, the first finding is usually mild hypercalcaemia (usually within 0.15 mmol/L of normal range, e.g. 1.19–1.29 mmol/L for ionised Ca) [3, 5]. The common presentation of *symptomatic* disease seen in the past, e.g. 'stones' (nephrolithiasis), 'bones' (osteitis fibrosis cystica) and constipation or ileus, is exceptional today [3, 9, 11, 12]. Typically, urinary calcium excretion is normal or increased, but hypocalciuria can also be found in individuals on thiazide or lithium or in long-standing PHP when the total body calcium is severely shrank [57]. High-serum PTH and normal-serum ionised calcium (in the lack of causes of secondary hyperparathyroidism) identify a *normocalcaemic variant* of PHP, whose epidemiology, natural history and management remain, at present, unclear [1, 3, 5, 9, 11, 58–61].

Secondary hyperparathyroidism, an adaptive response to conditions causing hypocalcaemia (as vitamin D deficiency, chronic kidney disease, idiopathic hypercalciuria, calcium malabsorption), presents with high-serum PTH and normo- or hypocalcaemia [5, 7, 8, 62, 63]. However, in the long run, it causes osteoporosis and can evolve into tertiary hyperparathyroidism [5, 7, 8, 25, 62–64]. The latter is characterised, like PHP, by a raise of both serum of PTH and ionised $Ca^{2+}$ levels [8, 64] and can be identified by the concomitance, in most circumstances, of advanced chronic kidney disease (CKD) [8, 63]. In all cases, serum 25-hydroxyvitamin D

**Table 33.2** Clinical findings suggesting familial PHP or parathyroid carcinoma

| | Familial syndromes | Parathyroid carcinoma |
|---|---|---|
| Clinical findings suggestive | 1. Early onset (<30 years)<br>2. Familial history of hypercalcaemia<br>3. Skin lesions (lipomas, facial angiofibromas, truncal collagenomas)<br>4. Pituitary adenomas and neuroendocrine tumours (including phaeochromocytomas) associated with *multiple endocrine neoplasia syndromes*<br>5. Jaw tumour with or without renal cysts (HPT-JT syndrome)<br>6. Hypercalcaemia associated with hypocalciuria (FHH) | 1. Severe hypercalcaemia<br>2. Extremely high PTH levels (>3 times the upper limit of normal)<br>3. Concomitant bone and kidney involvement, palpable neck mass, jaw tumour, family history of parathyroid or other endocrine disorders |
| Clinical investigations | 1. Ionised $Ca^{2+}$ measurement in first-degree relatives along with other clinical investigations<br>2. Testing for a *MEN1* mutation is recommended if MEN-1 is suspected<br>3. FHH diagnosis requires demonstration of a germ line mutation in CaSR, GNA11 and AP2S1<br>4. Severe neonatal HPT presenting with severe HPT and life-threatening hypercalcaemia in the first semester of life | 1. Earlier age of onset in both genders<br>2. More prominent increases of PTH predict parathyroid malignancy |

levels should be measured not only because vitamin D deficiency is the most common cause of secondary hyperparathyroidism but also because, when associated with PHP, its deficiency can factitiously mask the hypercalcaemia [3, 5, 10].

When familial disease is suspected, ionised serum calcium ($Ca^{2+}$) should be measured in first-degree relatives [3, 5, 10, 20]. If multi-glandular PHP and concomitant MEN-1-associated tumours raise the suspicion of MEN-1, testing for a *MEN1* mutation is recommended. A definitive diagnosis of FHH may ultimately require demonstration of a germ line mutation in *CaSR*, *GNA11* and *AP2S1* genes [3, 5, 10, 20, 25, 34, 64–76]. *Parathyroid carcinoma* is rare and occurs at an earlier age, with no gender preference. The clinical findings that suggest hereditary hyperparathyroidism and carcinoma are listed in Table 33.2.

## 33.4 Imaging of PHP

Imaging is necessary to guide the treatment decision-making, because skeletal and renal complications may justify surgery even in asymptomatic PHP patients [1, 3, 5, 9, 19, 25, 65–67]. Bone involvement can be assessed by dual-energy X-ray densitometry and CT imaging. Renal ultrasonography serves to investigate renal structures and exclude clinically ‘silent’ nephrocalcinosis and nephrolithiasis [1, 3, 5, 9, 19].

*Parathyroid imaging* is a key to plan the appropriate treatment, e.g. to differentiate single (adenoma or carcinoma) from multi-glandular disease (hyperplasia) [3, 5, 66, 67, 77, 78]. The most commonly used radiological tools are neck ultrasound and $^{99}$technetium-labelled sestamibi ($^{99m}$Tc-sestamibi) scintigraphy [3, 5, 66, 67, 77, 78]. The uptake of $^{99}$mTc-sestamibi is generally increased and prolonged in functioning neoplastic or hyperplastic parathyroid gland(s), but it occurs in both parathyroid and thyroid tissue. Hence, dual-tracer subtraction using $^{99m}$Tc-sestamibi in combination with radioactive iodine ($^{123}$I) is currently used to separate parathyroid uptake of sestamibi from thyroid uptake and achieve better visualisation of the functioning parathyroid tissue [3, 5, 66, 67, 77–79].

## 33.5 Diagnosis

An accurate diagnosis of PHP subtype is challenging and can even be impossible before surgery [24–26, 80–83]. Intraoperative pathological consultation is essential to confirm the presence of parathyroid tissue in the resected specimen and to exclude other tissues, such as lymph nodes or thymus mimicking an enlarged gland [24–26, 80, 81, 84, 85].

The adoption of rapid (within 10 min) PTH assay has become a standard practice in that it allows distinguishing adenoma from hyperplasia: in patients with single-glandular disease, removal of the culprit gland results in a brisk *intraoperative* reduction of PTH levels of >50% and often >75% [3, 19, 25, 26, 29, 86]. No further exploration is needed if PTH levels drop by >50%.

Pathologic examination of the surgical specimen can thereafter provide a definite diagnosis of the parathyroid pathology. Immediately after surgery, serum calcium levels should be monitored carefully as hypocalcaemia is common in patients with single-gland parathyroid disease [3, 19, 25, 26, 29, 87].

## 33.6 Histopathological Correlates of Hyperparathyroidism

Parathyroid tumours (*adenomas* 80–85% of PHP cases) are almost always uni-glandular (solitary) lesions; hyperplasia usually denotes multi-glandular proliferation [22–26, 80, 81, 87–90]. Parathyroid adenomas are composed of varying proportions of chief cells and lower amounts of clear, transitional and oncocytic cells [22, 24, 25, 81, 88, 90, 91]. Their proliferative index (assessed by Ki-67, MIB-1) is generally <5% although scattered mitotic figures can be seen [22, 24–26, 81, 84, 88, 90–100].

*Parathyroid hyperplasia* (10–15% of cases of PHP) is a multi-glandular disorder [3, 22, 24–26, 88, 91–93], which can be diffused, localised with one or more nodules (*nodular hyperplasia*) or comprised a mixture of *nodular hyperplasia* and *diffuse* patterns [22, 25, 81]. The hyperplastic glands are grossly increased in size and weight, as chief cells prevail in most cases, hence the classical term ‘chief cell hyperplasia’ [22, 24, 25, 88, 90]. *Secondary hyperparathyroidism* is generally caused by diffuse parathyroid hyperplasia [5, 8, 25].

*Tertiary hyperparathyroidism* is due to a progression from a secondary hyperplasia to an autonomous PTH-producing neoplasm (an adenoma or, rarely, a carcinoma) that involves clonal transformation from diffuse polyclonal hyperplasia due to decreased calcium-sensing receptor (CaSR) signalling from hypocalcaemia [5, 8, 25, 63, 64, 88, 90, 91, 97, 101, 102].

Parathyroid carcinomas involve <1–5% of patients with PHP and tend to be larger (mean diameter of 3.4 cm and weight of 19.15 g) and can be densely adherent to thyroid or surrounding soft tissues intraoperatively [3, 5, 24–26, 43, 65, 77, 80, 81, 92, 94, 103, 104].

The distinction between parathyroid carcinomas and adenomas is challenging on cytology and requires the use of ancillary biomarkers [22, 24–26, 80, 88, 92, 94], as loss of expression of retinoblastoma protein (Rb), Bcl-2a, p27, parafibromin, mdm2 and APC, as well as increased (>5%) MIB-1 (Ki-67) proliferative index, overexpression of p53 and positivity for galectin-3 (in the absence of multi-glandular disease) [21, 22, 25, 26, 28, 35, 43, 45, 70, 75, 80, 88, 92, 94, 95, 105–112]. The use of parafibromin immunostaining is particularly helpful to differentiate between parathyroid adenomas, which show intact nuclear and nucleolar parafibromin expression, and carcinomas, where these features are lost [21, 22, 25, 26, 28, 35, 43, 45, 70, 75, 80, 88, 92, 94, 95, 97, 105–112]. Most patients with inherited parathyroid disease present with multi-glandular parathyroid hyperplasia, although rare solitary tumours can also occur [20, 22, 25, 26, 88, 90, 97]. Most commonly familial PHP is due to familial cancer-predisposing syndromes or to hereditary syndromes related to aberrant CaSR signalling.

## 33.7 Sporadic Parathyroid Adenomas and Carcinomas

Most *parathyroid adenomas* are sporadic neoplasms [24, 25, 35, 80, 95]; sometimes they occur in patients with a history of ionising radiation [3, 5, 22, 25]. Somatic alterations in *MEN-1* and *CCND1/PRAD1* genes are found in 25–40% of sporadic parathyroid adenomas [25, 26, 35, 41, 95, 106, 107, 113]. An inherited mutant copy of the *MEN1* gene may be sufficient to cause multi-glandular hyperplasia and hyperparathyroidism (in MEN-1 syndrome or isolated familial hyperparathyroidism); however, an additional somatic inactivating mutation in the wild-type allele of *MEN1,* found in over a quarter of the cases, is required for the development of sporadic parathyroid tumours [25, 35, 41].

Alternatively, pure somatic mutations can result in bi-allelic inactivation of *MEN1* in some parathyroid adenomas [35, 108, 109]. Somatic activating alterations of *CCND1*/PRAD1 encoding cyclin D1 protein were found in 20–40% of sporadic adenomas [21, 35, 41, 111, 112, 114–117]. Moreover, somatic alterations of the *CDKI*-encoding genes (*CDKN1B*, *CDKN1A*, *CDKN2B*, *CDKN2C*), which cause familial hyperparathyroidism and were found in MEN-4 syndrome and isolated familial hyperparathyroidism, were also identified in sporadic parathyroid adenomas [21, 22, 26, 35, 41, 105, 114, 118].

Whole-exome sequencing revealed somatic mutations in a relatively small proportion of adenomas: they involve *ZFX* (in about 5%); CTNNB1 encoding β-catenin (in about 2–5%); *EZH2*, a putative oncogene involved in histone methyltransferase activity

causing aberrant β-catenin accumulation (in about 1%); and *POT1*, a regulator of telomere integrity and genome stability (in less than 1%) [35, 69, 106, 107, 119–123].

DNA methylation and microRNA profiling studies have also uncovered mutations in Wnt/β-catenin signalling (*APC*, *SFRP1*, *SFRP2*, *SFRP4*), cyclin D1 signalling (*CDKN2A, CDKN2B*), as well as *WT1*, *RIZ1*, *RASSF1A* and *HIC1*, and in sporadic parathyroid tumours [35, 42, 124–126], thus suggesting a role for altered gene transcription and microRNA deregulation in parathyroid tumourigenesis [126, 127].

These discoveries can be fundamental for understanding the biology of *parathyroid carcinomas*, as they can pave the way to identify novel diagnostic, prognostic biomarkers to improve patient care. For an in-depth description of recent advances in molecular pathology, genetic and epigenetic alterations and biomarkers of parathyroid cancer, the reader is referred elsewhere [5, 15, 25–27, 35, 77, 94–96, 103, 125, 128].

## 33.8 Cardiovascular Consequences of Hyperparathyroidism

PTH and PTH-related peptide increase aldosterone secretion [129, 130] and renin [131, 132], suggesting that hyperparathyroidism can contribute to raising blood pressure. Of note, even though a high prevalence of hypertension, excess cardiovascular damage, arterial calcification and stiffening, isolated systolic hypertension and excess left ventricular hypertrophy have been reported in PHP patients [133–136], many investigators wonder if these changes still occur today, when the diagnosis is generally made much earlier in the course of the disease.

Secondary hyperparathyroidism has been detected in the most common cause of endocrine hypertension, e.g. primary aldosteronism, particularly in its subtype involving aldosterone-producing adrenocortical adenoma [137, 138]. The detection of elevated PTH levels was shown to help in the differential diagnosis between aldosterone-producing adenoma and bilateral adrenocortical hyperplasia [139]. After adrenalectomy, PTH levels fall and serum ionised $Ca^{2+}$ levels increase, indicating a cause-effect relationship between hyperaldosteronism and hyperparathyroidism and therefore a link between the adrenocortical zona glomerulosa and the parathyroid gland [140]. The finding of hypercalciuria in rats infused with aldosterone supports the contention that a slight decrease of serum ionised $Ca^{2+}$ levels deriving from hypercalciuria can be the trigger for the release of PTH through the series of event described above [141].

## 33.9 Treatment and Outcome

After excluding secondary hyperparathyroidism, which is reversible with treatment of the underlying condition, the management of PHP depends on its cause: first-line treatment of tertiary hyperparathyroidism mainly involves using low-phosphate diet, phosphate binders, 1,25-dihydroxyvitamin $D_3$ (calcitriol or analogues to suppress PTH secretion) and/or calcimimetic agent (cinacalcet, an allosteric activator of CaSR) [1, 3, 5, 19, 29, 33, 142, 143]. Parathyroidectomy can be necessary to control hypercalcaemia and symptoms in severe cases refractory to medical treatment.

Percutaneous ethanol ablation may be an alternative to parathyroidectomy in selected cases of PHP [144, 145]. Nonetheless, surgical excision of abnormal 'hyperfunctioning' parathyroid gland(s) remains the optimal treatment. Surgery in asymptomatic hyperparathyroidism should be reserved to patients with (one or more) of the following conditions: drug-resistant arterial hypertension, *age* (<50 years), *kidney disease* (eGFR <60 mL/min, nephrolithiasis/nephrocalcinosis, hypercalciuria with increased stone risk), *bone disease* (osteoporosis), *overt hypercalcaemia* and in all cases in which routine surveillance is not feasible [1, 3, 5, 19, 29, 33, 142, 143].

An underlying genetic syndrome should be considered when multi-glandular parathyroid disease is detected [5, 10, 19, 20, 25, 137]. MEN-1, MEN-2A or familial isolated hyperparathyroidism patients require closer monitoring because of their increased risk of recurrent/persistent disease due to multi-glandular parathyroid involvement. Sporadic PHP is usually caused by single-gland parathyroid disease, commonly from a solitary adenoma. Minimally invasive parathyroidectomy is an increasingly popular approach, but open surgery with bilateral cervical exploration can be necessary in multi-glandular disease and/or recurrent hyperparathyroidism. The complete removal of abnormal parathyroid tissue should be confirmed biochemically with intraoperative PTH measurements. Following surgery, most patients with clinically and pathologically confirmed parathyroid adenoma are cured [5, 10, 19, 20, 25, 137].

In parathyroid carcinomas, an oncological surgical approach is paramount for controlling the disease. The finding that the 5-year and 10-year disease-specific survival rates can be as high as 100 and 80%, respectively, and the 5-year and 10-year disease-free survival rates can be 69 and 43% would imply a relatively indolent behaviour of parathyroid cancer [19, 27, 73, 77]. However, a risk of disease recurrence, even many years after initial treatment, is always there [27, 73, 77].

To decrease local recurrence rate, adjuvant radiotherapy can be an option [27, 77]. In patients diagnosed with a parathyroid carcinoma, the tumour should be further tested for loss of parafibromin expression, and those showing loss of parafibromin immunostaining should be offered genetic testing for germ line *CDC73/HRPT2* mutations [25, 27, 80, 96, 146].

## Conclusions

PHP is not uncommon and is usually due to parathyroid adenoma (80–85%), hyperplasia (10–15%) and carcinoma (<1–5%). The clinical and biochemical history, including intraoperative PTH measurements, number, size and weight of the affected gland(s), are key elements for diagnosis and treatment. In PHP after exclusion of a primary parathyroid cancer, diagnostic imaging and intraoperative rapid PTH assays should aim at distinguishing between single-glandular, usually a solitary parathyroid adenoma, and diffuse and/or nodular parathyroid hyperplasia. This distinction is key for choosing the optimal treatment and follow-up testing.

**Conflict of Interest** There are no conflict of interest and no financial disclosure concerning this manuscript to be disclosed.

## References


1. Bilezikian JP, Brandi ML, Eastell R et al (2014) Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab 99:3561–3569. doi:10.1210/jc.2014-1413
2. Bilezikian JP, Silverberg SJ (2010) Normocalcemic primary hyperparathyroidism. Arq Bras Endocrinol Metabol 54:106–109. S0004-27302010000200004 [pii]
3. Marcocci C, Cetani F (2011) Clinical practice. Primary hyperparathyroidism. N Engl J Med 365:2389–2397. doi:10.1056/NEJMcp1106636
4. Mackenzie-Feder J, Sirrs S, Anderson D et al (2011) Primary hyperparathyroidism: an overview. Int J Endocrinol 2011:251410. doi:10.1155/2011/251410
5. Fraser WD (2009) Hyperparathyroidism. Lancet 374(9684):145–158. doi:10.1016/S0140-673660507-9
6. Blanchard C, Mirallie E, Mathonnet M (2010) Sporadic primary hyperparathyroidism. J Visc Surg 147:e285–e295. doi:10.1016/j.jviscsurg.2010.08.018
7. Cunningham J, Locatelli F, Rodriguez M (2011) Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. Clin J Am Soc Nephrol 6:913–921. doi:10.2215/CJN.06040710
8. Jamal SA, Miller PD (2013) Secondary and tertiary hyperparathyroidism. J Clin Densitom 16:64–68. doi:10.1016/j.jocd.2012.11.012
9. Silverberg SJ, Walker MD, Bilezikian JP (2013) Asymptomatic primary hyperparathyroidism. J Clin Densitom 16:14–21. doi:10.1016/j.jocd.2012.11.005
10. Eastell R, Brandi ML, Costa AG et al (2014) Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the fourth international workshop. J Clin Endocrinol Metab 99:3570–3579. doi:10.1210/jc.2014-1414
11. Silverberg SJ, Clarke BL, Peacock M et al (2014) Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the fourth international workshop. J Clin Endocrinol Metab 99:3580–3594. doi:10.1210/jc.2014-1415
12. Walker MD, Rubin M, Silverberg SJ (2013) Nontraditional manifestations of primary hyperparathyroidism. J Clin Densitom 16:40–47. doi:10.1016/j.jocd.2012.11.008
13. Silva BC, Boutroy S, Zhang C et al (2013) Trabecular bone score (TBS)—a novel method to evaluate bone microarchitectural texture in patients with primary hyperparathyroidism. J Clin Endocrinol Metab 98:1963–1970. doi:10.1210/jc.2012-4255
14. Lewiecki EM, Miller PD (2013) Skeletal effects of primary hyperparathyroidism: bone mineral density and fracture risk. J Clin Densitom 16:28–32. doi:10.1016/j.jocd.2012.11.013
15. Marcocci C, Cianferotti L, Cetani F (2012) Bone disease in primary hyperparathyroidism. Ther Adv Musculoskelet Dis 4:357–368. doi:10.1177/1759720X12441869
16. Clarke BL (2013) Epidemiology of primary hyperparathyroidism. J Clin Densitom 16:8–13. doi:10.1016/j.jocd.2012.11.009
17. Griebeler ML, Kearns AE, Ryu E et al (2015) Secular trends in the incidence of primary hyperparathyroidism over five decades (1965-2010). Bone 73:1–7. doi:10.1016/j.bone.2014.12.003
18. Yeh MW, Ituarte PH, Zhou HC et al (2013) Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. J Clin Endocrinol Metab 98:1122–1129. doi:10.1210/jc.2012-4022
19. Udelsman R, Akerstrom G, Biagini C et al (2014) The surgical management of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. J Clin Endocrinol Metab 99:3595–3606. doi:10.1210/jc.2014-2000
20. Giusti F, Cavalli L, Cavalli T, Brandi ML (2013) Hereditary hyperparathyroidism syndromes. J Clin Densitom 16:69–74. doi:10.1016/j.jocd.2012.11.003
21. Arnold A, Shattuck TM, Mallya SM et al (2002) Molecular pathogenesis of primary hyperparathyroidism. J Bone Miner Res 17(Suppl 2):N30–N36
22. Carlson D (2010) Parathyroid pathology: hyperparathyroidism and parathyroid tumors. Arch Pathol Lab Med 134:1639–1644. doi:10.1043/2009-0578-CCR.1

23. Baloch ZW, LiVolsi VA (2001) Double adenoma of the parathyroid gland: does the entity exist? Arch Pathol Lab Med 125:178–179. doi:10.1043/0003-9985(2001)125<0178:DAOTPG>2.0.CO;2
24. Baloch ZW, LiVolsi VA (2013) Pathology of the parathyroid glands in hyperparathyroidism. Semin Diagn Pathol 30:165–177. doi:10.1053/j.semdp.2013.06.003
25. DeLellis RA (2011) Parathyroid tumors and related disorders. Mod Pathol 24(Suppl 2):S78–S93. doi:10.1038/modpathol.2010.132
26. DeLellis RA, Mazzaglia P, Mangray S (2008) Primary hyperparathyroidism: a current perspective. Arch Pathol Lab Med 132:1251–1262. doi:10.1043/1543-2165(2008)132[1251:PHACP]2.0.CO;2
27. Betea D, Potorac I, Beckers A (2015) Parathyroid carcinoma: challenges in diagnosis and treatment. Ann Endocrinol (Paris) 76:169–177. doi:10.1016/j.ando.2015.03.003
28. Do Cao C, Aubert S, Trinel C et al (2015) Parathyroid carcinoma: Diagnostic criteria, classification, evaluation. Ann Endocrinol (Paris) 76:165–168. doi:10.1016/j.ando.2015.03.016
29. Callender GG, Udelsman R (2014) Surgery for primary hyperparathyroidism. Cancer 120:3602–3616. doi:10.1002/cncr.28891
30. Dowthwaite SA, Young JE, Pasternak JD, Yoo J (2013) Surgical management of primary hyperparathyroidism. J Clin Densitom 16:48–53. doi:10.1016/j.jocd.2012.11.006
31. Van Udelsman B, Udelsman R (2013) Surgery in primary hyperparathyroidism: extensive personal experience. J Clin Densitom 16:54–59. doi:10.1016/j.jocd.2012.11.007
32. Lew JI, Solorzano CC (2009) Surgical management of primary hyperparathyroidism: state of the art. Surg Clin North Am 89:1205–1225. doi:10.1016/j.suc.2009.06.014
33. Davies M, Fraser WD, Hosking DJ (2002) The management of primary hyperparathyroidism. Clin Endocrinol (Oxf) 57:145–155
34. Li D, Opas EE, Tuluc F et al (2014) Autosomal dominant hypoparathyroidism caused by germline mutation in GNA11: phenotypic and molecular characterization. J Clin Endocrinol Metab 99:E1774–E1183. doi:10.1210/jc.2014-1029
35. Costa-Guda J, Arnold A (2014) Genetic and epigenetic changes in sporadic endocrine tumors: parathyroid tumors. Mol Cell Endocrinol 386:46–54. doi:10.1016/j.mce.2013.09.005
36. Shi Y, Hogue J, Dixit D et al (2014) Functional and genetic studies of isolated cells from parathyroid tumors reveal the complex pathogenesis of parathyroid neoplasia. Proc Natl Acad Sci U S A 111:3092–3097. doi:10.1073/pnas.1319742111
37. Marx SJ (2014) Uncoupling of secretion from growth in some hormone secretory tissues. J Clin Endocrinol Metab 99:4051–4059. doi:10.1210/jc.2014-2113
38. Alfadda TI, Saleh AM, Houillier P, Geibel JP (2014) Calcium-sensing receptor 20 years later. Am J Physiol Cell Physiol 307:C221–C231. doi:10.1152/ajpcell.00139.2014
39. Brown EM (2007) Clinical lessons from the calcium-sensing receptor. Nat Clin Pract Endocrinol Metab 3:122–133. doi:10.1038/ncpendmet0388
40. Cetani F, Pardi E, Borsari S et al (2011) Molecular pathogenesis of primary hyperparathyroidism. J Endocrinol Invest 34:35–39
41. Segiet OA, Deska M, Michalski M et al (2015) Molecular profiling in primary hyperparathyroidism. Head Neck 37:299–307. doi:10.1002/hed.23656
42. Varshney S, Bhadada SK, Sachdeva N et al (2013) Methylation status of the CpG islands in vitamin D and calcium-sensing receptor gene promoters does not explain the reduced gene expressions in parathyroid adenomas. J Clin Endocrinol Metab 98:E1631–E1635. doi:10.1210/jc.2013-1699
43. Brennan SC, Thiem U, Roth S et al (2013) Calcium sensing receptor signalling in physiology and cancer. Biochim Biophys Acta 1833:1732–1744. doi:10.1016/j.bbamcr.2012.12.011
44. Corbetta S, Mantovani G, Lania A et al (2000) Calcium-sensing receptor expression and signalling in human parathyroid adenomas and primary hyperplasia. Clin Endocrinol (Oxf) 52:339–348
45. Sudhaker Rao D, Han ZH, Phillips ER et al (2000) Reduced vitamin D receptor expression in parathyroid adenomas: implications for pathogenesis. Clin Endocrinol (Oxf) 53:373–381

46. Silverberg SJ, Lewiecki EM, Mosekilde L et al (2009) Presentation of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. J Clin Endocrinol Metab 94:351–365. doi:10.1210/jc.2008-1760
47. Lundstam K, Heck A, Mollerup C et al (2015) Effects of parathyroidectomy versus observation on the development of vertebral fractures in mild primary hyperparathyroidism. J Clin Endocrinol Metab 100:1359–1367. doi:10.1210/jc.2014-3441
48. Macfarlane DP, Yu N, Leese GP (2013) Subclinical and asymptomatic parathyroid disease: implications of emerging data. Lancet Diabetes Endocrinol 1(4):329–340. doi:10.1016/S2213-858770083-4
49. Cipriani C, Biamonte F, Costa AG et al (2015) Prevalence of kidney stones and vertebral fractures in primary hyperparathyroidism using imaging technology. J Clin Endocrinol Metab 100:1309–1315. doi:10.1210/jc.2014-3708
50. Bilezikian JP, Brandi ML, Rubin M et al (2005) Primary hyperparathyroidism: new concepts in clinical, densitometric and biochemical features. J Intern Med 257:6–17
51. Grant P, Velusamy A (2014) What is the best way of assessing neurocognitive dysfunction in patients with primary hyperparathyroidism? J Clin Endocrinol Metab 99:49–55. doi:10.1210/jc.2013-3115
52. Ludvigsson JF, Kampe O, Lebwohl B et al (2012) Primary hyperparathyroidism and celiac disease: a population-based cohort study. J Clin Endocrinol Metab 97:897–904. doi:10.1210/jc.2011-2639
53. Silverberg SJ (2002) Non-classical target organs in primary hyperparathyroidism. J Bone Miner Res 17(Suppl 2):N117–N125
54. Haglund F, Ma R, Huss M et al (2012) Evidence of a functional estrogen receptor in parathyroid adenomas. J Clin Endocrinol Metab 97:4631–4639. doi:10.1210/jc.2012-2484
55. Haglund F, Rosin G, Nilsson IL et al (2015) Tumour nuclear oestrogen receptor beta 1 correlates inversely with parathyroid tumour weight. Endocr Connect 4:76–85. doi:10.1530/EC-14-0109
56. Silverberg SJ, Bilezikian JP (2006) The diagnosis and management of asymptomatic primary hyperparathyroidism. Nat Clin Pract Endocrinol Metab 2:494–503. doi:10.1038/ncpendmet0265
57. Lehmann SW, Lee J (2013) Lithium-associated hypercalcemia and hyperparathyroidism in the elderly: what do we know? J Affect Disord 146:151–157. doi:10.1016/j.jad.2012.08.028
58. Chen G, Xue Y, Zhang Q et al (2015) Is Normocalcemic primary hyperparathyroidism harmful or harmless? J Clin Endocrinol Metab 100:2420–2424. doi:10.1210/jc.2014-4432
59. Touvier M, Deschasaux M, Montourcy M et al (2014) Interpretation of plasma PTH concentrations according to 25OHD status, gender, age, weight status, and calcium intake: importance of the reference values. J Clin Endocrinol Metab 99:1196–1203. doi:10.1210/jc.2013-3349
60. Cusano NE, Silverberg SJ, Bilezikian JP (2013) Normocalcemic primary hyperparathyroidism. J Clin Densitom 16:33–39. doi:10.1016/j.jocd.2012.12.001
61. Souberbielle JC, Cavalier E, Cormier C (2015) How to manage an isolated elevated PTH? Ann Endocrinol (Paris) 76:134–141. doi:10.1016/j.ando.2015.03.005
62. Coe FL, Canterbury JM, Firpo JJ et al (1973) Evidence for secondary hyperparathyroidism in idiopathic hypercalciuria. J Clin Invest 52:134–142. doi:10.1172/JCI107156
63. Rodriguez M, Canalejo A, Garfia B et al (2002) Pathogenesis of refractory secondary hyperparathyroidism. Kidney Int Suppl 80:155–160
64. Hendy GN, Cole DE (2013) Genetic defects associated with familial and sporadic hyperparathyroidism. Front Horm Res 41:149–165. doi:10.1159/000345675
65. Kassahun WT, Jonas S (2011) Focus on parathyroid carcinoma. Int J Surg 9:13–19. doi:10.1016/j.ijsu.2010.09.003
66. Hindie E, Zanotti-Fregonara P, Tabarin A et al (2015) The role of radionuclide imaging in the surgical management of primary hyperparathyroidism. J Nucl Med 56:737–744. doi:10.2967/jnumed.115.156018

67. Wong KK, Fig LM, Gross MD, Dwamena BA (2015) Parathyroid adenoma localization with 99mTc-sestamibi SPECT/CT: a meta-analysis. Nucl Med Commun 36:363–375. doi:10.1097/MNM.0000000000000262
68. Hendy GN, Canaff L, Newfield RS et al (2014) Codon Arg15 mutations of the AP2S1 gene: common occurrence in familial hypocalciuric hypercalcemia cases negative for calcium-sensing receptor (CASR) mutations. J Clin Endocrinol Metab 99:E1311–E1315. doi:10.1210/jc.2014-1120
69. Westin G, Bjorklund P, Akerstrom G (2009) Molecular genetics of parathyroid disease. World J Surg 33:2224–2233. doi:10.1007/s00268-009-0022-6
70. Nesbit MA, Hannan FM, Howles SA et al (2013) Mutations in AP2S1 cause familial hypocalciuric hypercalcemia type 3. Nat Genet 45:93–97. doi:10.1038/ng.2492
71. Pallauf A, Schopohl J, Makeschin M et al (2015) Lethal generalized calcinosis and hypercalcemic crisis in primary hyperparathyroidism. J Clin Endocrinol Metab 100:17–18. doi:10.1210/jc.2014-2813
72. Villar-del-Moral J, Jimenez-Garcia A, Salvador-Egea P et al (2014) Prognostic factors and staging systems in parathyroid cancer: a multicenter cohort study. Surgery 156:1132–1144. doi:10.1016/j.surg.2014.05.014
73. Schulte KM, Talat N, Galata G et al (2014) Oncologic resection achieving r0 margins improves disease-free survival in parathyroid cancer. Ann Surg Oncol 21:1891–1897. doi:10.1245/s10434-014-3530-z
74. Schulte KM, Gill AJ, Barczynski M et al (2012) Classification of parathyroid cancer. Ann Surg Oncol 19:2620–2628. doi:10.1245/s10434-012-2306-6
75. Guarnieri V, Canaff L, Yun FH et al (2010) Calcium-sensing receptor (CASR) mutations in hypercalcemic states: studies from a single endocrine clinic over three years. J Clin Endocrinol Metab 95:1819–1829. doi:10.1210/jc.2008-2430
76. Rogers A, Nesbit MA, Hannan FM et al (2014) Mutational analysis of the adaptor protein 2 sigma subunit (AP2S1) gene: search for autosomal dominant hypocalcemia type 3 (ADH3). J Clin Endocrinol Metab 99:E1300–E1305. doi:10.1210/jc.2013-3909
77. Schulte KM, Talat N (2012) Diagnosis and management of parathyroid cancer. Nat Rev Endocrinol 8:612–622. doi:10.1038/nrendo.2012.102
78. Wimmer G, Profanter C, Kovacs P et al (2010) CT-MIBI-SPECT image fusion predicts multiglandular disease in hyperparathyroidism. Langenbecks Arch Surg 395:73–80. doi:10.1007/s00423-009-0545-1
79. Mohebati A, Shaha AR (2012) Imaging techniques in parathyroid surgery for primary hyperparathyroidism. Am J Otolaryngol 33:457–468. doi:10.1016/j.amjoto.2011.10.010
80. Delellis RA (2008) Challenging lesions in the differential diagnosis of endocrine tumors: parathyroid carcinoma. Endocr Pathol 19:221–225. doi:10.1007/s12022-008-9050-2
81. Alwaheeb S, Rambaldini G, Boerner S et al (2006) Worrisome histologic alterations following fine-needle aspiration of the parathyroid. J Clin Pathol 59:1094–1096
82. Wong KS, Lewis JS Jr, Gottipati S, Chernock RD (2014) Utility of birefringent crystal identification by polarized light microscopy in distinguishing thyroid from parathyroid tissue on intraoperative frozen sections. Am J Surg Pathol 38:1212–1219. doi:10.1097/PAS.0000000000000204
83. Osamura RY, Hunt JL (2008) Current practices in performing frozen sections for thyroid and parathyroid pathology. Virchows Arch 453:433–440. doi:10.1007/s00428-008-0674-x
84. Abbona GC, Papotti M, Gasparri G, Bussolati G (1995) Proliferative activity in parathyroid tumors as detected by Ki-67 immunostaining. Hum Pathol 26:135–138
85. Wei S, LiVolsi VA, Baloch ZW (2015) Images in endocrine pathology: parathyroid adenoma with frozen section artifact mimics thyroid papillary carcinoma. Endocr Pathol 26:185–186. doi:10.1007/s12022-014-9309-8
86. Friedman E, Sakaguchi K, Bale AE et al (1989) Clonality of parathyroid tumors in familial multiple endocrine neoplasia type 1. N Engl J Med 321:213–218. doi:10.1056/NEJM198907273210402

87. Marx SJ (2013) Multiplicity of hormone-secreting tumors: common themes about cause, expression, and management. J Clin Endocrinol Metab 98:3139–3148. doi:10.1210/jc.2013-1511
88. Cavalier E, Betea D, Schleck ML et al (2014) The third/second generation PTH assay ratio as a marker for parathyroid carcinoma: evaluation using an automated platform. J Clin Endocrinol Metab 99:E453–E457. doi:10.1210/jc.2013-3730
89. Tominaga Y, Kohara S, Namii Y et al (1996) Clonal analysis of nodular parathyroid hyperplasia in renal hyperparathyroidism. World J Surg 20:744–750; discussion 750–752
90. Mete O, Asa SL (2013) Precursor lesions of endocrine system neoplasms. Pathology 45:316–330. doi:10.1097/PAT.0b013e32835f45c5
91. Khan MW, Worcester EM, Straus FH 2nd et al (2004) Parathyroid carcinoma in secondary and tertiary hyperparathyroidism. J Am Coll Surg 199:312–319. doi:10.1016/j.jamcollsurg.2004.04.014
92. Al-Kurd A, Mekel M, Mazeh H (2014) Parathyroid carcinoma. Surg Oncol 23:107–114. doi:10.1016/j.suronc.2014.03.005
93. Grzela T, Chudzinski W, Lasiecka Z et al (2006) The calcium-sensing receptor and vitamin D receptor expression in tertiary hyperparathyroidism. Int J Mol Med 17:779–783
94. Erovic BM, Harris L, Jamali M et al (2012) Biomarkers of parathyroid carcinoma. Endocr Pathol 23:221–231. doi:10.1007/s12022-012-9222-y
95. Juhlin CC, Nilsson IL, Johansson K et al (2010) Parafibromin and APC as screening markers for malignant potential in atypical parathyroid adenomas. Endocr Pathol 21:166–177. doi:10.1007/s12022-010-9121-z
96. Gill AJ (2014) Understanding the genetic basis of parathyroid carcinoma. Endocr Pathol 25:30–34. doi:10.1007/s12022-013-9294-3
97. Juhlin CC, Haglund F, Obara T et al (2011) Absence of nucleolar parafibromin immunoreactivity in subsets of parathyroid malignant tumours. Virchows Arch 459:47–53. doi:10.1007/s00428-010-1032-3
98. Truran PP, Johnson SJ, Bliss RD et al (2014) Parafibromin, galectin-3, PGP9.5, Ki67, and cyclin D1: using an immunohistochemical panel to aid in the diagnosis of parathyroid cancer. World J Surg 38:2845–2854. doi:10.1007/s00268-014-2700-2
99. Juhlin CC, Hoog A (2010) Parafibromin as a diagnostic instrument for parathyroid carcinoma-lone ranger or part of the posse? Int J Endocrinol 2010:324964. doi:10.1155/2010/324964
100. Gasparri G, Camandona M, Abbona GC et al (2001) Secondary and tertiary hyperparathyroidism: causes of recurrent disease after 446 parathyroidectomies. Ann Surg 233:65–69
101. Juhlin CC, Haglund F, Villablanca A et al (2009) Loss of expression for the Wnt pathway components adenomatous polyposis coli and glycogen synthase kinase 3-beta in parathyroid carcinomas. Int J Oncol 34:481–492
102. Nasrallah MP, Fraker DL, Livolsi VA (2014) Parathyroid carcinoma in the setting of tertiary hyperparathyroidism after renal transplant. Endocr Pathol 25:433–435. doi:10.1007/s12022-013-9278-3
103. Wei CH, Harari A (2012) Parathyroid carcinoma: update and guidelines for management. Curr Treat Options Oncol 13:11–23. doi:10.1007/s11864-011-0171-3
104. Talat N, Schulte KM (2010) Clinical presentation, staging and long-term evolution of parathyroid cancer. Ann Surg Oncol 17:2156–2174. doi:10.1245/s10434-010-1003-6
105. Costa-Guda J, Soong CP, Parekh VI et al (2013) Germline and somatic mutations in cyclin-dependent kinase inhibitor genes CDKN1A, CDKN2B, and CDKN2C in sporadic parathyroid adenomas. Horm Cancer 4:301–307. doi:10.1007/s12672-013-0147-9
106. Cromer MK, Starker LF, Choi M et al (2012) Identification of somatic mutations in parathyroid tumors using whole-exome sequencing. J Clin Endocrinol Metab 97:E1774–E1781. doi:10.1210/jc.2012-1743
107. Newey PJ, Nesbit MA, Rimmer AJ et al (2012) Whole-exome sequencing studies of nonhereditary (sporadic) parathyroid adenomas. J Clin Endocrinol Metab 97:E1995–E2005. doi:10.1210/jc.2012-2303

108. Heppner C, Kester MB, Agarwal SK et al (1997) Somatic mutation of the MEN1 gene in parathyroid tumours. Nat Genet 16:375–378. doi:10.1038/ng0897-375
109. Bergman L, Boothroyd C, Palmer J et al (2000) Identification of somatic mutations of the MEN1 gene in sporadic endocrine tumours. Br J Cancer 83:1003–1008. doi:10.1054/bjoc.2000.1385
110. Palanisamy N, Imanishi Y, Rao PH et al (1998) Novel chromosomal abnormalities identified by comparative genomic hybridization in parathyroid adenomas. J Clin Endocrinol Metab 83:1766–1770. doi:10.1210/jcem.83.5.4806
111. Hsi ED, Zukerberg LR, Yang WI, Arnold A (1996) Cyclin D1/PRAD1 expression in parathyroid adenomas: an immunohistochemical study. J Clin Endocrinol Metab 81:1736–1739. doi:10.1210/jcem.81.5.8626826
112. Vasef MA, Brynes RK, Sturm M et al (1999) Expression of cyclin D1 in parathyroid carcinomas, adenomas, and hyperplasias: a paraffin immunohistochemical study. Mod Pathol 12:412–416
113. Agarwal SK (2013) Multiple endocrine neoplasia type 1. Front Horm Res 41:1–15. doi:10.1159/000345666
114. Sharretts JM, Simonds WF (2010) Clinical and molecular genetics of parathyroid neoplasms. Best Pract Res Clin Endocrinol Metab 24:491–502. doi:10.1016/j.beem.2010.01.003
115. Imanishi Y, Hosokawa Y, Yoshimoto K et al (2001) Primary hyperparathyroidism caused by parathyroid-targeted overexpression of cyclin D1 in transgenic mice. J Clin Invest 107:1093–1102. doi:10.1172/JCI10523
116. Hemmer S, Wasenius VM, Haglund C et al (2001) Deletion of 11q23 and cyclin D1 overexpression are frequent aberrations in parathyroid adenomas. Am J Pathol 158:1355–1362. doi:10.1016/S0002-9440(10)64086-2
117. Zhao L, Sun LH, Liu DM et al (2014) Copy number variation in CCND1 gene is implicated in the pathogenesis of sporadic parathyroid carcinoma. World J Surg 38:1730–1737. doi:10.1007/s00268-014-2455-9
118. Costa-Guda J, Marinoni I, Molatore S et al (2011) Somatic mutation and germline sequence abnormalities in CDKN1B, encoding p27Kip1, in sporadic parathyroid adenomas. J Clin Endocrinol Metab 96:E701–E706. doi:10.1210/jc.2010-1338
119. Soong CP, Arnold A (2014) Recurrent ZFX mutations in human sporadic parathyroid adenomas. Oncoscience 1:360–366. doi: 10.18632/oncoscience.116
120. Soong CP, Arnold A (2014) Erratum: recurrent ZFX mutations in human sporadic parathyroid adenomas. Oncoscience 2:1–2
121. Arnold A, Soong CP (2014) New role for ZFX in oncogenesis. Cell Cycle 13:3465–3466. doi :10.4161/15384101.2014.980693
122. Svedlund J, Barazeghi E, Stalberg P et al (2014) The histone methyltransferase EZH2, an oncogene common to benign and malignant parathyroid tumors. Endocr Relat Cancer 21:231–239. doi:10.1530/ERC-13-0497
123. Bjorklund P, Lindberg D, Akerstrom G, Westin G (2008) Stabilizing mutation of CTNNB1/beta-catenin and protein accumulation analyzed in a large series of parathyroid tumors of Swedish patients. Mol Cancer 7:53. doi:10.1186/1476-4598-7-53
124. Sulaiman L, Juhlin CC, Nilsson IL et al (2013) Global and gene-specific promoter methylation analysis in primary hyperparathyroidism. Epigenetics 8:646–655. doi:10.4161/epi.24823
125. Starker LF, Svedlund J, Udelsman R et al (2011) The DNA methylome of benign and malignant parathyroid tumors. Genes Chromosomes Cancer 50:735–745. doi:10.1002/gcc.20895
126. Verdelli C, Forno I, Vaira V, Corbetta S (2015) Epigenetic alterations in human parathyroid tumors. Endocrine 49:324–332. doi:10.1007/s12020-015-0555-4
127. Verdelli C, Forno I, Vaira V, Corbetta S (2015) MicroRNA deregulation in parathyroid tumours suggests an embryonic signature. J Endocrinol Invest 38:383–388. doi:10.1007/s40618-014-0234-y
128. Svedlund J, Auren M, Sundstrom M et al (2010) Aberrant WNT/beta-catenin signaling in parathyroid carcinoma. Mol Cancer 9:294. doi:10.1186/1476-4598-9-294

129. Mazzocchi G, Aragona F, Malendowicz LK, Nussdorfer GG (2001) PTH and PTH-related peptide enhance steroid secretion from human adrenocortical cells. Am J Physiol Endocrinol Metab 280:E209–E213
130. Tomaschitz A, Ritz E, Pieske B et al (2012) Aldosterone and parathyroid hormone: a precarious couple for cardiovascular disease. Cardiovasc Res 94:10–19. doi:10.1093/cvr/cvs092
131. Smith JM, Mouw DR, Vander AJ (1983) Effect of parathyroid hormone on renin secretion. Proc Soc Exp Biol Med 172:482–487
132. Powell HR, McCredie DA, Rotenberg E (1978) Renin release by parathyroid hormone in the dog. Endocrinology 103:985–989. doi:10.1210/endo-103-3-985
133. Walker MD, Silverberg SJ (2008) Cardiovascular aspects of primary hyperparathyroidism. J Endocrinol Invest 31:925–931
134. Rubin MR, Maurer MS, McMahon DJ et al (2005) Arterial stiffness in mild primary hyperparathyroidism. J Clin Endocrinol Metab 90:3326–3330
135. Stefenelli T, Abela C, Frank H et al (1997) Cardiac abnormalities in patients with primary hyperparathyroidism: implications for follow-up. J Clin Endocrinol Metab 82:106–112. doi:10.1210/jcem.82.1.3666
136. Langle F, Abela C, Koller-Strametz J et al (1994) Primary hyperparathyroidism and the heart: cardiac abnormalities correlated to clinical and biochemical data. World J Surg 18:619–624
137. Maniero C, Fassina A, Guzzardo V et al (2011) Primary hyperparathyroidism with concurrent primary aldosteronism. Hypertension 58:341–346. doi:10.1161/HYPERTENSIONAHA.111.173948
138. Maniero C, Fassina A, Seccia TM et al (2012) Mild hyperparathyroidism: a novel surgically correctable feature of primary aldosteronism. J Hypertens 30:390–395. doi:10.1097/HJH.0b013e32834f0451
139. Rossi GP, Ragazzo F, Seccia TM et al (2012) Hyperparathyroidism can be useful in the identification of primary aldosteronism due to aldosterone-producing adenoma. Hypertension 60:431–436. doi:10.1161/HYPERTENSIONAHA.112.195891
140. Rossi GP (2010) Hyperparathyroidism, arterial hypertension and aortic stiffness: a possible bidirectional link between the adrenal cortex and the parathyroid glands that causes vascular damage? Hypertens Res 34:286–288. doi:10.1038/hr.2010.251
141. Weber KT (2005) The proinflammatory heart failure phenotype: a case of integrative physiology. Am J Med Sci 330:219–226
142. Marcocci C, Bollerslev J, Khan AA, Shoback DM (2014) Medical management of primary hyperparathyroidism: proceedings of the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. J Clin Endocrinol Metab 99:3607–3618. doi:10.1210/jc.2014-1417
143. Cozzolino M, Tomlinson J, Walsh L, Bellasi A (2015) Emerging drugs for secondary hyperparathyroidism. Expert Opin Emerg Drugs 20:197–208. doi:10.1517/14728214.2015.1018177
144. Singh Ospina N, Thompson GB, Lee RA et al (2015) Safety and efficacy of percutaneous parathyroid ethanol ablation in patients with recurrent primary hyperparathyroidism and multiple endocrine neoplasia type 1. J Clin Endocrinol Metab 100:E87–E90. doi:10.1210/jc.2014-3255
145. Alherabi AZ, Marglani OA, Alfiky MG et al (2015) Percutaneous ultrasound-guided alcohol ablation of solitary parathyroid adenoma in a patient with primary hyperparathyroidism. Am J Otolaryngol 36:701–703. doi:10.1016/j.amjoto.2015.04.006
146. Cetani F, Banti C, Pardi E et al (2013) CDC73 mutational status and loss of parafibromin in the outcome of parathyroid cancer. Endocr Connect 2:186–195. doi:10.1530/EC-13-0046

# Part VIII

# Special Types of Hypertension

# Phenotypic Changes in the Transition from Prehypertension to Established Hypertension

# 34

Stevo Julius

## 34.1 Background

Historically, investigators interested in marginal blood pressure elevation used such diverse terms as prehypertension, transient, labile, latent, borderline, incipient, uneventful, and benign hypertension. In this review, I will use the current generally accepted term "prehypertension."

The problem of interest in this chapter can best be illustrated by quotes from classical old literature about epidemiology [1] and hemodynamics [2] of prehypertension.

In 1939 Robinson and Brucer [1] investigated the blood pressure (BP) trends in 11,383 health insurance policy holders in Chicago. In the introduction, the authors lamented about physician attitude that:

> *if a subjectively-well and objectively-robust individual has a slightly elevated BP, then slightly elevated blood pressure must be normal. However a study over a period years of many subjectively well and robust persons with slightly elevated BP shows that they are not normal.*

Below are selected conclusions from their thorough and well-documented paper:

- *High blood pressure is a long-term disease having its genesis at an early age. Normal BP does not rise with age. Prehypertensive and hypertensive pressure do rise with age.*
- *A blood pressure history of 120 systolic and 80 diastolic over a 10-year span in man or woman is a sign of incipient hypertension. Once a pressure is established in this range, it seldom, if ever, will become normal.*
- *Slightly more than 40% of the adult population is either actually or incipiently hypertensive.*

S. Julius
Frankel Cardiovascular Center, University of Michigan Health System,
1500 East Medical Drive, Ann Arbor, MI 48109, USA
e-mail: sjulius@med.umich.edu



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_34

In 1960 Ed Freis revived the voluminous work on hemodynamics of hypertension [1]. Below is the relevant conclusion from his review:

> *The calculated total peripheral resistance is increased in about two-thirds of chronic human hypertension. It is not certain whether the remainder represents a group in which an elevation of cardiac output is the primary hemodynamic fault or whether apprehension associated with the procedure disturbed the basal hemodynamic state.*

In other words Dr. Freis did not accept Robinson's and Brucer's warning that transient blood pressure elevations should not be ignored. In fairness Freis may have had a point; at that time measurement of cardiac output required cardiac catheterization, injections of dyes, and cannulation of the brachial artery [2–6]. Such a complex procedure might have stressed some individuals beyond the borders of usual blood pressure variability. However, Freis' concern was misplaced. The hyperkinetic state of a slight BP elevation, tachycardia, and increased cardiac output is a precursor of future established hypertension. This was known already in 1945 when Levy et al. [7] examined BP trends in 22,741 US Army officers. Transient tachycardia proved to be a strong predictor of future established hypertension. When transient tachycardia was combined with transient hypertension, the risk of established hypertension increased exponentially. Thereafter it has been repeatedly shown [8–12] that tachycardia is an independent predictor of hypertension. Importantly the tachycardia in prehypertension is due to increased sympathetic drive and decreased parasympathetic inhibition of the cardiac pacemaker [13]. Thus, the pathological signal emanates from the brain where in the medulla oblongata, the sympathetic and parasympathetic tones are integrated in a reciprocal fashion.

Instead of the expected bell-shaped curve, in population studies, BP distribution is invariably skewed at the high end of pressure values. Schork et al. [14] used a computerized statistical mixture analysis of the BP distribution to determine whether the skewed at the high distribution consisted of one or more subpopulations. In each of three Michigan populations, the curve consisted of two homogenous subpopulations, a large normotensive and a smaller hypertensive group ($p < 0.0000001$). The hypertension group was associated with tachycardia and, when measured, also with high cardiac output. The mixture analysis method was also used in an American, Belgian, and Italian population [15]. In each population, there was a subpopulation with tachycardia and elevated BP levels. Thus the association of tachycardia with hypertension is a distinct pathophysiologic syndrome.

We used the mixture analysis in the Tecumseh population study [16, 17]. Of a total of 946 young untreated adults (average age 30.7 years), 13% were categorized as having prehypertension. Review of records from previous Tecumseh study health exams showed that the BP of the prehypertension group was significantly elevated already when they were children (6.4 years) or young adults (21.5 years). The prehypertension group had signs of vascular restructuring, cardiac dysfunction, glucose and insulin abnormalities, and dyslipidemia. We also had information about the parents of the Tecumseh BP study population. When they were on average

31 years of age, both mothers and fathers of the prehypertension group had significantly higher BP than the parents of normotensive individuals.

We focused on 691 Tecumseh study participants with complete sets of hemodynamic data. Cardiac output was measured by the stress-free noninvasive echo-Doppler method. The mixture analysis detected two groups, the larger one ($N$ = 594) with a lower BP and cardiac output and the smaller group ($N$ = 97) with a higher BP and cardiac output. Thereafter we used the clinic BP of 140/90 mmHg as the cutting point for normotension versus prehypertension. A hyperkinetic circulation was present in 37% of the prehypertension group and in only 10% of the normotensive group. The hyperkinetic prehypertension group had significantly elevated plasma norepinephrine, and their BP was significantly elevated at 5.2, 8.2, 21.5, and 23.2 years of age. A significantly higher heart rate was detected only at 21.5, 23.2, and 30.7 years of age.

That the hyperkinetic state is associated with increased sympathetic tone was also proved with newer methods such as norepinephrine spillover and microneurography [18].

Overall these findings indicate that a large proportion of persons with prehypertension have a hyperkinetic circulation. The hyperkinetic state is associated with markers of increased sympathetic drive. Hyperkinetic circulation is a predictor of future established hypertension. However the hemodynamic pictures of prehypertension (high cardiac output) and established hypertension (increased vascular resistance) are profoundly dissimilar.

This difference in the underlying hemodynamic profile in the course of hypertension raises a number of questions.

## 34.2 Is the Hyperkinetic State Precursor of Hypertension or a Marker of Transient Stress?

The development of hypertension is rather slow. However even a transient elevation of BP can affect the function and structure of many organs. This has been shown in dogs exposed to 9 weeks of repeated episodes of increased BP. Transient increases of BP (3 h in the morning and in the afternoon) did not cause persistent hypertension but did elicit cardiac hypertrophy and dysfunction [19, 20]. The Ann Arbor group focused on prehypertension on the theory that pathophysiologic changes found in individuals free of secondary functional or structural organ changes are likely to be related to the initiation of hypertension. In the Tecumseh BP study [16, 17], we recognized two different prehypertension phenotypes, the hyperkinetic state and the elevation of Li-Na counter-transport activity. In order to investigate “pure” hyperkinetic prehypertension [21], we removed from the analysis subjects with elevated Li-Na counter-transport. Figures 34.1 and 34.2 illustrate the age-related heart rate and BP trends in 787 normotensive and 24 “pure” prehypertensive study participants.

The group deemed to have “pure” hyperkinetic prehypertension at 30 years of age had significantly elevated heart rate also at 7 and 22 years exams. Furthermore,

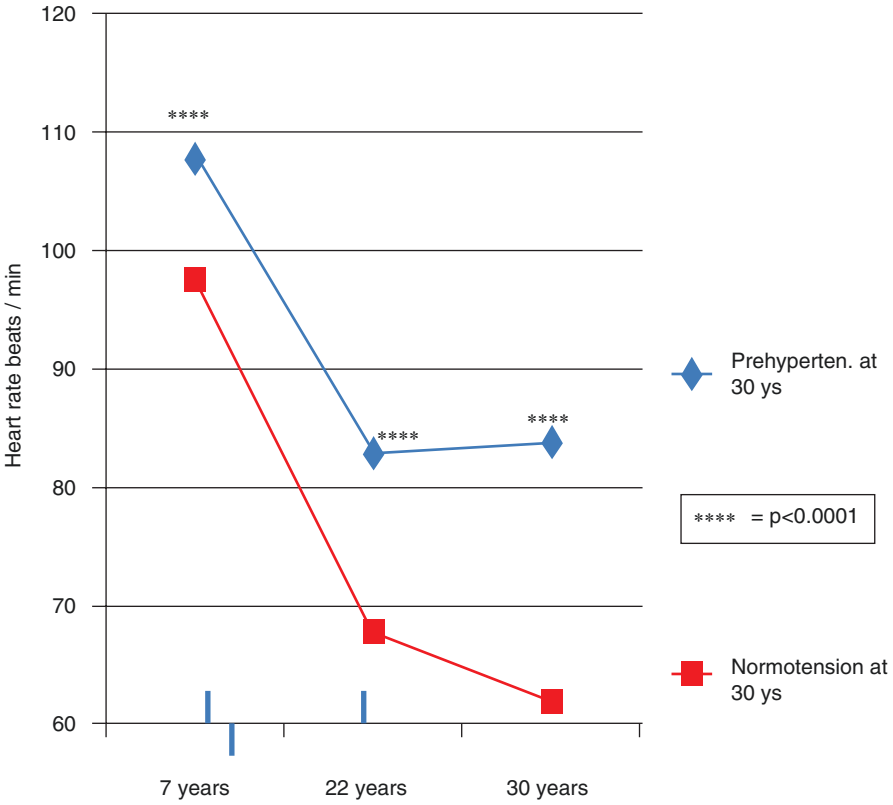



**Fig. 34.1** The Tecumseh study: heart rate at previous exams in groups classified as "pure" hyperkinetic prehypertension or normotension at 30 years of age

compared to the normotensive group, the age-related decrease of heart rate was lesser in the hyperkinetic group. Between age 22 and 30, the heart rate continued to decrease in the normotensive group, and no further decrease was seen in the hyperkinetic group.

In contrast to the heart rate (Fig. 34.2), the BP of the hyperkinetic group was not increased at 7 years. In the hyperkinetic group, there was a huge systolic pressure increase (+ 24 mmHg) between 7 and 22 compared to +8 mmHg in the normotensive group. At 30 years the BP of the hyperkinetic group remained in the prehypertensive range.

We conclude that in pure hyperkinetic prehypertension, the heart rate elevation precedes the increase of the BP. This finding should be considered as a "proof of the principle" that in some prehypertensives tachycardia can be the primary hemodynamic component of the hyperkinetic syndrome. It is important to note that "pure" hyperkinetic state was not a small group; nearly one quarter (24.3%) of prehypertensives examined at 30 years of age had "pure" hyperkinetic circulation.

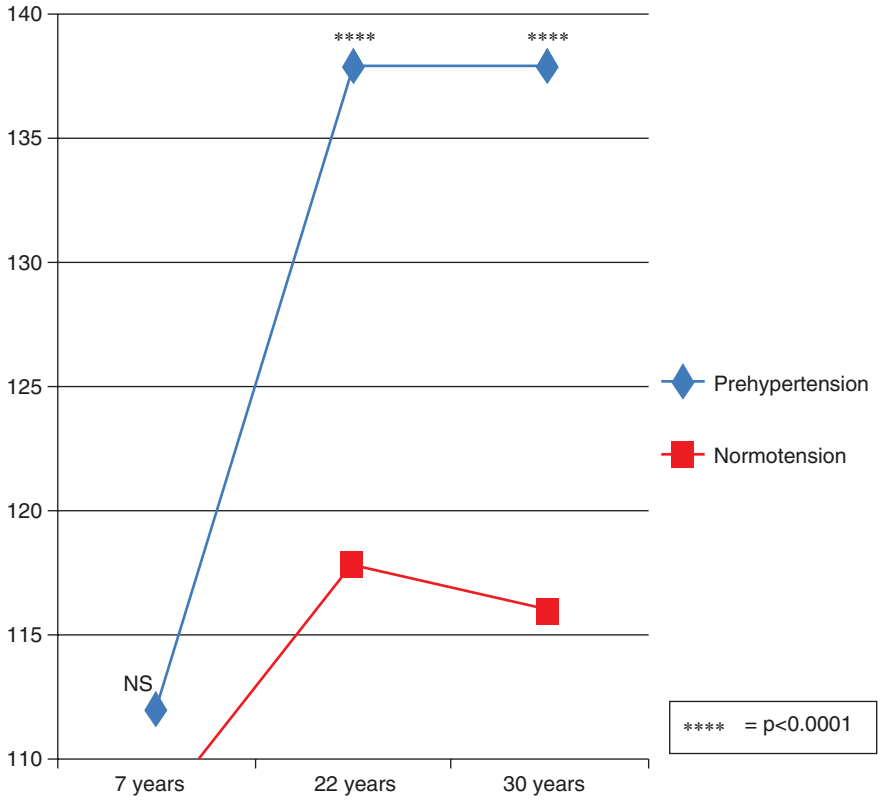



**Fig. 34.2** The Tecumseh study: systolic BP at previous exams in group classified as "pure" hyperkinetic prehypertension or normotension at 30 years of age

## 34.3 Is There Evidence for a Hemodynamic Transition from an Early Hyperkinetic to a Later High-Resistance State?

As stated earlier [8–11], resting tachycardia is a potent predictor of future hypertension. In addition high resting heart is an independent predictor of cardiovascular adverse events [22–28]. This strongly suggests that hyperkinetic state in prehypertension induces established hypertension which, in turn, is associated with increased vascular resistance and cardiovascular risk.

Unfortunately only a few cohort studies investigated the hemodynamic picture in the course of hypertension. Lund-Johansen and Omvik investigated the topic in the classic Bergen Study [28, 29]. Of particular interest are studies in young (17–29 years) subjects. After 10 years the cardiac output decreased and the vascular resistance increased, but the BP did not change. At 20 years of follow-up, the majority of patients received antihypertensive treatment. At that time point, the vascular

resistance increased further, and there was a modest increase of the mean BP. A few other investigators [30–33] repeated the hemodynamic measurements in hyperkinetic hypertension within a span of 2–5 years. All found a decrease of cardiac output and increase of vascular resistance at the second hemodynamic measurement. However, only one study [31] found a modest increase of the systolic blood pressure.

The fact that the Bergen Study [29, 34] found a steady increase of vascular resistance but could not document an increase of BP in the course of hypertension reflects the advances in the treatment of hypertension. In the early 1960s, it was still possible to follow untreated midrange hypertension, but in the late 1970s and early 1980s, seminal studies in the USA, Great Britain, and Australia proved that lowering BP pressure in "mild" hypertension saves lives. At 20 years of follow-up in the Bergen studies, almost all patients were treated, and the prolonged BP lowering may have altered the natural history of hypertension.

## 34.4 What Is the Mechanism of Tachycardia in Prehypertension?

Conceptually diverse mechanisms may be responsible for the fast heart rate in prehypertension. Frohlich et al. [35] described a group of predominantly hypertensive patients (12 out of 14) with hyperkinetic circulation. At baseline this group of middle-aged adults (average 39 years) had significantly higher heart rate and cardiac output than the normotensive controls. A graded infusion of beta-adrenergic agonist isoproterenol induced a substantially higher increase of heart rate than in the control group. According to the authors, "in nine of the fourteen patients isoproterenol produced a hysterical outburst, almost uncontrollable, which was promptly reversed with propranolol but not with placebo." Based on these findings, the authors correctly concluded that this particular group of patients had increased beta-adrenergic receptor reactivity. However, such hyper-reactivity must be quite rare and cannot account for the tachycardia seen in the large population hyperkinetic hypertension. Over a period of 30 years, the Ann Arbor group investigated the heart rate response to beta-adrenergic agonist infusion in three different hypertensive populations [36–38]. In each study, hypertensive patients had a suppressed heart rate response to beta-adrenergic stimulation. This suppression is likely to reflect a downregulation of beta-receptors in response to a prevailing increase of the sympathetic tone. In the last study [38], there was a negative correlation between the heart rate increase to isoproterenol and the plasma ($p = 0.004$) as well as the 24 h urinary noradrenalin ($p = 0.02$) levels.

In a previous study [13], we investigate another possible mechanism of tachycardia: that patients with tachycardia may have a pacemaker which inherently fires at a faster rate. We intravenously injected large doses of propranolol and atropine to block both the cardiac sympathetic and parasympathetic receptors (Fig. 34.3).

At baseline, by selection, there was a highly significant elevation of the heart rate in the hyperkinetic group. The autonomic nervous receptor blockade

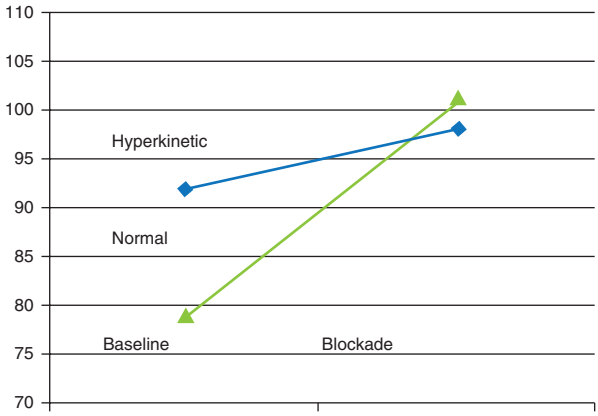



**Fig. 34.3** Illustrates the data from 11 patients with hyperkinetic prehypertension and 16 normal controls

abolished the heart rate difference between the two groups. We conclude that both groups had similar intrinsic pacemakers. Note that cardiac receptor blockade elicited an increase of the heart rate in both groups. It follows that in the resting state, the autonomic nervous system inhibits the intrinsic pacemaker. The figure also shows that the inhibition in the hyperkinetic group was lesser than in the normal controls. We conclude that tachycardia in prehypertension is neurogenic.

## 34.5 What Is the Mechanism of the Increased Cardiac Output in Hypertension?

Diverse mechanisms could also be responsible for the elevation of cardiac output in hypertension. Guyton and Coleman [39] proposed the concept of total body autoregulation. This theory postulates that all tissues tend to maintain a constant (and optimal in regard to their metabolic needs) blood flow. Over-perfusion will elicit vasoconstriction, and under-perfusion will cause vasodilation.

The next assumption is that in hypertension, there is a phase of expanded blood volume which elevates the cardiac output above the metabolic demands of the body. This in turn triggers an increase of both the vascular resistance and BP. Next the high BP increases the diuresis and in due time will result in a novel hemodynamic equilibrium. In this final phase, there is an increase of BP and vascular resistance, whereas the blood volume and cardiac output are normal. The crucial demonstration of autoregulation in the Guyton's model required a removal of 70% of dog's renal mass prior to the experimentation. Thereafter isotonic saline solution was infused at rate about five times above the dog's habitual salt intake. This induced in the first 4 days increases of blood volume, cardiac output, and BP. After 10 days there was a new hemodynamic equilibrium consisting of normal blood volume, normal cardiac output, and hypertension. Note that complex nonphysiologic experimentation was required to demonstrate

autoregulation. Nevertheless it is possible that autoregulation plays a role in volume-induced hypertensions such as licorice intake, hyperaldosteronism, and renal dysfunction and possibly in salt-sensitive hypertension.

We are confident that the Guyton's concept of increased blood volume as a trigger of increased cardiac output is not applicable to human prehypertension. Here are the arguments:

(a) There is no evidence of volume expansion in early phases of hypertension. To the contrary, the plasma volume is decreased in prehypertension and hypertension [40, 41]. One could argue that in hyperkinetic hypertension, there may have been a prior volume expansion which triggered an autoregulatory adjustment of the circulation. If this were the case, one would have to conclude that instead of normalizing the intravascular volume, the autoregulation resulted in a hypertension with decreased intravascular volume. There is no plausible explanation for such an overshoot of the volume regulation in hypertension.
(b) In animals, the autoregulation is triggered by luxurious perfusion, a condition in which the flow exceeds the metabolic needs of organs. However the increase of cardiac output in the hyperkinetic state is associated with increased oxygen consumption [34, 42, 43]. Therefore the high cardiac output in prehypertension is an appropriate circulatory adjustment to increased metabolic needs.
(c) The strongest argument against volume-related increase of blood flow in hyperkinetic prehypertension is the fact that after a "chemical denervation" of the heart with injections of propranolol and atropine, the cardiac output decreased into the normal range [13]. Thus the increase of the cardiac output in hypertension was neurogenic.

## 34.6 What Is the Mechanism of the Transition from High to Normal Cardiac Output and from Lower to Increased Vascular Resistance in the Course of Hypertension?

(a) Cardiac Output

In 1983, Per Lund-Johansen summarized his findings in young subjects (17–29 years) who had mild to moderate untreated hypertension [29]. At the baseline this group had elevated average BP (160/99 mmHg), higher cardiac output index (+13%), increased heart rate (+16%), and a normal stroke volume index. Some of the originally young subjects were reexamined after 10 years. At that point there was a decrease of stroke volume and cardiac output, whereas the vascular resistance increased. Eight untreated subjects participated in the third hemodynamic study after a follow-up of 17 years. During this last 7 years, there was a further decrease of cardiac output and stroke volume as well as an increase of mean arterial pressure. It is likely that the time-related decrease of stroke volume reflects an increased stiffening of the heart chambers.

Based on the longitudinal observations by Lund-Johansen [29, 34], we assumed that the majority of normokinetic prehypertensives may have transited from the hyperkinetic to a normokinetic state. Consequently we investigated 105 prehypertensives with normal cardiac output and compared them with 85 healthy volunteers [36]. The baseline stroke volume index in the normokinetic patients was 44.3 compared to 47.4 mL/beat/min in normotensive control group $p < 0.01$. In the 105 normokinetic prehypertensives, the stroke volume was substantially lower (44.3, $p < 0.01$). The stroke volume difference between the two groups increased further after an "autonomic nervous denervation of the heart" by large doses of propranolol and atropine (35.4 versus 32.0, $p < 0.001$).

Prehypertension [40] and hypertension [41] are associated with a significant decrease of plasma volume which may decrease the venous return to the heart and elicit a smaller stroke volume. In our study [7] we estimated the venous return to the heart by calculating the cardiopulmonary blood volume from dye dilution curves. There was a highly significant correlation between the cardiopulmonary blood volume and the stroke volume in both groups. However the cardiopulmonary blood volumes of the two groups were not different suggesting that the venous return in both groups was similar. These findings indicate that prehypertensives with normal cardiac output have stiffer hearts which do not sufficiently distend in response to an adequate venous return.

(b) Vascular Resistance

The normal cardiac output in prehypertension is associated with an increase of vascular resistance. The vascular resistance is calculated by division of the mean arterial pressure with cardiac output. Thus, if the BP is the same or increases and the cardiac output decreases, the calculated vascular resistance will increase. It is tempting to view the ensuing increase of vascular resistance as a simple mathematical outcome. However elevated vascular resistance in untreated hypertension reflects an anatomic restructuring of the small resistance vessels (arterioles). The Swedish physiologist Bjorn Folkow was the first to suggest and experimentally support the concept that the arteriolar wall-to-lumen ratio may be an "amplifier" of the BP in hypertension. In his view the elevated BP induces a muscular hypertrophy in the arteriolar wall. The thickened wall intrudes into the vessel's lumen and mechanically increases the vascular resistance. In response there is an increase of the BP and thereby starts the vicious circle of BP elevation. Folkow [44] postulated several criteria to verify the presence of wall-to-lumen aberrations in hypertension. Compared to normotensive individuals, hypertensives should:

(a) Show a nonspecific increased responsiveness to various vasoconstrictors.
(b) It is expected that at the baseline, the hypertensive will have a smaller arteriolar lumen. A smaller lumen ought to be associated with a steeper response since the resistance rises with fourth power of the radius.
(c) In hypertensives the structural reduction in the vascular cross-sectional area should be associated with greater resistance at maximum vasoconstriction.

(d) At maximal vasodilation the residual (minimal) resistance ought to be increased in hypertension.
(e) The sensitivity of the alpha-adrenergic receptors should not be increased.

Egan et al. [45] investigated the forearm circulation in a group of patients with mild hypertension and an age- and weight-matched normotensive control group. Intra-brachial artery infusions of norepinephrine and angiotensin elicited substantially steeper increase of forearm vascular resistance in the hypertension group. Similarly the vascular resistance at the highest dose of norepinephrine or angiotensin infusion was increased in the hypertension. The minimum forearm vascular resistance at maximal dilatation was increased in hypertension. The calculated sensitivity of brachial artery alpha-adrenergic receptors was similar in both groups. These findings strongly supported a structural reduction in the luminal cross-sectional area in hypertension, but the nature of vascular abnormality was not determined. We concluded that in addition to an increased wall thickness, our findings could also reflect "a reduction in the vessel size or a reduction in vessel number." Current literature indicates that hypertension is associated with inward arteriolar remodeling in which there is no evidence of smooth muscle hypertrophy, but the wall-to-lumen ratio is increased [46, 47]. In the Tecumseh study [16], we found an increased minimum forearm vascular resistance at the maximal dilatation also in prehypertension. Thus vascular abnormalities are present in the earliest phases of hypertension.

In summary one third of patients with prehypertension have increased sympathetic tone manifested as tachycardia and increased cardiac output. This hyperkinetic hemodynamic state is a predictor of future established hypertension. However patients with established hypertension characteristically have increased vascular resistance and a normal cardiac output. In this chapter, we describe the mechanism of the phenotypic transition from prehypertension to established hypertension. The "normalized" cardiac output in established hypertension reflects a decrease of the stroke volume due to increased cardiac stiffness. In parallel, the increased vascular resistance in established hypertension mirrors the ensuing restructuring of resistance arterioles. This restructuring enhances vascular contraction to all constricting agonists and, if untreated, predicts future increases of the blood pressure.

Despite of the notion that early tachycardia and minor blood pressure increases may be benign signs of transient nervousness, there is strong evidence that this condition is predictor of established hypertension. In clinical terms this suggests that hypertension starts early and calls for early detection and management of all stages of hypertension.

## References

1. Robinson SC, Brucer M (1939) Range of normal blood pressure, a statistical and clinical study of 11,383 persons. Arch Intern Med 64(3):409–444
2. Freis ED (1960) Hemodynamics of hypertension. Physiol Rev 40(1):27–54

3. Eich RH, Peters RJ, Cuddy RP et al (1962) The hemodynamics of labile hypertension. Am Heart J 63:188–195
4. Widimski J, Fejfarova MH, Fejfar Z (1957) Changes of cardiac output in hypertensive disease. Cardiologia 31:381–389
5. Messerli FH, DeCarvalho JG, Christie B, Frohlich ED (1979) Essential hypertension in black and white subjects. Hemodynamic findings and fluid volume state. Am J Med 67(1):27–31
6. Frohlich ED, Tarazi RC, Dustan HP (1969a) Re-examination of the hemodynamics of hypertension. Am J Med Sci 257(1):9–23
7. Julius S (1976) Neurogenic component in borderline hypertension. In: Julius S, Essler MD (eds) The nervous system in arterial hypertension. Charles C. Thomas, Springfield, pp 301–330
8. Levy RL, White PD, Stroud WD (1945) Transient tachycardia. Prognostic significance alone and in association with transient hypertension. JAMA 129(9):585–588
9. Palatini P, Julius S (1997) Heart rate and the cardiovascular risk. J Hypertens 15:1–15
10. Palatini P (2011) Role of elevated heart rate in the development of cardiovascular disease in hypertension. Hypertension 58:745–750
11. Julius S, Palatini P (2015) Resting heart rate as a cardiovascular risk factor. CESISRL, Rome
12. Wang A, Liu X, Guo X et al (2014) Resting heart rate and risk of hypertension: results of the Kailuan cohort study. J Hypertens 32(8):1600–1605
13. Julius S, Pascual AV, London R (1971) Role of parasympathetic inhibition in the hyperkinetic type of borderline hypertension. Circulation 44:413–418
14. Schork NJ, Weder AB, Schork MA et al (1990) Disease entities, mixed multi-normal distributions, and the role of the hyperkinetic state in the pathogenesis of hypertension. Stat Med 9:301–314
15. Palatini P, Casiglia E, Pauletto P et al (1997) Relationship of tachycardia with high blood pressure and metabolic abnormalities. A study with mixture analysis in three populations. Hypertension 30:1267–1273
16. Julius S, Jamerson K, Mejia A et al (1990) The association of borderline hypertension with target organ changes and higher coronary risk. Tecumseh Blood Pressure Study. JAMA 264:354–358
17. Julius S, Krause L, Schork NJ et al (1991) Hyperkinetic borderline hypertension in Tecumseh Michigan. J Hypertens 9:77–84
18. Grassi G, Mark L, Esler M (2015) The sympathetic nervous system alterations in human hypertension. Circ Res 116:976–990
19. Julius S, Li Y, Brant D et al (1989) Neurogenic pressor episodes fail to cause hypertension, but do induce cardiac hypertrophy. Hypertension 13:422–429
20. Buda AJ, Li Y, Brant D et al (1991) Changes in left ventricular diastolic filling during the development of left ventricular hypertrophy: observations using Doppler echocardiography in a unique canine model. Am Heart J 121:1759–1767
21. Julius S, Jamerson K (1994) Sympathetics, insulin resistance and coronary risk in hypertension: the 'chicken and egg' question. J Hypertens 12:495–502
22. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA (1987) Heart rate and cardio vascular mortality: the Framingham study. Am Heart J 113:1489–1494
23. Jouven X, Desnos M, Guerot C, Ducimetiere P (1999) Predicting sudden death in the population: the Paris Prospective Study 1. Circulation 99:1978–1983
24. Palatini P, Casiglia S, Julius S, Pessina AC (1999) Heart rate, a risk factor for cardio vascular mortality in elderly men. Arch Intern Med 159(6):585–592
25. Jensen MT, Marott JL, Allin KH et al (2012) Resting heart rate is associated with cardiovascular and all-cause mortality after adjusting for inflammatory markers: the Copenhagen City heart study. Eur J Prev Cardiol 19(1):102–108
26. Kolloch R, Legler UF, Champion A et al (2008) Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: findings from the International VErapamil-SR/trandolapril STudy (INVEST). Eur Heart J 29:1327–1334

27. Okin PM, Kjeldsen SE, Julius S et al (2010) All-cause and cardiovascular mortality in relation to changing heart rate during treatment of hypertensive patients with electrocardiographic left ventricular hypertrophy. Eur Heart J 31:2271–2279
28. Julius S, Palatini P, Kjeldsen S et al (2012) Tachycardia predicts cardiovascular events in the VALUE trial. Am J Cardiol 109:685–692
29. Lund-Johansen P, Omvik P (1995) Hemodynamic patterns of untreated hypertensive disease. In: Laragh JH, Brenner BM (eds) Hypertension: pathophysiology, diagnosis and management, 2nd edn. Raven Press, New York, pp 323–342
30. Weiss YA, Safar ME, London GM et al (1978) Repeat hemodynamic determinations in borderline hypertension. Am J Med 64:382–387
31. Andersson OK, Sannerstedt R, Beckman M et al (1983) Essential hypertension—implications for pathogenesis from repeated haemodynamic investigations in young men with elevated blood pressure. J Hypertens Suppl 1(2):91–93
32. Binkenhager WH, de Leuwe PW (1984) Cardiac aspects of essential hypertension. J Hypertens 2:121–125
33. Julius S, Quadir H, Gajendragadkar S (1979) Hyperkinetic state: a precursor of hypertension? A longitudinal study of borderline hypertension. In: Gross FH, Strasser T (eds) Mild hypertension: natural history and management. Year Book Medical, Chicago, pp 116–126
34. Lund-Johansen P (1967) Hemodynamics in early essential hypertension. Acta Med Scand 181(Suppl 482):1–101
35. Frohlich E, Tarazi R, Dustan H (1969) Hyperdynamic beta-adrenergic circulatory state. Increased beta-receptor responsiveness. Arch Intern Med 123(1):1–7
36. Julius S, Randall OS, Esler MD et al (1975) Altered cardiac responsiveness and regulation in the normal cardiac output type of borderline hypertension. Circ Res 36(6 Suppl 1):199–207
37. Kjeldsen SE, Moan A, Petrin J et al (1996) Effects of increased arterial epinephrine on insulin, glucose and phosphate. Blood Press 5:25–31
38. Valentini M, Julius S, Palatini P et al (2004) Attenuation of haemodynamic, metabolic and energy expenditure responses to isoproterenol in patients with hypertension. J Hypertens 22:1999–2006
39. Guyton AC, Coleman TG (1969) Quantitative analysis of the pathophysiology of hypertension. Circ Res 24(5 Suppl):1–19
40. Julius S, Pascual A, Reilly K, London R (1971) Abnormalities of plasma volume in borderline hypertension. Arch Intern Med 127:116–119
41. Tarazi R, Frohlich E, Dustan H (1968) Plasma volume in men with essential hypertension. New Engl J Med 278:762–765
42. Sannerstedt R (1966) Hemodynamic response to exercise in patients with arterial hypertension. Acta Med Scand Suppl 458:1–83
43. Julius S, Conway J (1968) Hemodynamic studies in patients with borderline blood pressure elevation. Circulation 38:282
44. Folkow B, Grimby G, Thulesius O (1970) Adaptive structural changes of the vascular walls in hypertension and their relation to the control of peripheral resistance. Acta Physiol Scand 44:255–272
45. Egan B, Panis R, Hinderliter A et al (1987) Mechanism of increased alpha adrenergic vasoconstriction in human essential hypertension. J Clin Invest 80:812–817
46. Mulvany MJ (1999) Vascular remodeling of resistance vessels: can we define this? Cardiovasc Res 41:9–13
47. Izzard AS, Rizzoni D, Agabiti-Rosei E, Heagerty AM (2005) Small artery structure and hypertension: adaptive changes and target organ damage. J Hypertens 23(2):247–250

# White Coat and Masked Hypertension

# 35

Cesare Cuspidi, Carla Sala, Marijana Tadic, and Guido Grassi

## 35.1 Introduction

Combined office and out-of-office blood pressure (BP) measurement provides a comprehensive evaluation of cardiovascular risk related to hypertension and has gained increasing popularity in recent years. Both techniques allowed to identify four BP patterns: (1) true normotension (i.e. normal office and out-of-office BP), (2) sustained hypertension (elevated in-office and out-of-office BP), (3) white coat hypertension (elevated office and normal out-of-office BP) and (4) masked hypertension (normal office and elevated out-of-office BP) [1].

These BP phenotypes substantially differ in terms of prevalence, demographic and clinical features and degree of subclinical cardiac and extra-cardiac damage, as well as cardiovascular risk [2].

In the last decades, growing attention has been paid to white coat or isolated clinical hypertension and to masked hypertension, both conditions characterized by the fact that classification of BP status by clinic measurements is not confirmed by home and/or ambulatory BP monitoring (ABPM).

C. Cuspidi (✉)
Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

Istituto Auxologico Italiano, Milan, Italy
e-mail: cesare.cuspidi@unimib.it

C. Sala
Department of Clinical Sciences and Community Health, University of Milano and Fondazione Ospedale Maggiore Policlinico di Milano, Milan, Italy

M. Tadic
University Clinical Hospital Centre "Dragisa Misovic", Belgrade, Serbia

G. Grassi
Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

Istituto di Ricerche a Carattere Scientifico Multimedica, Sesto San Giovanni, Italy



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_35

In this chapter white coat hypertension (WCH) and masked hypertension (MH) will be discussed in separate sections.

## 35.2 White Coat Hypertension

Since several decades, it has been increasingly recognized that office BP measured by the physician or nurse may not accurately reflect BP levels outside medical environment [3, 4]. The alert reaction induced by BP measurement by the physician in his office may substantially reduce the value of this traditional procedure in estimating "true" BP levels of a subject.

WCH currently defines the subjects whose BP is high (i.e. ≥140 and/or 90 mmHg) in the medical setting, but normal when detected away from medical environment by 24-h ABPM and/or home BP measurement [5, 6]. Since the pioneering paper by Pickering et al. [5] in which the term WCH was used for the first time to define untreated hypertensive subjects, the large majority of studies have indicated that this condition accounts for a noticeable fraction of the hypertensive population. It has been reported, indeed, that WCH is not infrequent in the general population and is relatively common in the hypertensive one; the prevalence of this condition partly depending on the methods used (home or 24-h ABPM) and definition of normal out-of-office BP values.

WCH has been estimated to occur in approximately 20–25% of mild to moderate hypertensive population. According to normal cut-offs of clinic BP <140/90 mmHg and daytime ABP <135/85 mmHg, WCH prevalence may range from 15 to 45%.

Dolan et al. [7] documented that WCH prevalence was 15.4% in 5176 hypertensive patients (mean age 54 years) referred at a single outpatient hypertension clinic over a 22-year period. A higher prevalence was observed among older patients, females and non-smokers. In 1564 nondiabetic stage 1 hypertensive subjects free from renal disease and previous cardiovascular events, Verdecchia et al. [8] reported that WCH prevalence (daytime BP <130/80 mmHg) was 10.4%. Subjects with WCH were more frequently women, non-smokers and those who had *lower* clinical BP and left ventricular (LV) mass.

Trenkwalder et al. [9] using less tight diagnostic criteria for defining normal clinical BP (<160/95 mmHg) and ABPM (<146/87 mmHg) reported that WCH prevalence in 50 elderly and very elderly hypertensive patients was 19%. Authors failed to observe any difference related to gender, weight, comorbidities, pre-study treatment and systolic or diastolic LV function between WCH and sustained hypertensives. Patients with WCH compared to their counterparts showed lower office BP, LV mass index and more pronounced alerting reactions.

In 611 never-treated grades 1 and 2 uncomplicated essential hypertensives (mean age 46 years), our own group found that WCH prevalence was 7.1%, when this condition was diagnosed according to mean daytime BP values <135/85 mmHg and 5.4% according to mean 24-h BP values <125/80 mmHg [10].

Among 1637 untreated subjects from the Pressioni Monitorate e Loro Associazioni (PAMELA) population, WCH prevalence ranged from 9 to 12% depending on

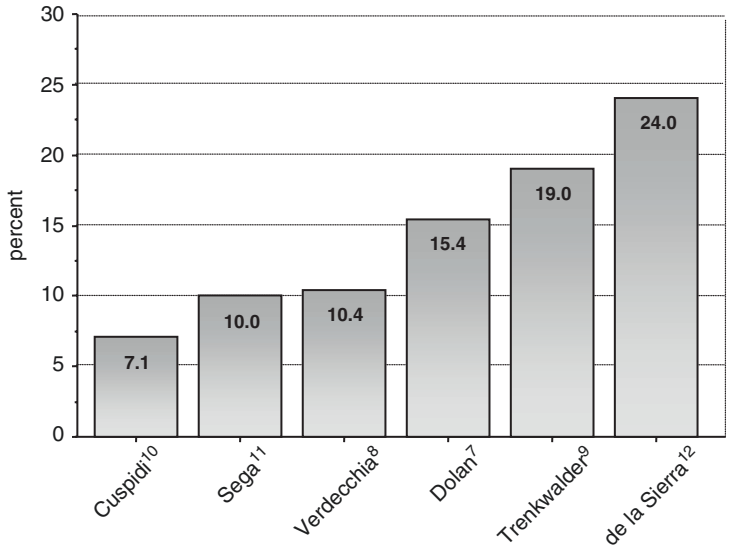



**Fig. 35.1** Prevalence rates of white coat hypertension in six studies published from 1993 to 2016

whether the definition of normal out-of-office BP was based on ambulatory (24-h < 125/80 mmHg) or home (<135/85 mmHg) BP values [11]. More recently, de la Sierra et al. [12] investigated the prevalence and reproducibility of hypertension phenotypes defined by combined clinical and ABPM measurements in a group of 869 untreated patients from the Spanish ABPM Registry. The proportion of true normotensives and white coat hypertensives at first ABPM was 17% and 24%, respectively (Fig. 35.1).

In most of the above-mentioned studies, unfortunately, WCH was defined according to a single ABPM recording. Although more reproducible than clinical BP measurement, ABPM has an intrinsic variability from one recording session to another depending on physical activity, environmental stimuli, duration and quality of sleep. This variability may affect WCH definition that for this reason should not be regarded as a stable phenotype.

In the Hypertension and Ambulatory Recording Venetia Study (HARVEST), this issue has been investigated by Palatini et al. [13] in 565 grade 1 hypertensive subjects and in 95 normotensive individuals by repeated ABPM recordings within a 3-month interval. According to the results provided by the first ABPM (mean daytime <130/80 mmHg), 90 hypertensive subjects were classified as having WCH, whereas after the second ABPM, only 38 out of 90 subjects (42.2%) were confirmed to have the WCH pattern.

We also examined the reproducibility of WCH [10] by performing two 24-h ABPMs at a 1–4-week interval in untreated hypertensives with a broader range of age and BP values (40% with grade 2 hypertension) than in Palatini's study [13]. In about 50% of the patients diagnosed as having WCH by the first ABPM, daytime ABPM values obtained at a second ABPM were >135 mmHg systolic or 85 mmHg

diastolic, shifting them into the category of sustained hypertensives. In the Spanish ABPM Registry [12], the prevalence of switch from WCH to sustained hypertension observed from the first to the second ABPM (median interval 3 months) was approximately 25%. Overall, these findings indicate that the diagnosis of WCH based on a single ABPM has a short-time limited reproducibility, due to the high proportion of patients moving into the sustained hypertension category at the second ABPM.

Despite its remarkable prevalence, the association of WCH with subclinical organ damage and increased risk of cardiovascular events is not fully established and is still a matter of debate.

The presence of target organ damage has been proven useful in predicting cardiovascular and all-cause mortality in the general as well as hypertensive population [14, 15]; searching for subclinical cardiac and extra-cardiac damage is recommended by current guidelines for refining cardiovascular risk stratification [16].

Cross-sectional studies on the association between WCH and target organ damage have provided conflicting results. Some studies have indicated an independent association between WCH and left ventricular hypertrophy (LVH), diastolic dysfunction, renal damage and micro- as well as macro-vascular alterations [17, 18]. In contrast, other studies have provided evidence that cardiac and vascular structures in individuals with WCH are not different from those of normotensive subjects, after adjusting for confounders, and only differ from those of age- and sex-matched sustained hypertensives [19, 20].

A recent meta-analysis of 25 studies published in the last two decades has provided a comprehensive information on echocardiographic markers of cardiac damage (i.e. LV mass index, LV diastolic function and left atrium diameter) in a pooled population of 1705 WCH subjects from different clinical settings compared to true normotensive and hypertensive individuals [21].

The principal findings of this meta-analysis can be summarized as follows: (1) LV mass index showed a gradual increase from normotensive (88 g/m$^2$) to WCH (96 g/m$^2$) and to sustained hypertensive subjects (109 g/m$^2$) (Fig. 35.2a); (2) mitral early to late flow velocity ratio (an established index of diastolic function) was significantly reduced in WCH as compared to normotensive subjects; (3) left atrium diameter was larger in WCH (33 mm) than in normotensive counterparts (32 mm); (4) in WCH subjects, office, but not ambulatory, BP showed a direct, significant correlation with LV mass index.

Recently, new echocardiographic techniques such as multilayer and three-dimensional (3DE) strain analyses have been applied to investigate LV mechanics in WCH. In a study by Tadic et al. [22], LV deformation, as assessed by these new techniques as well as by two-dimensional traditional strain, has been shown to be impaired in WCH as compared to normotensive controls. The reduced layer-specific strain documented for the first time by this study in the WCH setting reflects the impact of the earliest stages of LV remodelling on LV mechanics.

As for the association between WCH and vascular damage, the first study on this issue published in the early 1990s by Cavallini et al. compared carotid ultrasonographic findings in age- and gender-matched true normotensive, WCH and sustained hypertensive patients. The authors demonstrated that common intima-media thickness (IMT) was significantly greater in WCH (840 μm) than in normotensive

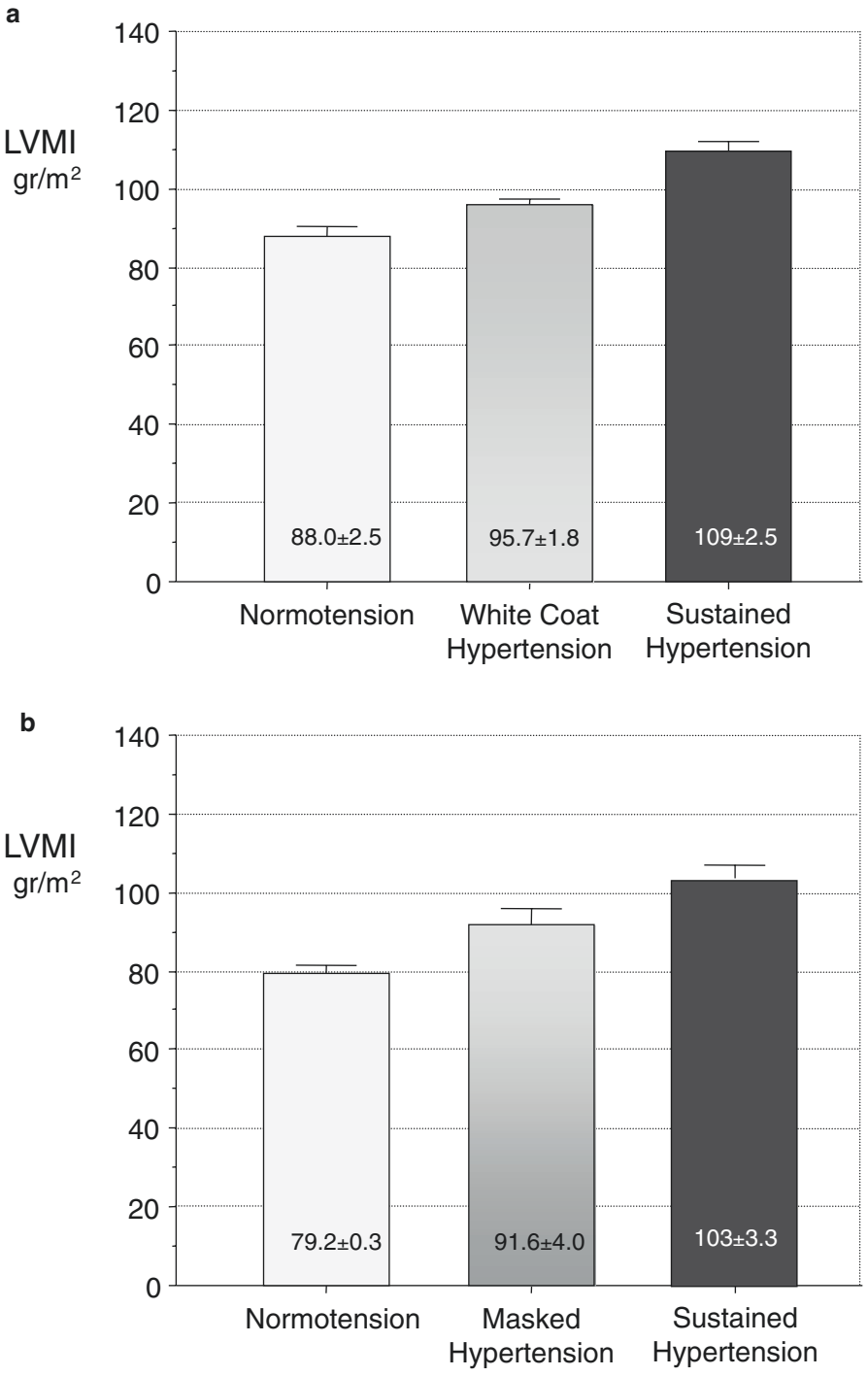



**Fig. 35.2** (**a**) Average left ventricular mass index (LVMI) in true normotensive, white coat hypertensive and sustained hypertensive subjects (ref. [21]). (**b**) Average left ventricular mass index (LVMI) in true normotensive, masked hypertensive and sustained hypertensive subjects (ref. [45])

subjects (760 μm, $p$ 0.001). After this pioneering report, numerous studies carried out in untreated and treated hypertensives have investigated the association between carotid damage and WCH. We also performed a meta-analysis on a pooled population from ten studies including 3478 untreated subjects, namely, 940 normotensive, 666 WCH and 1872 hypertensive individuals [23]. Our results documented that a progressive increase in common carotid IMT occurred from normotensive (718 ± 36 μm) to WCH (763 ± 47 μm) and hypertensive subjects (817 ± 47 μm) (Fig. 35.3a).

Taken together these findings convey the notion that WCH is a risk factor for development of subclinical cardiac and extra-cardiac organ damage.

Although numerous studies have addressed the prognostic significance of WCH, cardiovascular risk related to this condition is still debated [24].

In recent meta-analyses, the incidence of cardiovascular disease and mortality in WCH individuals has been reported to be either similar as in normotensive subjects or intermediate between normotensive and hypertensive patients.

In a pooled population of 7961 untreated subjects (16% WCH), Pierdomenico et al. [25] showed that cardiovascular risk was similar in WCH as in true normotensive subjects. The International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes (IDACO) Study [26] evaluating the prognostic significance of WCH in older persons with isolated systolic hypertension reported that untreated WCH and normotensive subjects were at similar risk.

On the contrary, a recent meta-analysis by Briasoulis et al. [27], including 29,100 participants from 14 studies (13,538 normotensive, 4806 WCH and 10,756 sustained hypertensive subjects), documented that WCH subjects had higher rates of cardiovascular morbidity and mortality, but not significantly different rates of all-cause mortality and stroke compared to normotensive subjects. Of note, in this study, cardiovascular events, all-cause mortality, and stroke rates were significantly greater in sustained hypertensive than in WCH subjects.

## 35.3 Masked Hypertension

The term MH was first used in the early 2000s by Pickering et al. [28] to define the hypertensive condition not identified by routine office BP measurements. An increasing number of cross-sectional and longitudinal studies have subsequently reported that this BP phenotype is associated with prevalent organ damage and, more importantly, with an increased risk of cardiovascular events [29, 30]. Out-of-office BP, indeed, either monitored at home or in ambulatory conditions over 24 h, has been shown to have a greater prognostic value than clinical BP readings. Several aspects concerning MH are still debated; in particular controversy exists about methods (i.e. home versus ambulatory BP) more reliably detecting subjects with elevated BP in out-of-the office environment and about MH actual prevalence in the general population, its clinical correlates and reproducibility over time [31–33].

MH has been estimated to occur in approximately 10–25% of individuals, this wide range depending on methods and diagnostic criteria used to detect this condition as well as on clinical characteristics of study samples (i.e. general population,

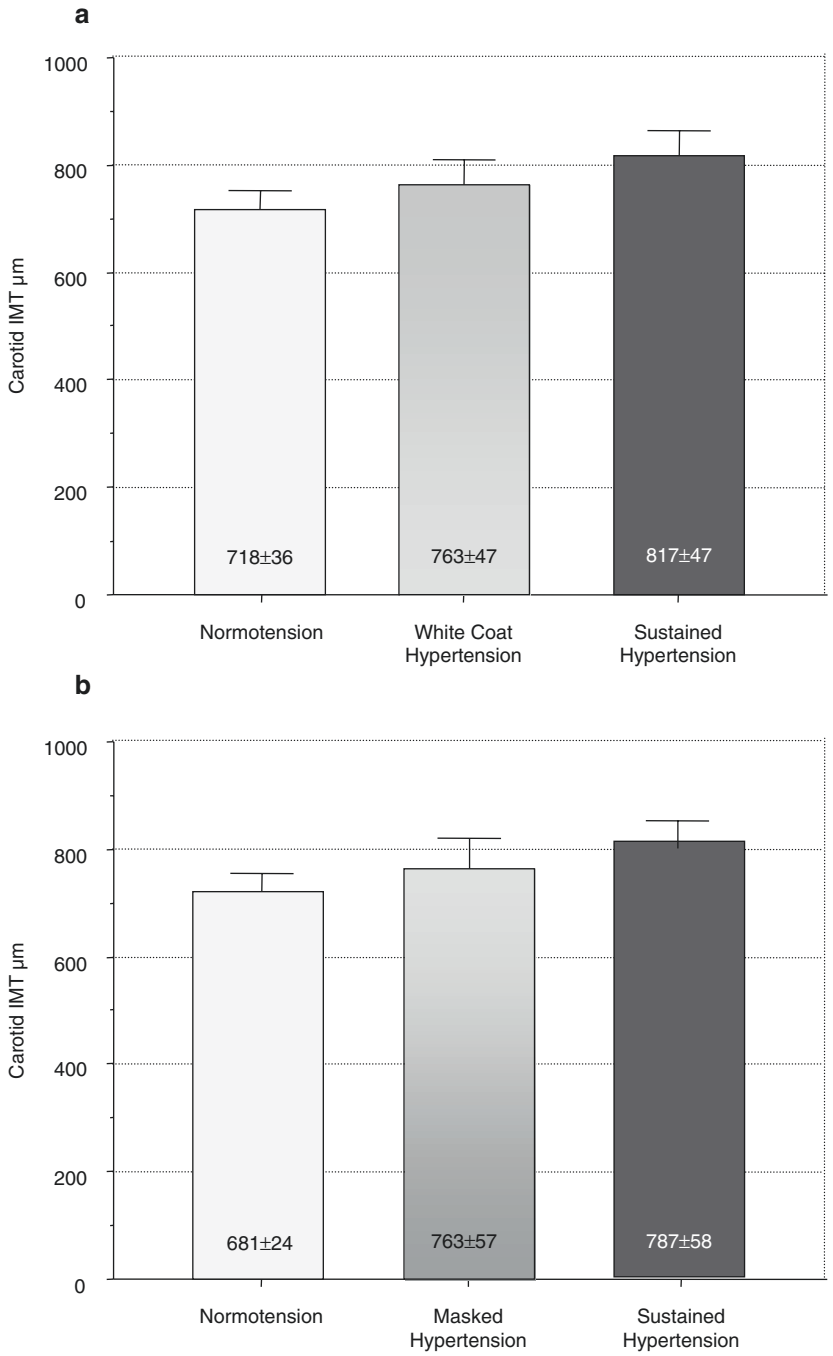



**Fig. 35.3** (**a**) Average carotid intima-media thickness (IMT) in true normotensive, white coat hypertensive and sustained hypertensive subjects (ref. [23]). (**b**) Average carotid intima-media thickness (IMT) in true normotensive, masked hypertensive and sustained hypertensive subjects (ref. [46])

subjects with suspected hypertension, diabetes, chronic renal disease, obesity, sleep apnoea syndrome).

In their landmark study, Liu et al. [29] reported that 61 out of 295 clinically normotensive subjects (20%) examined in a hypertension outpatient clinic had daytime ambulatory systolic or diastolic BP exceeding 134/90 mmHg. Body mass index, cholesterol levels and nicotine use tended to be higher in MH subjects compared to true normotensives. In a retrospective analysis of 1494 ABPMs performed in untreated and treated subjects of a community hospital for clinical indications, Ben-Dov et al. [34] reported an 11% prevalence of MH defined according to office and daytime ABPM cut-offs of 140/90 mmHg and 135/85 mmHg, respectively. MH prevalence was related with male gender, younger age and higher daytime heart rate. In a study by de La Sierra et al. [12], based on a sub-analysis of the Spanish ABPM Registry, 76 out of 839 untreated subjects (9%) were found to have office BP <140/90 mmHg and 24-h ABPM >130/80 mmHg.

In a cross-sectional study including 1492 untreated and treated men and women affected by chronic kidney disease enrolled in the Chronic Renal Insufficiency Cohort Study, MH prevalence was 27.8% [35]. Compared with patients with sustained normotension, those with MH had a more advanced renal damage in terms of lower glomerular filtration rate and higher proteinuria.

A number of studies evaluated the magnitude of MH phenomenon in general population cohorts. In the Ohasama population, 10% of subjects with normal screening BP values displayed mildly elevated average 24-h ABPM (i.e. ranging between 134/79 and 144/85 mmHg). A fraction of these subjects, approximately 3%, showed 24-h ABPM levels equal or even higher than 145/86 mmHg [36]. In the PAMELA study, the only published study providing information on MH based on either home self-measured BP or ABPM, this condition involved from 9 to 12% of the population sample of untreated adult and elderly individuals, the variable prevalence depending on whether MH was defined by ambulatory or home BP, diastolic or systolic BP values [11]. Findings from the Jackson Heart Study, an African American population-based cohort including 909 participants, provided a new piece of information about the association of MH and prehypertension (office systolic BP from 120 to 139 mmHg and diastolic BP from 80 to 89 mmHg) [37]. Among participants with office systolic/diastolic BP <140/90 mm Hg, the prevalence of MH (average daytime BP > 135/85 mmHg) and prehypertension was 27.5% and 62.4%, respectively. Notably, MH prevalence among subjects with prehypertension was significantly higher than in those with normal BP (36.3% versus 12.9%, respectively) (Fig. 35.4).

Clinical factors associated with MH have not been fully elucidated, so far. Some reports indicated that male sex, older age, high normal office BP, low physical activity, obesity, current smoking and habitual alcohol drinking were the main variables differentiating MH individuals from true normotensives [38–40]. The association between older age and MH has not been confirmed by a study aimed at assessing the age-specific prevalence of MH in 9550 individuals out of antihypertensive treatment. The prevalence rate of such BP phenotype in men >70 years was twofold lower than in men aged 40 to 50 years [41].

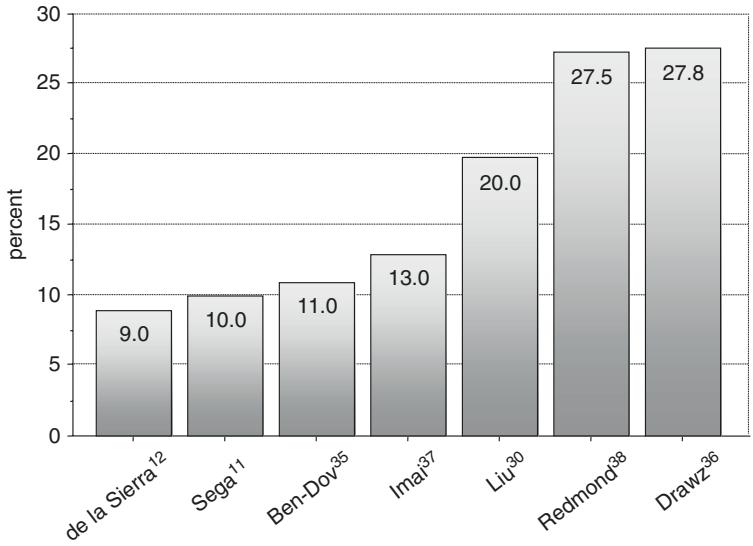



**Fig. 35.4** Prevalence rates of masked hypertension in seven studies published from 1999 to 2016

Viera et al. [42] examined the factors that, in addition to prehypertensive office BP levels, may improve MH detection among 340 individuals at otherwise low risk. The authors found that no demographic, clinical or psychosocial parameters, such as gender, physical activity or working out of home, ameliorated MH prediction in subjects with prehypertension. Although literature findings on demographic and clinical correlates of MH are inconclusive, it is conceivable that sympathetic activation triggered by stress, anxiety, job or physical activity, smoking, alcohol consumption or sleep apnoea plays a central role in subjects with MH.

One major limitation of studies assessing demographic and clinical characteristics related to MH is the limited evidence about the persistence of this BP pattern over time. In the vast majority of studies, indeed, MH was diagnosed on the basis of a single ABPM or home monitoring. A report by Trudel et al. [33] examining the reproducibility of MH among 1669 white-collar workers over a 5-year period of follow-up showed that prevalence of this BP pattern was 38% and 18.5% after 3 and 5 years, respectively, and the progression from MH to sustained hypertension was 26% and 37%, respectively [33]. Data from the Spanish ABPM showed that progression from MH to sustained hypertension involved approximately one third of patients during a median period of observation of 3 months [12]. Overall, these findings support the view that MH may be regarded as transient status in a large fraction of the population.

MH phenomenon has been consistently reported to be associated to subclinical damage in a variety of organs. More than two decades ago, Liu et al. [29] investigated for the first time the impact of MH on target organ damage in 295 clinically normotensive adults and 64 sustained hypertensive patients. The authors showed that LV mass index in 61 MH subjects was higher than in 234 true normotensives

(86 ± 16 g/m$^2$ versus 73 ± 14 g/m$^2$, respectively) and similar as in sustained hypertensives (90 ± 18 g/m$^2$), despite an average difference in the office BP of 35/16 mmHg between these groups.

In the early 2000s, Mancia's group [11] documented that in the PAMELA population, LVH prevalence in MH subjects (14%) was similar as in WCH subjects (15%), lower than in sustained hypertensives (26%), but much greater than in subjects with office and out-of-office normotension (4%).

After these pioneering observations, a number of studies have evaluated the association between MH and organ damage in different clinical settings. We investigated the impact of MH on LV mass index and microalbuminuria long-term variations in 80 treated nondiabetic hypertensives [43]. Clinic BP and ABPM measurements, echocardiography and 24-h urine collection for microalbuminuria were undertaken at baseline and after an average follow-up of 30 months. A significant decrease of LV mass index and microalbuminuria was observed in the 51 patients with office and ambulatory BP control, but not in the 29 patients with MH.

A subsequent cross-sectional study by Tomiyama et al. [44] conducted in 332 treated hypertensive patients confirmed previous evidence by showing that LVMI was higher in MH than in counterparts with normal office and out-of-office BP (136 ± 31 vs. 115 ± 28 g/m$^2$, respectively), and the same was true for LV relative wall thickness (0.49 ± 0.09 vs. 0.46 ± 0.07, respectively). As for LV geometric patterns, the rate of concentric LVH was higher in MH compared to controlled group (48 vs. 28%). From multivariate analyses, MH turned out to be a predictor of LV concentric hypertrophy independent of age, sex, hypertension duration, antihypertensive treatment and ABPM levels.

The study by Sharman et al. [32] was focused on the association between MH and left ventricular remodelling in a sample of 72 nondiabetic subjects free of cardiovascular disease with an exaggerated BP response to maximal treadmill exercise (i.e. systolic BP ≥ 210 mmHg in men, ≥190 mmHg in women or diastolic BP >105 mmHg in both genders). The authors found that ambulatory hypertension was present in the majority of these subjects (58%) and was associated with higher LV mass, LV relative wall thickness and prolonged mitral deceleration time.

Two recent meta-analyses of our own group provided a further contribution on MH and cardiovascular organ damage, as assessed by cardiac and carotid ultrasonography.

From the analysis of pooled data from 12 studies published since 1999, including a total of 2467 normotensive, 776 MH and 1641 sustained hypertensive subjects identified by ABPM, we found that LV mass index showed a progressive increase from normotensive (79.2 ± 0.35 g/m$^2$), to MH (91.6 ± 4.0 g/m$^2$), to hypertensive subjects (102.9 ± 3.3 g/m$^2$) [45] (Fig. 35.2b). Prevalence rates of LVH in normotensive controls, MH and sustained hypertensive subjects were 3.7%, 14.1% and 11.3%, respectively.

A further meta-analysis of 2752 untreated subjects (1039 normotensive, 497 MH and 766 hypertensive individuals) from five studies revealed that common carotid IMT progressively increased from normotensive (681 ± 24 μm), to MH (763 ± 57 μm), to sustained hypertensive subjects (787 ± 58 μm) [46] (Fig. 35.3b).

A consisting body of evidence supports the notion that MH is a BP trait associated with increased risk of cardiovascular events as compared to sustained normotension [2, 25, 30]. In a population-based cohort of 578 untreated 70-year-old men, Bjorklund et al. [47] reported that individuals with MH exhibited a similar incidence of fatal and non-fatal coronary events, stroke and peripheral vascular deaths as sustained hypertensives, the relative risk being approximately threefold in MH than in true normotensives.

In the PAMELA population, the incidence of cardiovascular deaths showed a gradual increase from true normotension to WCH, MH and sustained hypertension independently of major cardiovascular risk factors including age and sex [2]. The different trend in mortality across the four BP phenotypes was independent on whether these conditions were detected by office versus ambulatory or office versus home BP.

The adverse prognostic significance of MH reported by single studies was confirmed by the findings of meta-analyses performed in the last decade [25, 48–50] and is in keeping with the view that out-of-office BP, either monitored at home or in ambulatory conditions, is a powerful predictor of cardiovascular events.

Tailored interventions on lifestyle aimed at treating the modifiable risk factors associated with MH, including obesity, diabetes, stress and sleep apnoea, and avoidance of smoking and alcohol abuse are strongly recommended by current hypertension guidelines.

A further emerging strategy in managing MH is the reduction of ambulatory BP (or home BP) using antihypertensive drugs, despite the presence of normal office BP, and then performing periodic ABPM to assess on-treatment ambulatory or home BP. So far, the effect of BP-lowering medications in the MH setting has been tested by few studies. In a randomized, placebo-controlled study of 115 patients with an exaggerated response to exercise (40% with MH), administration of 25 mg/dL of spironolactone for 3 months reduced exercise BP, 24-h ambulatory BP and LV mass index [51]. Effectiveness and safety of olmesartan-based therapy in WCH and MH has been recently evaluated in a large-scale Japanese study [52]. The authors reported that olmesartan was safe and useful in both BP categories, by reducing office BP in WCH and home BP in MH, respectively. In a practical therapeutic approach, a sub-classification of MH in isolated daytime or nocturnal MH may be useful for guiding anti-antihypertensive treatment. Indeed, in isolated daytime MH morning, administration of relatively short-acting antihypertensive medications would be the preferred choice; conversely, in nocturnal MH, a chrono-therapeutic intervention with bedtime administration of BP-lowering drugs is recommended (see chapter on nocturnal hypertension).

**Conclusions**

WCH and MH are frequent BP phenotypes in the general population that can be detected by combined office and out-of-office BP measurements. Both conditions convey an increased risk of incident-sustained hypertension, target organ damage and cardiovascular morbidity and mortality. In particular, MH phenotype appears to have a worse cardiovascular prognosis than WCH [16, 50] and to

carry a similar risk as sustained hypertension, at variance from WCH. Accordingly, a different approach is recommended by guidelines for the management of these conditions [16]: both lifestyle measures and antihypertensive drug treatment should be considered in MH, whereas in WCH at low cardiovascular risk (i.e. without additional risk factors and or target organ damage), interventions should be limited to lifestyle changes accompanied by a close follow-up.

**Disclosure** The authors report no conflicts of interest.

## References


1. Mancia G, Verdecchia P (2015) Clinical value of ambulatory blood pressure, evidence and limits. Circ Res 116:1034–1045
2. Mancia G, Facchetti R, Bombelli M et al (2006) Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. Hypertension 47:846–853
3. Ayman D, Goldshine AD (1940) Blood pressure determinations by patients with essential hypertension: the difference between clinic and home readings before treatment. Am J Med Sci 200:465–470
4. Mancia G, Bertinieri G, Grassi G et al (1983) Effects of blood pressure measurements by the doctor on the patient's blood pressure and heart rate. Lancet 2:695–698
5. Pickering TG, James GD, Boddie G et al (1988) How common is white-coat hypertension? JAMA 259:225–228
6. Owens P, Atkins N, O'Brien E (1999) Diagnosis of white coat hypertension by ambulatory blood pressure monitoring. Hypertension 34:267–272
7. Dolan E, Stanton A, Atkins N et al (2004) Determinants of white-coat hypertension. Blood Press Monit 9:307–309
8. Verdecchia P, Palatini P, Schillaci G et al (2001) Independent predictors of isolated clinic ("white-coat hypertension"). J Hypertens 19:1015–1020
9. Trenkwalder P, Plaschke M, Steffes-Tremer I, Lydtin H (1993) "white coat" hypertension and alerting reaction in elderly and very elderly hypertensive patients. Blood Press 2:262–271
10. Cuspidi C, Meani S, Fusi V et al (2007) How reliable is isolated clinic hypertension defined by a single ambulatory blood pressure monitoring? J Hypertens 25:315–320
11. Sega R, Trocino G, Lanzarotti A et al (2001) Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension: data from the general population (Pressione Arteriose Monitorate E Loro Associazioni [PAMELA] Study). Circulation 104:1385–1392
12. de la Sierra A, Vinyoles E, Banegas JR et al (2016) Short-term and long-term reproducibility of hypertension phenotypes obtained by office and ambulatory blood pressure measurements. J Clin Hypertens (Greenwich) 18(9):927–933. doi:10.1111/jch.12792. [Epub ahead of print]
13. Palatini P, Dorigatti F, Roman E et al; on behalf of the Harvest Study Investigators. (1998) White-coat hypertension: a selection bias? J Hypertens 16:977–984
14. Schillaci G, Verdecchia P, Porcellati C et al (2000) Continuous relation between left ventricular mass and cardiovascular risk in essential hypertension. Hypertension 35:580–586
15. O'Leary DH, Polak JF, Kronmal RA et al (1999) Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med 340:14–22
16. Mancia G, Fagard R, Narkiewicz K et al (2013) 2013 ESH/ESC guidelines for the management of hypertension. J Hypertens 31:1281–1357
17. Palatini P, Mormino P, Santonastaso M et al (1998) Target-organ damage in stage I hypertensive subjects with white-coat and sustained hypertension: results from the Harvest study. Hypertension 31:57–63

18. Muldoon ME, Nazzaro P, Sutton-Tyrrell K, Manuck SB (2000) White-coat hypertension and carotid artery atherosclerosis: matching study. Arch Intern Med 160:1507–1512
19. Cavallini MC, Roman MJ, Pickering TG, Schwartz JE, Pini R, Devereux RB (1995) Is white coat hypertension associated with arterial disease or left ventricular hypertrophy? Hypertension 26:413–419
20. Cuspidi C, Marabini M, Lonati L et al (1995) Cardiac and carotid structure in patients with established hypertension and white-coat hypertension. J Hypertens 13:1707–1711
21. Cuspidi C, Rescaldani M, Tadic M et al (2015) White-coat hypertension, as defined by ambulatory blood pressure monitoring, and subclinical cardiac organ damage: a meta-analysis. J Hypertens 33:24–32
22. Tadic M, Cuspidi C, Ivanovic B et al (2016) Influence of white-coat hypertension on left ventricular deformation 2- and 3-dimensional speckle tracking study. Hypertension 67:592–596
23. Cuspidi C, Sala C, Tadic M et al (2015) Is white-coat hypertension a risk factor for carotid atherosclerosis? A review and meta-analysis. Blood Press Monit 20:57–63
24. Mancia G (2016) Clinical significance of white-coat hypertension. J Hypertens 34:623–626
25. Pierdomenico SD, Cuccurullo F (2011) Prognostic value of white coat and masked hypertension diagnosed by ambulatory monitoring in initially untreated subjects: an updated meta-analysis. Am J Hypertens 24:52–58
26. Franklin SS, Thijs L, Hansen TW et al (2012) Significance of white coat hypertension in older persons with isolated systolic hypertension: a meta-analysis using the International Database on ambulatory blood pressure monitoring in relation to cardiovascular outcomes population. Hypertension 59:564–571
27. Briasoulis A, Androulakis E, Palla M et al (2016) White-coat hypertension and cardiovascular events: a meta-analysis. J Hypertens 34:593–599
28. Pickering TG, Davidson K, Gerin W, Schwartz JE (2002) Masked hypertension. Hypertension 40:795–796
29. Liu JE, Roman MJ, Pini R et al (1999) Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure. Ann Intern Med 31:564–572
30. Bobrie G, Clerson P, Menard J et al (2008) Masked hypertension: a systematic review. J Hypertens 26:1715–1725
31. Hanninen MRA, Niiranen TJ, Puukka PJ, Jula AM (2010) Comparison of home and ambulatory blood pressure measurement in the diagnosis of masked hypertension. J Hypertens 28:709–714
32. Sharman JE, Hare JM, Thomas S et al (2011) Association of masked hypertension and left ventricular remodeling with the hypertensive response to exercise. Am J Hypertens 24:898–903
33. Trudel X, Milot A, Brisson C (2013) Persistence and progression of masked hypertension: a-5 year prospective study. Int J Hypertens 2013:836387
34. Ben-Dov IZ, Ben-Arie L, Mekler J, Bursztyn M (2005) In clinical practice, masked hypertension is a common as isolated clinic hypertension: predominance of younger men. Am J Hypertens 18:589–593
35. Drawz PE, Alper AB, Anderson AH et al (2016) Masked hypertension and elevated Nighttime blood pressure in CKD: prevalence and association with target organ damage. Clin J Am Soc Nephrol 11:642–652
36. Imai Y, Tsuji I, Nagai K et al (1996) Ambulatory blood pressure monitoring in evaluating the prevalence of hypertension in adults in Ohasama, a rural Japanese community. Hypertens Res 19:207–212
37. Redmond N, Booth JN, Tanner RM et al (2016) Prevalence of masked hypertension and its association with subclinical cardiovascular disease in African Americans: results from the Jackson Heart Study. J Am Heart Assoc 5:e002284
38. Hanninen MRA, Niiranen TJ, Puukka PJ et al (2011) Determinants of masked hypertension in the general population: the Finn-Home study. J Hypertens 29:1880–1888
39. Kramer CK, Leitao CB, Canani LH et al (2009) Blood pressure response to exercise in type II diabetes mellitus patients with masked hypertension. J Hum Hypertens 23:620–622

40. Makris TK, Thomopoulos C, Papadopoulos DP et al (2009) Association of passive smoking with masked hypertension in clinically normotensive nonsmokers. Am J Hypertens 22:853–859
41. Conen D, Aeschbacher S, Thijs L et al (2014) Age-specific differences between conventional and ambulatory daytime blood pressure values. Hypertension 64:1073–1079
42. Viera AJ, Lin FC, Tuttle LA et al (2015) Examination of several physiological and psychosocial factors potentially associated with masked hypertension among low-risk adults. J Clin Hypertens (Greenwich). doi:10.1111/jch.12761. [Epub ahead of print]
43. Cuspidi C, Meani S, Fusi V et al (2005) Isolated ambulatory hypertension and changes in target organ damage in treated hypertensive patients. J Hum Hypertens 19:471–477
44. Tomiyama M, Horio T, Yoshii M et al (2006) Masked hypertension and target organ damage in treated hypertensive patients. Am J Hypertens 19:880–886
45. Cuspidi C, Sala C, Tadic M et al (2015) Untreated masked hypertension and subclinical cardiac damage: a systematic review and meta-analysis. Am J Hypertens 28:806–813
46. Cuspidi C, Sala C, Tadic M et al (2015) Untreated masked hypertension and carotid atherosclerosis: a meta-analysis. Blood Press 24:65–71
47. Bjorklund K, Lind L, Zethelius B et al (2003) Isolated ambulatory hypertension predicts cardiovascular morbidity in elderly men. Circulation 107:1297–1302
48. Bobrie G, Chatellier G, Genes N et al (2004) Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. JAMA 291:1342–1349
49. Fagard RH, Cornelissen VA (2007) Incidence of cardiovascular events in white coat, masked and sustained hypertension versus true hypertension. J Hypertens 25:2193–2198
50. Stergiou GS, Asayama K, Thijs L et al (2014) Prognosis of white coat and masked hypertension: International Database of Home blood pressure in relation to Cardiovascular Outcome. Hypertension 63:675–682
51. Hare JL, Sharman JE, Leano R et al (2013) Impact of spironolactone on vascular, myocardial, and functional parameters in untreated patients with a hypertensive response to exercise. Am J Hypertens 26:691–699
52. Kushiro T, Kario K, Saito I et al (2015) Effectiveness of olmesartan-based treatment on home and clinic blood pressure in elderly patients with masked and white coat hypertension. Hypertens Res 38:178–185

# Isolated Systolic Hypertension: In the Young and in the Elderly

# 36

Csaba Farsang

## Abbreviations

| | |
|---|---|
| ACCOMPLISH | Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension |
| ACEI | Angiotensin-converting enzyme inhibitors |
| ARB | Angiotensin AT-1 receptor antagonists |
| BBL | Beta blockers |
| BP | Blood pressure |
| BPLTTC | Blood Pressure Lowering Treatment Trialists' Collaboration |
| CCB | Calcium channel blockers |
| CHD | Coronary heart disease |
| CHEP | Canadian Hypertension Educational Programme |
| CHF | Congestive heart failure |
| CKD | Chronic kidney disease |
| cPP | Central pulse pressure |
| cSBP | Central SBP |
| CV | Cardiovascular |
| CVD | Cardiovascular disease |
| DALY | Disability-adjusted life-years |
| DBP | Diastolic blood pressure |
| DIU | Diuretics |
| eGFR | Estimated glomerular filtration rate |
| ESC | European Society of Cardiology |
| ESH | European Society of Hypertension |

C. Farsang
St. Imre University Teaching Hospital, Metabolic Centre,
Tétényi Street 12-16, Budapest 1115, Hungary
e-mail: hunghyp@t-online.hu



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_36

| | |
|---|---|
| EUROPA | EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease |
| EWPHE | European Working Party on High Blood Pressure in the Elderly |
| HOPE | Heart Outcomes Prevention Evaluation |
| HR | Hazard ratio |
| HTN | Hypertension |
| HYVET | Hypertension in the Very Elderly Trial |
| INSIGHT | International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment |
| INVEST | International Verapamil SR/Trandolapril Study |
| ISH | Isolated systolic hypertension |
| JNC | Joint National Committee |
| LIFE | Losartan Intervention for Endpoint Reduction |
| MI | Myocardial infarction |
| MRC | Medical Research Council |
| NORDIL | Nordic diltiazem |
| NSAID | Nonsteroidal anti-inflammatory drug |
| NT | Normotension |
| PP | Pulse pressure |
| PROGRESS | Perindopril Protection against Recurrent Stroke Study |
| PWV | Pulse wave velocity |
| RAAS | Renin-angiotensin-aldosterone system |
| RAS | Renin-angiotensin system |
| RCT | Randomised controlled trial |
| RR | Relative risk |
| SAVE | Survival and ventricular enlargement |
| SBP | Systolic blood pressure |
| SCOPE | Study on COgnition and Prognosis in the Elderly |
| SHEP | Systolic Hypertension in the Elderly Program |
| SNS | Sympathetic nervous system |
| SOLVD | Studies of Left Ventricular Dysfunction |
| SPRINT | Systolic Blood Pressure Intervention Trial |
| STONE | Shanghai Trial of Nifedipine in the Elderly |
| Syst-China | Systolic Hypertension in China |
| Syst-Eur | Systolic Hypertension in Europe |
| WCH | White coat hypertension |
| WHO-ISH | World Heart Organisation-International Society of Hypertension |

## 36.1 Definition and Classification

The *definition* of isolated systolic hypertension (ISH) is unchanged in 2003–2007–2013 ESH/ESC guidelines [1]. It can be diagnosed when systolic blood pressure (SBP) ≥140 and diastolic blood pressure (DBP) <90 mmHg.

The *classification* of ISH is similar to other forms of hypertension (HTN):

- Grade I: SBP ≥140, DBP <90 mmHg
- Grade II: SBP: 160–179 mmHg, DBP <90 mmHg
- Grade III: SBP: ≥180 mmHg, DBP <90 mmHg

The same classification is used in young, middle-aged and elderly subjects.

## 36.2 Prevalence

A study of 27,783 subjects, aged 15–60 years, untreated for HTN from a cohort of employees formed to study the incidence of HTN in the French working population showed that the prevalence of ISH in the young was 6.9% in men, 2.3% in women. This prevalence increased at 40–44 years to about 10%. The pulse pressure (PP) in subjects with ISH (46.9 mmHg) was significantly higher than in the normotensive group. Heart rate was higher in ISH than in normotensives (NT) [2]. ISH is more prevalent in elderly hypertensives, since SBP rises with advancing age, whereas DBP usually tends to decrease. As a consequence, PP increases. It appears that elevated PP is a better predictor of cerebro- and cardiovascular events in elderly hypertensives than a high SBP [3, 4].

Studies indicated that SBP is more predictive for the risk of cardio- cerebrovascular events than DBP. Importance of the increased SBP is underlined by data from 8.69 million participants in studies from 154 countries and used models for 41 other countries to estimate country-level rates of elevated SBP and lost disability-adjusted life-years (DALYs) and deaths from cardiovascular and chronic kidney disease. This study showed that from 1990 to 2015, the number of people with ISH rose by 18%, and the number of death rose by 51%. The DALYs related to elevated SBP increased from 96 million to 143 million [5].

## 36.3 Hypertension in Children and in Adolescents

Many young healthy males have elevated values of brachial SBP (≥140 mmHg) with normal values of brachial DBP (<90 mmHg). These subjects usually have normal central BP. Up to now no evidence is available that they benefit from antihypertensive treatment, as there are prospective data showing that this condition does not necessarily develop into systolo-diastolic hypertension [6]. Diagnostic criteria and treatment for elevated BP in children and adolescents are described in details in the recent ESH guidelines [1, 7]. It is based on the concept that BP in children increases with age and body size, making it impossible to utilise a single-BP level to define HTN, as done in adults. The decision of the 2009 ESH guidelines [8] to use the normative data on auscultatory clinic measurements, providing BP percentiles for each sex, ages from 1 to 17 years and for seven height percentile categories, was confirmed in the recent guidelines [7]. Accordingly, HTN in children, age <16 years, is defined as SBP and/or DBP persistently at least 95th percentile for sex, age and

height measured on at least three separate occasions. In addition, HTN is further classified as Grade I (95th percentile to the 99th percentile plus 5 mmHg) and Grade II (>99th percentile plus 5 mmHg). A consensus in these guidelines was also given that for boys and girls aged 16 or older, the definition of HTN should be based on the absolute cut-off value used for adults, which defines high-normal (130–139/85–89 mmHg) and HTN (≥140/90 mmHg).

## 36.4 Isolated Systolic Hypertension in the Young

### 36.4.1 Prevalence

ISH of youth was first described in 2000 [9]. The pressure wave was recorded at the radial artery by applanation tonometry. In all subjects the mean arterial pressure was normal, and they had a sharper-than-usual systolic peak. The estimated central aortic pressure was considered also normal (<126 mmHg), implying that the abnormality in these young men was an exaggerated amplification of the arterial pressure wave as it progressed to the periphery. By applanation tonometry, an exaggerated amplification of the PP was found in the peripheral circulation. The difference between the aortic and brachial SBP was 31 mmHg [10]. In another study the prevalence of ISH among 174 medical students, who were active in sports, was 12%. Their brachial BP was 147/70 mmHg; the estimated aortic pressure was 116/70 mmHg [11].

### 36.4.2 Pathophysiology

If the peaks of the two (incident and reflected) pressure waves coincide, there will be an exaggerated systolic pressure. The factors that determine where the reflected wave will impinge on the incident wave are those that influence the timing of the reflected wave. If it returns quickly, it amplifies the systolic peak of the next incident wave, but if it comes back later, it will arrive in the diastolic downslope of the wave. The principal factors determining the amplification are the pulse wave velocity (PWV), the distance the wave has to go before it is reflected and the heart rate. In younger subjects, because of more compliant arteries, the PWV is slower, so it takes more time to return, and therefore it is superimposed on the diastolic component of the pressure wave. The distance is related to the height of an individual: in a tall subject the reflected wave will return later than in a short person, so it may not affect the systolic peak. The high heart rate is associated with an increased amplification of the wave in the peripheral circulation, because the duration of systole is shortened, and the reflected wave will begin to impinge on the diastolic portion of the wave [12].

In young persons with high SBP, it takes longer for the reflected wave to return to the ascending aorta than in normotensives. Therefore, the low PWV, which indicates elastic vessels, can enhance the amplification of the pressure wave, while the slow heart rate tends to reduce it. The brachial artery pressure increases because these subjects have a high stroke volume. This is because when the resting cardiac output is normal and the heart rate is slow, there is a compensatory increase in stroke volume.

Elasticity of the great vessels is higher in children, whose SBP amplification is greater (about 20 mmHg), almost twice as in adults [13]. If the aorta is very compliant, it may be able to accommodate the increased stroke volume without any increase of aortic SBP, but the enhanced amplification of the pressure wave in these subjects may lead to an increased systolic pressure in the periphery to above-normal values [9–12].

This condition in youth is defined as SBP at least 95th percentile specific for sex, age and height, with DBP less than 90th percentile [7]. PWV is used for characterising arterial stiffening. Reference values of PWV for children have been defined by recent studies [13–15]. In children the BP only variably predicts increased PWV [16]. Functional changes in large vessels may be the earliest detectable findings in children, for example, in those with familial hypercholesterolemia and chronic kidney disease [17, 18].

The greater amplification of SBP increases SBP in upper limb arteries; consequently this phenomenon increases the presence of ISH. The potential value of central SBP and central pulse pressure (cPP), in the assessment of adolescents with ISH, is still a controversial issue, and the clinical significance of ISH in youth is still debated. The central BP may be especially relevant in asymptomatic children incidentally found to have ISH without target organ damage [7].

It is known that white coat hypertension (WCH) also occurs in children. This phenomenon also contributes to the relative high prevalence of ISH, because the white coat effect predominantly affects SBP. This condition may occur in about 10% of healthy young men. In one study of children with SBP above the 95th percentile, 44% were classified as having WCH [19].

### 36.4.3 Treatment

The best advice is to follow these individuals carefully, but not to start them immediately on medication. On the basis of current evidence, they should be given recommendations on lifestyle. It could be rational to target BP to a BP below the 95th percentiles for age, sex and height, but it is probably wiser and safer to aim at a BP below the 90th percentile, provided this goal can be attained and well tolerated [7].

For pharmacological therapy, long-acting, once-daily drugs are preferred. Special attention should be paid to special conditions (e.g. sport activities) and concomitant diseases (e.g. metabolic abnormalities, diabetes mellitus, chronic kidney diseases, endocrine syndromes). If BP target is not achieved by monotherapy, or in children with higher metabolic or cardiovascular risk, the use of combination therapy (fix combinations are preferred) is recommended, as in adults. Evidence from large randomised clinical trials is lacking for the selection of the best antihypertensive drug in the young with ISH. It seems to be logical that those drugs should be used which have a licence for use in children: angiotensin-converting enzyme inhibitors (ACEI), angiotensin AT-1 receptor antagonists (ARB), calcium channel blockers (CCB) beta blockers (BBL) and diuretics (DIU) and their combinations according to guidelines [1, 7, 8].

## 36.5 Isolated Systolic Hypertension in the Young Adults

### 36.5.1 Importance

Although ISH is also the majority hypertensive subtype in adolescents and young adults, it is frequently unrecognised. An analysis of data from 15,868 men and 11,213 women (mean age of 34, 85% were non-Hispanic white) of the observational study based on outcomes from 18- to 49-year-olds in the *Chicago Heart Association Detection Project in Industry Study* showed that men and women with ISH had a much higher risk of dying from coronary heart disease (CHD) or cardiovascular disease (CVD) during a 31-year follow-up compared with their peers with normal-optimal blood pressure. Women had an especially high risk. Subjects did not have CHD and were not taking antihypertensives when they were enrolled in 1967–1973. About 25% of the men and 13% of the women had ISH. They were more likely to smoke and have higher body mass index and higher cholesterol level as compared with those having normal BP. During a 31-year average follow-up period, both men and women with ISH were more likely to die from CVD than those with optimal-normal blood pressure (the hazard ratio (HR) of men, 1.23, and women, 1.55, after adjustment for several confounders). With ISH men (HR, 1.28) and women (HR, 2.12) had a higher risk of dying from CHD than those in the reference group. Interestingly, having ISH was not linked to an increased risk of dying from stroke [20]. One of the reasons why the prevalence of ISH is increasing in the USA (and probably in other countries) is the obesity epidemic.

### 36.5.2 Treatment

It is well established that the benefits of treatment for ISH among the elderly have been proven. Such evidence does not exist for younger and middle-aged adults. Further research including clinical trials and studies investigating other factors (e.g. central BP monitoring, biomarkers, etc.) to identify younger and middle-aged adults with ISH who are at especially greater risk for developing CV events is needed.

## 36.6 Isolated Systolic Hypertension in the Elderly

### 36.6.1 Importance

#### 36.6.1.1 The Increased SBP

Importance of ISH is stressed because in people 50 years and older, ISH is by far the most common form of clinical hypertension. Because of increasing of elderly population, ISH will soon be the most prevalent form of hypertension. At the age of 65 or more, about 70% of patients have ISH, and in those older than 80 years, the prevalence is above 90% [21]. Until the ages of 50–60 years, both SBP and DBP increase with age. Thereafter, in the majority of cases, SBP increases with age but

DBP reaches a plateau or decreases. The most common cause for the disruption of the correlation between SBP and DBP is the progressive stiffening of the arterial wall indicated by increasing PP. The consequence is the low DBP.

#### 36.6.1.2 The Decreased DBP

Importance of very low DBP is also dangerous [22]. If it is associated with high SBP and high PP, the consequence is the increased risk for CVD. In the analysis of data of >7500 elderly patients with ISH and placebo treatment during randomised controlled trials, a higher death rate was seen with progressively higher SBP, but increases also in mortality were showed with progressively lower DBP at entry [23]. The importance of the low DBP in patients with ISH was stressed also by the *Framingham Heart Study* showing that patients with untreated ISH and DBP <70 mmHg had equivalent CVD risk as those with approximately 20 mmHg higher SBP values and DBP in the range of 70–89 mmHg. In the analysis of the course of >7500 elderly patients with ISH who were left on placebo during multiple randomised controlled trials (RCTs), a continually higher death rate was seen, as expected, with progressively higher SBP on entry, but, surprisingly, similar increases in mortality were seen with progressively lower DBP on entry. When DBP is lowered too much by antihypertensive therapy, similar increase in CV events has also been seen [24–28]. The increased CV risk was shown in a sub-study of *STOP-2* trial including elderly patients with ISH [29]. The analysis of data from the *Systolic Hypertension in the Elderly Program (SHEP)* trial, those who had a cardiovascular event while on antihypertensive drug therapy, had lower DBP than those who did not have an event. The decrease of 5 mmHg in DBP during active treatment was associated with a significant 11% to 14% increases in stroke and cardiovascular events [30].

Low DBP in patients with ISH is frequently associated with diabetes and CVD. In the *National Health and Nutrition Examination Surveys (NHANES)* in the USA between 1999 and 2006, 1520 older (average age, 61.3 years) untreated persons with ISH (average BP, 153.3/73.8 mmHg) were identified. Among them greater prevalence of diabetes (12.6 vs. 6.2%) and also CVD (CHD, heart failure, stroke) and kidney disease, but a lower prevalence of the metabolic syndrome, was found than in those persons with ISH where DBP was higher, 70–89 mmHg [31].

#### 36.6.1.3 The Increased PP

Important role of the increased PP in the *National Health and Nutrition Examination Survey NHANES* was also demonstrated: for each 10-mmHg increase in PP, an 11% increase in risk of stroke and a 16% increase in risk of all-cause mortality were found [32]. Increased PP is also associated with higher risk for developing dementia as shown in the *Hypertension in the Very Elderly Trial (HYVET)* [33]. The 2013 ESH–ESC guidelines on the management of hypertension [1] have suggested that PP may represent an independent risk factor, and that therapeutic studies should henceforth be conducted to assess the benefits of reducing PP in terms of cardiovascular morbidity and mortality, especially among those over 60 years of age. Unfortunately, most of patients with ISH have uncontrolled BP. In a study involving

a general elderly population (over 60 years of age), among uncontrolled patients, 84% were uncontrolled only for SBP (>140 mmHg) [34].

### 36.6.2 Structural Changes

Ageing is associated with increased arterial stiffness due to endothelial dysfunction, vascular remodelling and a change in the extracellular matrix. The development of ISH is also associated with an age-related increase of sodium sensitivity and with the deterioration of endothelial function, mainly responsible for phenotypic changes of aortic smooth muscle cells of arterial compliance through structural and functional changes in large arteries, resulting in collagen accumulation and increased vascular stiffness. In the presence of a high sodium diet, an increased number of attachments between vascular smooth muscle cells and collagen fibres develop. This, with early wave reflections which stresses the arterial wall, also contributes to the increase in stiffness, mainly independent of the mean blood pressure [35]. The increasing arterial stiffness is caused by structural and functional changes in the vascular wall, affecting collagen, extracellular protein matrix and elastin. Structural changes are accompanied with increased collagen with cross-linking and degradation of elastin fibres. These processes mainly involve the intima and media of vascular wall. Consequently the lumen-to-wall ratio and the cross-sectional area of lumen decrease. On the other hand, arterial stiffness of the aorta and other elastic arteries increase. SBP becomes elevated, whereas DBP stays normal or decreases. Aortic calcification is also associated with aortic stiffness in patients with ISH [36, 37].

### 36.6.3 Functional Changes

The development of ISH with increasing age is partly explained by a deterioration of arterial compliance mostly in the large conduit arteries. Endothelial dysfunction together with vascular remodelling and fibrosis will decrease arterial elasticity or increase arterial stiffness [38].

Because of a decrease in elastin fibres and an increase in collagen fibres in the arterial wall, the wave reflections increase leading to a higher second systolic peak. These processes enhance development of ISH. After the ejection of blood from the left ventricle of the heart, the peaks of the forward and backward pulse waves coincide. The brachial artery and aortic waves show a late systolic peak that causes an amplification of the more central waveform; consequently there will be an exaggerated SBP. As the arteries become stiffer with age, pulse wave velocity (PWV) increases, resulting in more rapid wave reflection, and the late systolic peak of the pressure wave causes augmentation in brachial BP. However, in older subjects there is little or no amplification of the wave as it travels to the periphery. The increased arterial load due to increased SBP and arterial wave reflections will promote left ventricular hypertrophy and consequently heart failure and atherosclerotic disease, resulting in CHD, CVD and aortic aneurysms [39]. The proliferation of connective

tissue results in intimal thickening and fibrosis. The increasing vascular stiffness itself also causes a reduction in arterial compliance and the decrease of the 'Windkessel function' of the large arteries. Accordingly, PP and PWV increase, and this is associated with an earlier and enhanced reflection of pressure waves from the periphery, thus causing a disproportionate increase in SBP. However, DBP does not increase and may even be lower as a result of increased arterial stiffness. Ageing is associated with an increase in activity of sympathetic nervous system (SNS) and of renin-angiotensin system (RAS). The increased activity of SNS and the RAS contributes to ventricular remodelling, fibrosis and impaired diastolic relaxation leading to diastolic heart failure in the elderly with ISH. Decreased sensitivity of beta adrenergic receptors can also be found, but the alpha adrenoceptors do not change. So, a shift towards arterial vasoconstriction can be observed [40, 41]. Increased secretion of thyroid hormones—hyperthyroidism—also increases SBP [42, 43]. In addition to the progression of arterial stiffness, a decline in renal function also accelerates the process of increased BP [44].

### 36.6.4 Complications

Although ISH was once thought to be benign, multiple studies over the past decades have shown increased cardiovascular morbidity and mortality in older persons with ISH [32, 44, 45]. Data from large-scale studies demonstrated several complications of ISH, because higher SBP was associated with an increase in several CV risk factors. In addition to office and home blood pressure measurements, ambulatory blood pressure monitoring (ABPM) is also a helpful tool to predict CV risk in patients with ISH [46]. The use of ABPM is stressed because elderly hypertensive patients are at higher risk not only for CVD but also for arrhythmias including atrial fibrillation. The *SHEP* study shed light also on the increased risk of atrial fibrillation in patients with ISH [30, 47, 48]. The *Framingham Heart Study* showed that ISH was associated not only with increased mortality but also CV morbidity as the risk of nonfatal stroke and myocardial infarction was increased three and two times, respectively, in the presence of ISH [44]. In addition to these complications, increased risk of cognitive dysfunction, HF, heart attack, premature death and blindness should also be emphasised.

Ageing process is associated with decreased renal function, and this is also an important factor of patients with ISH [49–51]. The *Kidney Disease: Improving Global Outcomes (KDIGO)* clinical practice guideline for the management of BP in chronic kidney disease (CKD) recommends a BP target of <140/90 mmHg in patients with CKD who have no proteinuria and a stricter target of <130/80 mmHg in patients with albuminuria/proteinuria. In a study multiple SBP and DBP combinations in a national cohort of US veterans with CKD were analysed and found that having a slightly elevated SBP (130–159 mmHg) and DBP 70–98 mmHg was linked with the lowest all-cause mortality. Combinations of lower SBP and DBP were associated with relatively lower mortality only if the lower DBP was above 70 mmHg.

Researchers in an observational study analysed data from more than 650,000 veterans (mean age, 73.8 years) with ISH who were enrolled in Veterans Affairs healthcare facilities throughout the USA from 2004 to 2006 and had CKD but were not on dialysis. 62% of them had stage 3A CKD, and 43% had diabetes. Patients mean baseline BP was 135/72 mmHg. Authors examined 96 possible combinations of SBP and DBP from <80/<40 to >210/>120 mmHg, in 10-mmHg increments. Median follow-up was 5.8 years. During this period more than one third of the patients died. A J-shaped association was found between SBP or DBP and death. Those patients who had stage-1 hypertension had the highest mortality rates, independent of confounders. Having a SBP less than 130 mmHg was associated with greater risk for death across all DBP categories. For the explanation authors opinion was that the patients with lower systolic or diastolic BP may have been sicker [52].

A secondary analysis was made of the data of *International Verapamil SR/Trandolapril Study* (*INVEST*), involving 22,576 clinically stable hypertensive patients with CAD (age ≥50 years). Patients were grouped by age in 10-year increments (aged ≥80, $n = 2180$; 70–<80, $n = 6126$; 60–<70, $n = 7602$; <60, $n = 6668$). They were randomised to either verapamil SR- or atenolol-based treatment strategies, and primary outcome was first occurrence of all-cause death, nonfatal MI, or nonfatal stroke. Increasing age was associated with higher SBP, lower DBP and wider PP ($p < 0.001$). The very old patients had the widest PP and the highest prevalence (23.6%) of primary outcome. The HR for primary outcomes showed a J-shaped relationship among each age group with on-treatment SBP and DBP. At the HR the nadir of SBP increased with increasing age, and then highest (140 mmHg) was in the very old patients. At the HR the nadir of DBP was lower for the very old (70 mmHg). Results were independent of treatment strategy. Authors concluded that the optimal SBP target in very old hypertensive patients with CAD should be somewhat higher and the DPB somewhat lower than in other groups of patients with lower age [53].

In another study data of a population-based prospective study with 9-year follow-up (mean 3.5 years) of 601 people (mean BP was 149/82 mmHg) aged 85 years and above were analysed. During follow-up 479 participants (86.6%) died. Multivariate analysis showed that death was linked—among other medical conditions—to SBP less than 140 mmHg (HR, 1.35). There was a tendency towards lower mortality among persons with a SBP of 160 mmHg or greater. Quite unexpectedly the DBP, the history of hypertension and the use of antihypertensive drugs were not related to mortality. Interestingly, the effect of lower SBP on mortality was particularly evident in patients without cancer, dementia or a history of stroke [54]. However, it is important to note that the low SBP may have been partially related to poor general health and poor vitality, but the very old age represents a special group of people which needs a special attention, particularly when antihypertensive treatment is given to them. The use of BP-lowering medications needs to be further evaluated in this group.

The *Sleep Heart Health Study* showed that sleep disorders are also contributing to the increased BP in patients with ISH [55].

It is interesting to note that in the very-very elderly persons (90+) *development* of hypertension in late-life—if its onset occurs after age 80 years—may protect against dementia. In *The 90+ Study* data of more than 500 participants of survivors from the *Leisure World Cohort Study* (mean age of 93 years) have been analysed. Those who developed hypertension between the ages of 80 and 90 years had a 42% lower risk for dementia than those without hypertension, and those who developed it after age 90 had a 63% lower risk [56].

### 36.6.5 Treatment

When DBP is decreased too much by antihypertensive therapy, increases in CV events have also been seen. Therefore, the high SBP should be lowered with caution not to lower the already low diastolic pressure much further [57]. The primary goal of antihypertensive treatment in the elderly with ISH is to delay and reduce the extent of damage to the heart, the cerebrovascular system and the kidneys and to reduce cardiovascular morbidity and mortality. The necessity to carefully balance the benefits and risks of antihypertensive therapy in the elderly indicates that patients with suspected ISH should undergo careful BP measurements on at least three different occasions before the diagnosis is established and an orthostatic reaction should be evaluated mainly when α-blockers are used. α-Blockers are frequently given to elderly patients with benign prostatic hypertrophy. It is well known that the antihypertensive agents might be causing some harm with respect to falls. One needs to be cautious in the elderly because the majority of older hypertensive patients have other medical conditions, which need to be treated medically, are at higher risk for orthostatic hypotension and are at risk for drug interaction and decreased drug metabolism [58, 59].

The data of a subgroup analysis of the *Felodipine Event Reduction* (*FEVER*) study provided evidence that reducing BP to below 140 mmHg is beneficial in uncomplicated hypertensive patients with Grade I hypertension [60] and also in elderly hypertensives [61].

According to the recent European guidelines, the target BP is to lower BP below 140/90 mmHg, but in patients with diabetes or CKD, the BP target is <130/85 or <130/80 mmHg, respectively [1].

#### 36.6.5.1 Non-pharmacological Treatment

Lifestyle interventions are a crucial element of successful treatment, including a diet low in sodium (salt) and rich in whole grains, fruits and vegetables. Clinical trials have also documented the beneficial effects of weight loss, increased physical activity and limiting alcohol consumption. Losing excess weight, getting regular exercise (which can also help lose weight), stop smoking, reducing sodium (salt) intake to below 6 g/day and consuming fruits, vegetables and whole grains all together may decrease SBP by 8–14 mmHg [1].

#### 36.6.5.2 Pharmacotherapy

If non-pharmacological procedures fail, drug therapy should be considered, especially in elderly patients with a SBP ˃160 mmHg, since their risk of complications is markedly higher. The target for hypertensive elderly patients is based on some data from randomised controlled trials.

Several drug classes, with different mechanisms of action and different side effects, are available for the treatment of hypertension. Five classes of antihypertensive drugs, including DIU, BBL, CCB, ACEI and ARB, are suitable for the initiation and maintenance of antihypertensive therapy (1). In the guidelines, the α-blockers or the BBLs are less frequently suggested as first-line therapy. In addition, if needed for special reasons, other classes of drugs—α-2 adrenoceptor agonists, imidazoline I-1 receptor agonists, direct vasodilators and drugs with combined pharmacodynamics actions—can also be used.

Early clinical trials involving elderly subjects proved that treatment of hypertension in this group of patients protects against the complications of hypertension. In these trials no analysis was made for the subgroup of patients with ISH, but according to epidemiological data, a major percentage of the elderly hypertensive patients in these studies had ISH.

A meta-analysis of outcome trials in patients with ISH showed that active treatment reduced total mortality by 13%, CV mortality by 18%, all CV complications by 26%, stroke by 30% and coronary events by 23%. With drug therapy a better protection against stroke than against acute coronary syndromes was shown. The absolute benefit was best in patients older than 70 years and in those with a history of CV complications or a high PP [23].

According to recent hypertension guidelines and recommendations for clinical practice, pharmacological treatment should be strongly considered in patients with a SBP between 140 and 160 mmHg with concomitant CV risk factors as diabetes, angina pectoris and left ventricular hypertrophy. The drug regimen should be simple, starting with a low dose of a single drug that is titrated slowly [1, 62, 63]. Furthermore, it is important to note that the pharmacokinetic and pharmacodynamic properties change in the elderly [64].

#### 36.6.5.3 Hypertension in the Very Elderly (80+)

Several trials and meta-analyses investigated the effects of antihypertensive management of octogenarians.

The use of antihypertensive drugs (indapamide SR, with perindopril added when needed) to reduce high blood pressure in patients aged 80 years or more in the *Hypertension in the Very Elderly Trial* (*HYVET*) was associated with a significant and marked reduction in the incidence of stroke and heart failure. It also found that treatment reduces all-cause mortality, which means that CV protection translates into increased life expectancy [65]. The 1-year open-label active treatment extension of patients in *HYVET* compared data of octogenarian people previously treated with active drug and those previously on placebo, but continued on active treatment (indapamide SR + perindopril 2–4 mg when needed) with the same target BP of <150/80 mmHg. There were no significant differences for stroke or CV events, but

significant differences were found for total mortality (HR, 0.48; $p = 0.02$) and CV mortality (HR, 0.87; $p = 0.03$). Authors concluded that very elderly patients with hypertension may gain immediate benefit from treatment, and sustained differences in reductions of total mortality and CV mortality reinforce the benefits and support the need for early and long-term treatment [66]. Although the results should be interpreted with caution, the rate of CV events decreased during the additional years of treatment (despite the increased age); the benefits may start soon after the initiation of treatment and increase as it continues. This also means that great attention should be given to maintain BP control in octogenarians [67].

Target BP has been discussed frequently since the publication of the *Systolic Blood Pressure Intervention Trial (SPRINT)* in which authors used unattended BP measurement. It was showing a significant (34%) decrease in the primary endpoint (MI, non-MI-acute coronary syndrome, stroke, acute decompensated HF and CV death) and all-cause mortality (33%) in the group of high CV risk patients with lower SBP in the more intensive arm (SBP ~ 120 mmHg) than in the group in the standard treatment arm (SBP ~ 137 mmHg) [68, 69].

Several data of the *SPRINT* have not been explained. Among them the lack of significant effect in the more intensive arm on some secondary endpoints (stroke, MI, acute coronary syndrome, in patients with CKD, in those aged <75 years, in females, in blacks and in those with previous CVD) should be outlined. Furthermore, no significant effect of the more intensive treatment was found in patients with baseline SBP ˃ 132 mmHg. Most probably the lower incidence of HF drove the primary endpoint to significance range. In addition, more DIU or ACEI or ARB were used in the more intensive arm (all of these types of drugs are indicated also to treat HF), so it is questionable if the lower SBP or the specific pharmacodynamics actions of more antihypertensive drugs can be responsible for the better results [70]. Data from the *SPRINT* also show that in patients without CKD at baseline, the renal outcome of ≥30% decline in eGFR to a value <60 mL/min per 1.73 $m^2$ occurred more frequently in the intensive arm compared to the standard arm. Furthermore, serious adverse events or emergency department visits related to acute kidney injury or acute renal failure were more common in the intensive arm (4.4% vs. 2.6%; HR, 1.71). This is most important when treating patients with CKD [71].

A recent publication investigated the achieved BP levels in older treated hypertensive patients and analysed the data of a representative sample (2551 respondents from a random and representative sample of the adult—20–79 years—population) from the *Ontario Survey on the Prevalence and Control of Hypertension* study. Results showed that intensive BP control (BP <130 or <120 mmHg) was achieved in many patients. Most of these patients (about 93% of them) have ISH [72]. In this study also unattended BP measurement was used, and this probably contributed to the lower SBP by excluding the white coat effect; therefore, it does not correspond to the usual office BP measurement in most clinical trials and surveys. To solve these problems, ambulatory BP monitoring may be helpful [73].

A meta-analysis, based on 6701 patients 80 years and older, of whom 3617 have been treated with at least one antihypertensive drug, showed that a reduction in mortality was achieved in trials with the least BP reductions and the lowest intensity

of therapy. Antihypertensive therapy significantly reduced ($p < 0.001$) the risk of stroke (by 35%), CV events (by 27%) and HF (by 50%) [74].

Meta-regression analysis using data of 123 studies with 613,815 participants showed relative risk reductions proportional to the magnitude of the BP reductions achieved. Every 10 mmHg reduction in SBP significantly reduced the risk of major CVD events (relative risk (RR), 0.80), CHD (RR, 0.83), stroke (RR, 0.73) and HF (RR, 0.72) with a significant, 13% reduction in all-cause mortality (RR, 087). The effect of decreasing SBP on renal failure was not significant (HR, 0.95) [75].

In a more recent meta-analysis, data of 55,163 patients included in 17 trials were analysed. Authors assessed the optimal SBP target to balance improved outcomes with potential adverse effects. The target SBP of <120 mmHg was associated with a significant decrease in the risk of stroke and MI compared with SBP <140 mmHg, or <150, and <160 mmHg. There were no significant differences in the risk of death, CVD or HF between the data from these four groups. However, the target of <120 mmHg was associated with a significantly increased risk of adverse effects compared with <140 or <150 mmHg. For the estimation of the optimal SBP, a target <130 mmHg was found balancing efficacy and safety [76].

#### 36.6.5.4 Selection of Drugs

The selection of the antihypertensive agent should be based on a careful assessment of pathophysiological and clinical parameters in each individual geriatric patient [77]. When deciding on drug therapy, it is important to note that pathophysiological changes associated with ageing can affect both the pharmacokinetics and pharmacodynamics of many cardiovascular drugs [64]. Decrease in renal function, reduction of hepatic blood flow, increased body fat and reduced muscle mass in elderly people can affect distribution, metabolism and elimination of cardiovascular drugs. In addition, changes in end-organ responsiveness (e.g. adrenergic and angiotensinergic receptors) and change in baroreflex sensitivity can also have influence on effects of drugs. As a consequence, orthostatic hypotension may be exaggerated with the use of vasodilators, α-1 adrenoceptor blockers and thiazides (by causing hyponatremia). Slowing of sinus node activity and decreasing atrioventricular conduction can lead to increased sensitivity to the bradycardic effects of BBLs and non-dihydropyridine CCBs such as verapamil or diltiazem. In addition, comorbidities and the drugs against them may increase the risk of side effects of drugs.

It has been long known that non-adherence to prescription drugs among the elderly is a major concern [64, 78].

Numerous RCTs have shown that reducing elevated systolic BP ≥160 mmHg in older adults decreases CV events. Early BP trials compared active treatment—typically with a DIU alone or in combination with a BBL or other drugs—with placebo, whereas trials conducted in the past decade have compared two or more different antihypertensive regimens. In hypertensive adults of any age, however, the initial agent chosen appears less important than the extent of BP reduction achieved, as demonstrated by the *Blood Pressure Lowering Treatment Trialists' Collaboration* (*BPLTTC*) [79]. The European guidelines [1] do not stress the importance of a specific drug class, but it puts more emphasis on the importance of BP reduction.

Several drugs were used in trials involving patients with ISH.

### Diuretics and Beta-Blockers

DIUs have been used for several decades and have been shown to be effective in lowering BP in the elderly population. However, one has to be cautious in using diuretics in the elderly hypertensives because they often do not take enough fluid during the day and get easily dehydrated and develop prerenal insufficiency. Because of a potential hypovolemic status, they are more prone for orthostatic hypotension. Long-term diuretic treatment may have also several metabolic disturbances. It is well known that thiazide DIUs increase serum level of uric acid and, consequently, older hypertensives can become at risk to develop gout. Elderly hypertensives are often prediabetic or have type 2 diabetes, and the intake of thiazide DIU can increase insulin resistance. Aldosterone antagonists are used in resistant hypertension and may cause hyperkalaemia. In the elderly patients, serum electrolyte (potassium, sodium) levels and renal function need to be monitored carefully because elderly hypertensive patients have often renal insufficiency [80, 81].

For decades several guidelines (WHO-ISH, JNC, ESH/ESC, CHEP, etc.) recommended a thiazide or a thiazide-type DIU for treatment of hypertension in the elderly and also to enhance the efficiency of other antihypertensive drugs.

Thiazides have been shown to be more protective than $\beta$-blockers [82–84].

*Hydrochlorothiazide*, *chlorthalidone* and recently *indapamide* are suggested for antihypertensive drug therapy in the elderly. These agents are generally well tolerated, especially in the lower doses currently recommended. Several RCTs have demonstrated reductions in the incidence of CV events among elderly patients with ISH taking these drugs.

In *European Working Party on High Blood Pressure in the Elderly* (*EWPHE*) trial, 840 patients aged ≥60 years with BP 160/90–239/119 mmHg were randomly assigned to receive *hydrochlorothiazide* (25–50 mg) plus the potassium-sparing DIU *triamterene* (50–100 mg) or to *placebo*. An α-2 adrenoceptor agonist, *methyldopa* 500 mg, was added if BP remained elevated. Active treatment lowered BP by 19/5 mmHg when compared with placebo. Over 7 years of follow-up, active treatment was associated with reduction in CV events of 29 per 1000 person-years and a 38% reduction in the number of CV deaths [85].

In the *Systolic Hypertension in the Elderly Program* (*SHEP*) trial, 4736 patients aged ≥60 years with BP 160–219/<90 mmHg were randomly assigned to receive *chlorthalidone* 12.5 mg or placebo. The dose was doubled and *atenolol* (25–50 mg) was added sequentially if the BP goal was not attained. After 4.5 years the results showed that there was a significantly lower rate of CV events (stroke, MI and HF) in the chlorthalidone-based group than in the placebo group, but effects of drugs on mortality were not significant. After completion of the study, the patients were then given the active chlorthalidone therapy, and the follow-up was 22 years. Then the therapy was associated with a longer life expectancy [30, 83, 86].

In the *HYVET* study (see also above), octogenarian patients were randomised to either a DIU (indapamide 2.5 mg) or placebo. The target BP was <150/80 mmHg. If needed, either an ACEI (*perindopril* 2 or 4 mg) or placebo was added. At ~2 years follow-up, the BP in the active treatment group was 15.0/6.1 mmHg lower than in the placebo group. In an intention-to-treat analysis, active treatment was associated

with a 30% reduction in the rate of fatal or nonfatal stroke, a 39% reduction in the rate of death from stroke, a 21% reduction in the rate of death from any cause, a 23% reduction in the rate of death from CV causes and a 64% reduction in the rate of CHF. Interestingly, fewer serious adverse events were reported in the active treatment group (358 vs. 448) than in the placebo group ($p = 0.001$). An important finding was also that this combination therapy of a DIU and ACEI did not reduce the risk of dementia and cognitive function [65, 87, 88]. There are some limitations of the *HYVET* study as patients with stage I hypertension were not included. Patients were in relatively good physical and mental condition and with a low rate of previous cardiovascular disease. It is not known whether the beneficial effects persist for a longer than 1.8 years period.

Mineralocorticoid receptor antagonist (MRA), *spironolactone*, can be used in resistant hypertension. In this case serum potassium and renal function need to be monitored, because elderly hypertensive patients have often renal insufficiency and the use of this drug can cause hyperkalaemia.

In the *MRC elderly* trial, 4396 hypertensive patients (age, 65–74 years) were randomly assigned to receive a DIU or the BBL atenolol for a follow-up period of 5.8 years. Despite of similar BP reduction in the two active arms, only the DIU reduced significantly the incidence of stroke, coronary events and total CV events. Furthermore, tolerability of the BBL was poor, as dropout rate was of 63% [89].

Despite BBLs being used for the treatment of hypertension in the elderly for decades, the benefits have been less convincing than diuretics. A meta-analysis of ten studies involving 16,154 hypertensive patients (age ≥ 60 years), comparing BBLs with DIUs in hypertensive patients, showed that DIUs were superior to BBLs in preventing strokes, CHD, CV death and all-cause mortality. Thus, the use of BBLs for antihypertensive therapy in the elderly is not favoured [84, 89, 90]. Inferiority of BBLs compared to other antihypertensives may stem from the lesser reduction of central BP [91]. BBLs were inferior to other drugs also for the prevention of major CVD events, stroke and renal failure in a meta-regression analysis of data of 123 studies with 613,815 participants [75].

However, there are still several comorbid conditions in which BBLs need to be considered for the management of hypertensive elderly patients, such as CAD, post-MI, HF, senile tremor and certain types of arrhythmias.

### Calcium Channel Blockers

CCBs have been shown to be well tolerated and very effective in ISH. Several large RCTs have demonstrated the efficiency and safety of CCBs in older patients with hypertension, usually with increased arterial stiffness and reduced vascular compliance, because of their beneficial effects on central BP [91]. Most frequently used ones are the dihydropyridines. Their adverse effects relate to vasodilation (e.g. ankle oedema, headache and, rarely, postural hypotension). There are several indications to choose a CCB in cases of hypertension with concomitant diseases: CAD, angina pectoris and chronic obstructive pulmonary diseases. Non-dihydropyridines (e.g. verapamil and diltiazem) are used to a lesser extent as antihypertensive agents, but mainly in cases of supraventricular arrhythmias, or if dihydropyridines are not tolerated.

In the *Shanghai Trial of Nifedipine in the Elderly (STONE)* study, major reductions in CV endpoints with *nifedipine* were shown [92].

In the *Nordic diltiazem (NORDIL)* prospective, randomised, open, blinded endpoint study, 10,881 patients (aged 50–74 years) were enrolled to show the effects of antihypertensive therapy by diltiazem or BBL and DIU on CV morbidity or mortality (the combined primary endpoint was fatal and nonfatal stroke, MI and other CV deaths). Both SBP and DBP were lowered effectively in the diltiazem-treated patients and also in the DIU and BBL groups by 20.3/18.7 vs. 23.3/18.7 mmHg, respectively ($p < 0.001$). No significant difference was found between the two arms of the study in the primary endpoint. However, in spite of the higher achieved BP in the diltiazem group, fatal and nonfatal stroke occurred only in 159 patients, but 196 in the DIU and BBL (6.4 vs. 7.9 events per 1000 patient-years; $p = 0.04$) [93]. *Systolic Hypertension in Europe* (*Syst-Eur*) double-blind trial included 4695 patients (age ≥ 60 years) with ISH (BP, 160–219/<95 mmHg). Patients were randomly given the dihydropyridine CCB, nitrendipine (with optional add-on enalapril and/or hydrochlorothiazide) or placebo. Data from the active treatment arm were compared with those in placebo. Nitrendipine caused a significant and striking reduction in the incidence of stroke by 42%, and there was also a clear tendency towards a reduction of MI [94, 95]. Nitrendipine therapy was also associated with reductions in the rates of cognitive disorders as well [96].

In the *Systolic Hypertension in China* (*Syst-China*) *study*, Chinese patients with ISH were treated with nitrendipine or placebo. Active treatment with nitrendipine significantly reduced total stroke by 38%, stroke mortality by 58%, all-cause mortality by 39%, CV mortality by 39% and fatal and nonfatal CV events by 37% [97].

The *International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment* (*INSIGHT*) study included more than 11,000 hypertensive patients with coronary artery disease older than 66 years were involved. Patients had additional risk factor, such as diabetes mellitus and hypercholesterolemia. Treatment consisted of nifedipine GITS or hydrochlorothiazide. Although INSIGHT was not a selective ISH trial, it contained a subgroup of patients with ISH which was analysed separately. These patients were more responsive to treatment with nifedipine GITS than those with non-ISH hypertension. It is interesting to note that patients with ISH whose DBP significantly decreased under treatment were smokers with evidence of atherosclerosis [98].

As compared to other types of antihypertensive agents, the beneficial effects of amlodipine were emphasised in older patients [99].

In the *International Verapamil SR/Trandolapril Study* (*INVEST*), two management strategies were compared. Patients were randomised either to the BBL atenolol or to the CCB verapamil. Those randomised to the BBL strategy had lower on-treatment heart rates, but there was no difference in death, MI or stroke compared with a verapamil strategy [100].

In a meta-regression analysis of data of 123 studies with 613,815 participants, CCBs were superior to other drugs for the prevention of stroke. For the prevention of HF, CCBs were inferior and DIUs were superior to other drug classes [75].

### Angiotensin-Converting Enzyme Inhibitors

ACEIs systemically and locally block the conversion of angiotensin I to angiotensin II. Angiotensin II levels are lower with ageing; therefore, theoretically, ACEI should not be as effective as other therapies, but multiple studies (involving mainly HF patients or those with high CV risk) have shown the contrary. There are extensive evidence-based medical data from large trials (SOLVD, SAVE, HOPE, EUROPA, PROGRESS) that ACEIs are beneficial in hypertensive patients frequently having complications (HF, MI, diabetic nephropathy and atherosclerotic disease) being more frequent with advanced age [101–104]. Therefore, ACEI should be considered as the antihypertensive therapy of choice in elderly patients with hypertension with complications (HF, post-MI, diabetes mellitus or CKD). The main adverse effects of ACEI include dry cough, hypotension and, rarely, angioedema or rash. Renal failure and hyperkalaemia can develop mostly if nonsteroidal anti-inflammatory drugs (NSAIDS) or mineralocorticoid receptor antagonists (spironolactone, eplerenone) are also used; therefore, regular monitoring of renal function and electrolytes is mandatory.

Although several randomised clinical trials have demonstrated the beneficial effects of ACEIs either alone or mostly in combinations in elderly hypertensive patients, no specific RCT was aimed at the effects of ACEIs in patients with ISH [63].

### Angiotensin AT-1 Receptor Antagonists

In hypertensive elderly patients preferably in those with diabetes mellitus, ARBs are considered as one of the first-line drugs and also as an alternative to ACEIs in patients with hypertension and HF, who cannot tolerate ACEIs. Although many clinical trials have documented the benefit of ARBs in treating hypertension, experience specific to the elderly is more limited than with DIU or BBL or ACEIs, but there are specific studies aiming at the effects of ARBs in ISH.

Beneficial antihypertensive effect and less side effects of losartan were found in comparison with atenolol in patients with ISH [105].

In the *Losartan Intervention For Endpoint Reduction* (*LIFE*) trial, losartan was more effective than atenolol in reducing the incidence of CV events, particularly stroke, among 9193 patients aged 55–80 years who had hypertension and left ventricular hypertrophy diagnosed by electrocardiography [106]. In a sub-study of the *LIFE* trial involving patients with ISH and older than 67 years, the effect of the losartan-based therapy was more effective for the prevention of the primary endpoint (CV death, nonfatal stroke and nonfatal MI) than in those patients who were younger than 67 years [107]. This difference was not explained by a more pronounced effect of losartan-based treatment on any of the CV risk factors demonstrated to have independent prognostic importance [108].

In a sub-study of the *Study on Cognition and Prognosis in the Elderly* (*SCOPE*), the stroke preventive effect of candesartan was also shown [109]. In another sub-study of *SCOPE* involving patients with ISH, *candesartan* was able also to mitigate the deterioration of cognitive function [110, 111].

In the prospective, randomised, open-label, blinded endpoint study, *Valsartan in Elderly Isolated Systolic Hypertension Study* was investigating if strict BP control

(SBP <140 mmHg) is superior to moderate BP control (SBP between 140 and 150 mmHg) in patients aged more than 70 years with ISH. There was no significant difference in the composite CV endpoint (sudden death, fatal or nonfatal stroke, fatal or nonfatal MI, death because of HF, other CV death, unplanned hospitalisation for CVD and renal dysfunction) between the two groups (intensive vs. moderate) treated by valsartan (40–160 mg daily) with addition of CCB or DIU if needed [112].

### Alpha-1 Adrenoceptor Antagonists

α-Adrenergic blocking agents are used for relieving urinary symptoms related to prostate hypertrophy, a disease frequent in older persons. It is important to note that α-blockers can cause postural (orthostatic) hypotension, which is also frequent in older patients especially if those are treated by thiazide-type diuretics. RCTs investigating the effect of these drugs in patients with ISH are missing.

### 'Centrally Acting' Antihypertensives

The older drugs (e.g. clonidine, guanfacine) are rarely used in some countries, because many patients experience troublesome sedation or dry mouth or some psychiatric complications (e.g. reserpine). The newer drugs, the imidazoline I-1 receptor agonists (rilmenidine, moxonidine), are more frequently used in some countries, mostly in combinations. No results of RCT are available involving patients with ISH.

### Combinations

The most elderly patients with ISH require dual or even triple antihypertensive therapy to control SBP. The preferential double combinations are ACEI + DIU, ARB + DIU, ACEI + CCB, ACEI + CCB + DIU or ARB + CCB + DIU [1].

According to the *Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH)* trial, the combination of ACEI + CCB (benazepril + amlodipine) was superior to that of ACEI + DIU (benazepril + thiazide) in reducing CV events and death among 11,500 high-risk patients with hypertension (mean age was 68.4 years). 66% of patients were 65 years or older and 41% were 75 years or older. For the primary outcome (the composite of death from CV causes, nonfatal MI, nonfatal stroke, hospitalisation for angina, resuscitation after sudden cardiac arrest and coronary revascularization), there was a RR reduction of 19.6% (HR, 0.80; $p < 0.001$). For the secondary endpoint of death from CV causes plus nonfatal MI and nonfatal stroke, there was a RR reduction of 21.2% (HR, 0.79; $p = 0.002$), while for CV events, a RR reduction of 17.4% (HR, 0.83; $p = 0.002$) was found [113].

Physician inertia is still a major problem in treatment of elderly hypertensive patients including those with ISH, as they are reluctant to add more drugs or use of fix combinations (single-pill combination, SPC) if BP is not at target. The advantage of using SPCs is that the number of pills can be reduced and as the components in the SPC have synergism in their antihypertensive and other beneficial effects; therefore, a lower dose can be used with fewer side effects. This leads to a better therapeutic adherence/persistence and consequently to greater patient satisfaction and better BP control.

**Conclusions**

For the drug treatment of patients with ISH, a dihydropyridine CCBs in combination with DIUs, or ACEIs or ARBs could be favoured. BBLs seem to be less effective for prevention of CV events and disease protection in comparison with other antihypertensive drug classes; therefore, they are indicated only for specific concomitant diseases (e.g. CAD, HF). It is important to reduce doctors' therapeutic inertia and to increase patients' adherence/persistence for achieving better blood pressure control in the elderly patients with ISH.

## References


1. Mancia G, Fagard R, Narkiewicz K et al (2013) 2013 ESH/ESC guidelines for the management of arterial hypertension. J Hypertens 31:1281–1357
2. Mallion J-M, Hamici L, Chatellier G et al (2003) Isolated systolic hypertension: data on a cohort of young subjects from a French working population (IHPAF). J Hum Hypertens 17:93–100
3. Nielsen WB, Vestbo J, Jensen GB (1995) Isolated systolic hypertension as a major risk factor for stroke and myocardial infarction and an unexploited source of cardiovascular prevention: a prospective population-based study. J Hum Hypertens 9:175–180
4. Safar ME, Rudnichi A, Asmar R (2000) Drug treatment of hypertension: the reduction of pulse pressure does not necessarily parallel that of systolic and diastolic blood pressure. J Hypertens 18:1159–1163
5. Forouzanfar MH, Liu P, Roth GA et al (2017) Global burden of hypertension and systolic blood pressure of at least 110 to 115 mmHg, 1990-2015. JAMA 317:165–182
6. O'Rourke MF, Adji A (2013) Guidelines on guidelines: focus on isolated systolic hypertension in youth. J Hypertens 31:649–654
7. Lurbe E, Agabiti-Rosei E, Cruickshank JK et al (2016) European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens 34:1887–1920
8. Lurbe E, Cifkova R, Cruickshank JK et al (2009) European Society of Hypertension. Management of high blood pressure in children and adolescents: recommendations of the European Society of Hypertension. J Hypertens 27:1719–1742
9. O'Rourke MF, Vlachopoulos C, Graham RM (2000) Spurious systolic hypertension in youth. Vasc Med 5:141–145
10. O'Rourke MF (2002) From theory into practice: arterial haemodynamics in clinical hypertension. J Hypertens 20:1901–1915
11. Mahmud A, Feely J (2003) Spurious systolic hypertension of youth: fit young men with elastic arteries. Am J Hypertens 16:229–232
12. Wilkinson IB, MacCallum H, Flint L et al (2000) The influence of heart rate on augmentation index and central arterial pressure in humans. J Physiol 525:263–270
13. Milne L, Keehn L, Guilcher A et al (2015) Central aortic blood pressure from ultrasound wall-tracking of the carotid artery in children: comparison with invasive measurements and radial tonometry. Hypertension 65:1141–1146
14. Reusz GS, Cseprekal TM et al (2010) Reference values of pulse wave velocity in healthy children and teenagers. Hypertension 56:217–224
15. Elmenhorst J, Hulpke-Wette M, Barta C et al (2015) Percentiles for central blood pressure and pulse wave velocity in children and adolescents recorded with an oscillometric device. Atherosclerosis 238:9–16
16. Juonala M, Järvisalo MJ, Mäki-Torkko N et al (2005) Risk factors identified in childhood and decreased carotid artery elasticity in adulthood: the Cardiovascular Risk in Young Finns Study. Circulation 112:1486–1493

17. Riggio S, Mandraffino G, Sardo MA et al (2010) Pulse wave velocity and augmentation index, but not intima-media thickness, are early indicators of vascular damage in hypercholesterolemic children. Eur J Clin Investig 40:250–257
18. Sinha MD, Keehn L, Milne L et al (2015) Decreased arterial elasticity in children with nondialysis chronic kidney disease is related to blood pressure and not to glomerular filtration rate. Hypertension 66:809–815
19. Hornsby JL, Mongan PF, Taylor T et al (1991) 'White coat' hypertension in children. J Fam Pract 33:617–623
20. Yano Y, Stamler J, Garside DB et al (2015) Isolated systolic hypertension in young and middle-aged adults and 31-year risk for cardiovascular mortality: the Chicago Heart Association Detection Project in Industry study. J Am Coll Cardiol 65:327–335
21. Burt VL, Whelton P, Roccella EJ et al (1995) Prevalence of hypertension in the U.S. adult population: results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension 25:305–313
22. Smulyan H, Safar ME (2000) The diastolic blood pressure in systolic hypertension. Ann Intern Med 132:233–237
23. Staessen JA, Gasowski J, Wang JG et al (2000) Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. Lancet 355:865–872
24. O'Rourke MF, Frohlich ED (1999) Pulse pressure: is this a clinically useful risk factor? Hypertension 34:372–374
25. Safar ME, Levy BI, Struijker-Boudier H (2003) Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. Circulation 107:2864–2869
26. O'Rourke MF, Nichols WW (2005) Aortic diameter, aortic stiffness, and wave reflection increase with age and isolated systolic hypertension. Hypertension 45:652–658
27. Franklin SS, Lopez VA, Wong ND et al (2009) Single versus combined blood pressure components and risk for cardiovascular disease. The Framingham Heart Study. Circulation 119:243–325
28. Benetos A, Salvia P, Lacolley P (2011) Blood pressure regulation during the aging process: the end of the 'hypertension era'? J Hypertens 29:646–652
29. Ekbom T, Linjer E, Hedner T et al (2004) Cardiovascular events in elderly patients with isolated systolic hypertension: a subgroup analysis of treatment strategies in STOP-Hypertension-2. Blood Press 13:137–141
30. SHEP Cooperative Research Group (1991) Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 265:3255–3264
31. Franklin SS, Chow VH, Mori AD, Wong D (2011) The significance of low DBP in US adults with isolated systolic hypertension. J Hypertens 29:1101–1108
32. Domanski MJ, Davis BR, Pfeffer MA et al (1999) Isolated systolic hypertension: prognostic information provided by pulse pressure. Hypertension 34:375–380
33. Peters R, Beckett N, Fagard R et al (2013) Increased pulse pressure linked to dementia: further results from the Hypertension in the Very Elderly Trial ^ HYVET. J Hypertens 31:1868–1875
34. Perret-Guillaume C, Miget P, Aubry C et al (2006) Blood pressure control by antihypertensive agents in people older than 60. Rev Med Interne 27:285–290
35. Safar ME (2005) Systolic hypertension in the elderly: arterial wall mechanical properties and the renin–angiotensin–aldosterone system. J Hypertens 23:673–681
36. Wallace SM, Yasmin MECM et al (2007) Isolated systolic hypertension is characterized by increased aortic stiffness and endothelial dysfunction. Hypertension 50:228–233
37. McEniery CM, McDonnell BJ, So A et al (2009) Aortic calcification is associated with aortic stiffness and isolated systolic hypertension in healthy individuals. Hypertension 53:524–531
38. Duprez DA, Jacobs DR Jr, Lutsey PL et al (2011) Association of small artery elasticity with incident cardiovascular disease in older adults: the multi-ethnic study of atherosclerosis. Am J Epidemiol 174:528–536
39. Pepe S, Lakatta EG (2005) Aging hearts and vessels: masters of adaptation and survival. Cardiovasc Res 66:190–193

40. Messerli FH, Sundgaard-Riise K, Ventura HO et al (1983) Essential hypertension in the elderly: haemodynamics, intravascular volume, plasma renin activity, and circulating catecholamine levels. Lancet 2:983–986
41. Kocemba J, Kawecka-Jaszcz K, Gryglewska B, Grodzicki T (1998) Isolated systolic hypertension: pathophysiology, consequences and therapeutic benefits. J Hum Hypertens 12:621–626
42. Kahaly GJ, Nieswandt J, Mohr-Kahaly S (1998) Cardiac risks of hyperthyroidism in the elderly. Thyroid 8:1165–1169
43. Volzke H, Alte D, Dorr M et al (2006) The association between subclinical hyperthyroidism and blood pressure in a population-based study. J Hypertens 24:1947–1953
44. Vokonas PS, Kannel WB, Cupples LA (1988) Epidemiology and risk of hypertension in the elderly: the Framingham Study. J Hypertens Suppl 6:s3–s9
45. Shekelle RB, Ostfeld AM, Klawans HL Jr (1974) Hypertension and risk of stroke in an elderly population. Stroke 5:71–75
46. Schillaci G, Pucci G (2011) Central and 24-h blood pressure: dwarfs standing upon the shoulders of giants? J Hypertens 29:430–433
47. Staessen JA, Thijs L, Fagard R et al (1999) Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension: Systolic Hypertension in Europe Trial Investigators. JAMA 282:539–546
48. Vagaonescu TD, Wilson AC, Kostis JB (2008) Atrial fibrillation and isolated systolic hypertension: the systolic hypertension in the elderly program and systolic hypertension in the elderly program-extension study. Hypertension 51:1552–1556
49. Verhave JC, Fesler P, du Cailar G et al (2005) Elevated pulse pressure is associated with low renal function in elderly patients with isolated systolic hypertension. Hypertension 45:586–591
50. Young JH, Klag MJ, Muntner P et al (2002) Blood pressure and decline in kidney function: findings from the Systolic Hypertension in the Elderly Program (SHEP). J Am Soc Nephrol 13:2776–2782
51. Peralta CA, Jacobs DR Jr, Katz R et al (2012) Association of pulse pressure, arterial elasticity, and endothelial function with kidney function decline among adults with estimated GFR >60 ml/min/1.73 $m^2$: the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Kidney Dis 59:41–49
52. Kovesdy CP, Bleyer AJ, Molnaret MZ et al (2013) Blood pressure and mortality in U.S. veterans with chronic kidney disease: a cohort study. Ann Intern Med 159:233–242
53. Denardo SJ, Gong Y, Nichols WW et al (2010) Blood Pressure and Outcomes in Very Old Hypertensive Coronary Artery Disease Patients: An INVEST Substudy. Am J Med 123:719–726
54. Rastas S, Pirttilä T, Viramo P et al (2006) Association between blood pressure and survival over 9 years in a general population aged 85 and older. J Am Geriatr Soc 54:912–918
55. Haas DC, Foster GL, Nieto FJ et al (2005) Age-dependent associations between sleep-disordered breathing and hypertension: importance of discriminating between systolic/diastolic hypertension and isolated systolic hypertension in the Sleep Heart Health Study. Circulation 111:614–621
56. Corrada MM, Hayden KM, Paganini-Hill A et al (2017) Age of onset of hypertension and risk of dementia in the oldest-old: the 90+ study. Alzheimers Dement 13:103–110
57. Somes GW, Pahor M, Shorr RI et al (2009) The role of diastolic blood pressure when treating isolated systolic hypertension. Arch Intern Med 159:2004–2009
58. Duprez D (2012) Treatment of isolated systolic hypertension in the elderly. Expert Rev Cardiovasc Ther 10:1367–1373
59. Tinetti ME, Han L, Lee DS et al (2014) Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. JAMA Intern Med 174:588–595
60. Liu L, Zhang Y, Liu G et al; for the FEVER Study Group (2005) The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. J Hypertens 23: 2157–2172

61. Zhang Y, Zhang X, Liu L, Zanchetti A (2011) Is a systolic blood pressure target <140 mmHg indicated in all hypertensives? Subgroup analyses of findings from randomized FEVER trial. Eur Heart J 32:1500–1508
62. Chobanian AV (2007) Clinical practice: isolated systolic hypertension in the elderly. N Engl J Med 357:789–796
63. Tonkin A, Wing L (1996) Management of isolated systolic hypertension. Drugs 51:738–749
64. Mangoni AA, Jackson SH (2004) Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol 57:6–14
65. Beckett NS, Peters R, Fletcher AE et al; HYVET Study Group (2008) Treatment of hypertension in patients 80 years of age or older. N Engl J Med 358: 1887–1898
66. Beckett NS, Peters R, Tuomilehto J et al (2012) Immediate and late benefits of treating very elderly people with hypertension: results from active treatment extension to Hypertension in the Very Elderly randomised controlled trial. BMJ 344:d7541. doi:10.1136/bmj.d7541
67. Mancia G (2012) Antihypertensives in octogenarians. Treatment has lasting benefits. BMJ 343:d7293
68. Wright JT Jr; for the SPRINT Research Group (2015) A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 373: 2103–2116
69. Williamson JD, Supiano MA, Applegate WB et al; for the SPRINT Research Group (2016) . Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. JAMA 315:2673–2682
70. Mancia G, Kjeldsen SE (2017) Adopting Systolic Pressure Intervention Trial (SPRINT)-like office blood pressure measurements in clinical practice. J Hypertens 35:471–472
71. Rocco MV, Alfred K, Cheung AK (2015) A SPRINT to the finish, or just the beginning? Implications of the SPRINT results for nephrologists. N Engl J Med 373:2103–2116
72. Fodor JG, Baker P, Li C (2017) On-treatment blood pressures of older hypertensive patients in Canada: implications for Systolic blood PRessure INtervention Trial. J Hypertens 35:621–626
73. Filipovsky J, Seidlerová J, Kratochvílet Z (2000) Automated compared to manual office blood pressure and to home blood pressure in hypertensive patients. Blood Press 25:228–234
74. Bejan-Angoulvanta T, Saadatian-Elahia M, Wright JM et al (2010) Treatment of hypertension in patients 80 years and older: the lower the better? A meta-analysis of randomized controlled trials. J Hypertens 28:1366–1372
75. Ettehad D, Emdin CA, Kiran A et al (2016) Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 387(10022):957–967
76. Bangalore S, Toklu B, Schartzbard A et al (2017) Optimal systolic blood pressure target after SPRINT: insights from a network meta-analysis of randomized trials. Am J Med. doi:10.1016/j.amjmed.2017.01.004
77. Fagard RH, Staessen JA, Lutgarde T et al (2000) Response to antihypertensive therapy in older patients with sustained and nonsustained systolic hypertension. Circulation 102:1139–1144
78. Goldberg RM, Mabee J, Chan L, Wong S (1996) Drug-drug and drug-disease interactions in the ED: analysis of a high-risk population. Am J Emerg Med 14:447–450
79. Law MR, Morris JK, Wald NJ (2009) Use of blood pressure lowering drugs in the prevention of cardiovascular disease: a meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiologic studies. BMJ 338:b1665
80. Savage PJ, Pressel SL, Curb JD et al (1998) Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension: the Systolic Hypertension in the Elderly Program. SHEP Cooperative Research Group. Arch Intern Med 158:741–751
81. Franse LV, Pahor M, Di BM et al (2000) Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). J Hypertens 18:1149–1154
82. Avanzini F, Alli B, Betteli G et al (1994) Antihypertensive efficacy and tolerability of different drug regimes in isolated systolic hypertension in the elderly. Eur Heart J 14:206–212

83. Kostis JB, Pressel SL, Cutler JA et al (1997) Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. JAMA 278:212–216
84. Messerli FH, Grossman E, Goldbourt U (1998) Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. JAMA 279:1903–1907
85. Amery A, Birkenhäger W, Brixko P et al (1985) Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. Lancet 1:1349–1354
86. Kostis JB, Cabrera J, Cheng JQ et al (2011) Association between chlorthalidone treatment of systolic hypertension and long-term survival. JAMA 306:2588–2593
87. Perry HM Jr, Davis BR, Price TR et al (2000) Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke: the Systolic Hypertension in the Elderly Program (SHEP). JAMA 284:465–471
88. Peters R, Beckett N, Forette F et al (2008) HYVET investigators. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol 7:683–689
89. MRC Working Party (1992) Medical Research Council trial of treatment of hypertension in older adults: principal results. BMJ 304:405–412
90. Fleg JL, Aronow WS, Frishman WH (2011) Cardiovascular drug therapy in the elderly: benefits and challenges. Nat Rev Cardiol 8:13–28
91. Williams B, Lacy PS, Thom SM et al (2006) Differential impact of blood pressure lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 113:1213–1225
92. Gong L, Zhang W, Zhu Y et al (1996) Shanghai trial of nifedipine in the elderly (STONE). J Hypertens 14:1237–1245
93. Hansson L, Hedner T, Lund-Johansen P et al (2000) Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. Lancet 29(356):359–365
94. Staessen JA, Fagard R, Thijs L et al (1997) Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet 350:757–764
95. Staessen JA, Thijis L, Fagard R et al (2004) Effects of immediate versus delayed antihypertensive therapy on outcome in the Systolic Hypertension in Europe Trial. J Hypertens 22:847–857
96. Forette F, Seux ML, Staessen JA et al (1998) Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 352:1347–1351
97. Wang JG, Staessen JA, Gong L, Liu L (2000) Chinese trial on isolated systolic hypertension in the elderly. Systolic Hypertension in China (Syst-China) Collaborative Group. Arch Intern Med 160:211–220
98. Mancia G, Ruilope L, Palmer C et al (2009) Effects of nifedipine GITS and diuretics in isolated systolic hypertension—a subanalysis of the INSIGHT study. Blood Press 13:310–315
99. Ostrowski M, Zanchetti A, Nikfar S et al (2014) The effect of hypertension pharmacotherapy in older adults. The results of a meta-analysis of 11 randomized control trials with 40325 patients. Eur Heart J 35(Suppl):1192
100. Kolloch R, Legler UF, Champion A et al (2008) Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: findings from the INternational VErapamil SR/Trandolapril study (INVEST). Eur Heart J 29:1327–1334
101. Investigators SOLVD (1991) Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 325:293–302
102. Pfeffer MA, Braunwald E, Moyé LA et al (1992) Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 327:669–677
103. Heart Outcomes Prevention Evaluation Study Investigators (2000) Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICROHOPE substudy. Lancet 355:253–259

104. Fox KM (2003) EURopean trial on reduction of cardiac events with perindopril in stable coronary artery disease investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 362(9386):782–788
105. Farsang C, Garcia-Puig J, Niegowska J et al (2000) The efficacy and tolerability of losartan versus atenolol in patients with isolated systolic hypertension: Losartan ISH Investigators Group. J Hypertens 18:795–801
106. Dahlöf B, Devereux RB, Kjeldsen SE et al (2002) Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 359:995–1003
107. Ruwald AC, Westergaard B, Sehestedt T et al (2012) Losartan versus atenolol-based antihypertensive treatment reduces cardiovascular events especially well in elderly patients: the Losartan Intervention for Endpoint reduction in hypertension (LIFE) study. J Hypertens 30:1252–1259
108. Kjeldsen SE, Dahlöf B, Devereux RB et al (2002) Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention for Endpoint Reduction (LIFE) substudy. JAMA 288:1491–1498
109. Papademetriou V, Farsang C, Elmfeldt D et al; for the SCOPE Study Group (2004) Stroke Prevention With the Angiotensin II Type 1-Receptor Blocker Candesartan in Elderly Patients With Isolated Systolic Hypertension. The Study on Cognition and Prognosis in the Elderly (SCOPE). J Am Coll Cardiol 44:1175–1180
110. Skoog I, Lithell H, Hansson L et al (2005) Effect of baseline cognitive function and antihypertensive treatment on cognitive and cardiovascular outcomes: study on COgnition and Prognosis in the Elderly (SCOPE). Am J Hypertens 18:1052–1059
111. Saxby BK, Harrington F, Wesnes KA et al (2008) Candesartan and cognitive decline in older patients with hypertension: a substudy of the SCOPE trial. Neurology 70:1858–1866
112. Ogihara T, Saruta T, Rakugi H et al (2010) Target blood pressure for treatment of isolated systolic hypertension in the elderly valsartan in elderly isolated systolic hypertension study. Hypertension 56:196–202
113. Jamerson K, Weber MA, Bakris GL et al; for the ACCOMPLISH Trial Investigators (2008) Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 359: 2417–2428

# Treatment of Resistant Hypertension

# 37

Gino Seravalle, Guido Grassi, and Giuseppe Mancia

## 37.1 Introduction

Hypertension cannot always be controlled by the classical antihypertensive treatment strategies whose therapeutic failure leads to a condition known as resistant hypertension [1]. This chapter will discuss the prevalence within a hypertensive state of individuals in whom blood pressure (BP) remains uncontrolled despite appropriate treatment. It will then briefly describe the fundamental diagnostic steps to detect resistant hypertension as well as its usual clinical characteristics and phenotypes. It will finally deal more extensively with the therapeutic options that might offer the best chance to effectively lower the elevated blood pressure (BP) values in a resistant hypertensive state, hopefully leading the patient's status to BP control (<140/90 mmHg) [1, 2]. Although invasive procedures such as renal denervation and carotid baroreflex stimulation can achieve this goal in a number of patients [3, 4], there is no question that the first treatment approach to consider is the (1) removal of lifestyle factors that may oppose the BP-lowering effect of the administered drugs, such as a high intake of salt, abuse of alcohol, obesity [5, 6], or co-treatments that have direct or indirect pressor effects [7] and (2) modification of the existing treatment regimen by an increase of the dose or the extension of the medicaments already prescribed.

G. Seravalle
Istituto Auxologico Italiano IRCCS, S. Luca Hospital, Milan, Italy

G. Grassi
Clinica Medica, S. Gerardo Hospital, University of Milano-Bicocca, Monza, Italy

G. Mancia (✉)
Emeritus Professor of Medicine, University of Milano-Bicocca, Monza, Italy
e-mail: giuseppe.mancia@unimib.it



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_37

## 37.2 Resistant Hypertension: Definition and Prevalence

Resistant hypertension is defined as a BP controlled with four or more medications or as a BP above goal despite adherence to at least three different optimally dosed antihypertensives, one of which is a diuretic [8, 9]. According to data from the National Health and Nutrition Examination Survey, approximately 9% of US adult patients with hypertension meet criteria for resistant hypertension [10]. The percentage is similar to that observed in data obtained in European countries, while an increased prevalence is observed in the Eastern Europe [11]. The AHA definition of resistant hypertension does not make an attempt to distinguish between resistant and pseudo-resistant hypertension [12]. Individuals, with elevated office BPs due to white coat hypertension, improper BP measurement, or medication nonadherence, do not have true resistant hypertension but have the so-called pseudo-resistant hypertension. Pseudo-resistant hypertension would need to be excluded by an established method of establishing adequate medication adherence, standardized BP measurement, and 24-h ambulatory BP monitoring.

Hypertension registries are attractive data sets for estimating prevalence, because they are a more representative sample of the larger hypertensive population. Two are the most important study cohorts to date to estimate the prevalence of resistant hypertension. The first is a cross-sectional study on >29,000 hypertensive adults in a primary care research database from 2002 to 2005 [13]. Using a definition of BP > 140/90 mmHg (or >130/80 mmHg in kidney disease or diabetes), the prevalence of resistant hypertension was 9.1% of the total hypertensive population and 12.4% of the treated hypertensive population. The second study attempted to distinguish between resistant and pseudo-resistant hypertension due to white coat hypertension in the Spanish ambulatory BP monitoring registry in 2009 [14]. The prevalence of true resistant hypertension was estimated at 7.6% in this treated hypertensive population. As regards the population studies [10], the prevalence of resistant hypertension is underestimated due to the high percentage of subjects uncontrolled but with less than two antihypertensive drugs. Optimizing the medical regimen (ensuring maximum drug dosing, different drug classes, and diuretic use) in patients on three medications may lead to more BP control, making suboptimal antihypertensive therapy a potential overestimation of resistant hypertension prevalence. Egan et al. [15] subdivided the NHANES data set into time periods in order to estimate trends of resistant hypertension prevalence. They observed a rise in resistant hypertension despite an improvement in overall BP control rates [16] due to the increased prescription of antihypertensive medications. With a more optimized medication regimen, the 2005–2008 prevalence of 11.8% of all hypertensive patients likely represents a truer estimate of the prevalence of AHA-defined resistant hypertension.

## 37.3 Pseudo-Resistance and Resistant Hypertension: How to Identify

“Pseudo-resistance” refers to lack of BP control with appropriate treatment in a patient who does not have resistant hypertension. In this case an accurate evaluation of treatment adherence and reliable BP measurement (see below) is essential to

reject pseudo-resistance. As regard BP measurement, several common mistakes often produce falsely elevated BP readings. Such mistakes include not allowing the patients to sit quietly for adequate time, taking single instead of triple readings, using cuffs not adequate to the arms (usually too small), recent smoking, and not supporting the arm at heart level [8, 9]. Taking into account subjects with advanced age and with an atherosclerotic process, they could be accompanied by a BP overestimation during measurements due to the difficulties of full compression of arteries [8]. The white coat effect, defined as an elevation of BP during office measurements than at home or ambulatory BP readings [1, 12], is another cause of pseudo-resistance. Usually patients with apparent resistant hypertension due to the white coat effect have less target organ damage (TOD) compared with truly resistant hypertensive patients [14, 17]. A complete clinical history might look for length, severity, and development of the hypertension, as well as actual treatment and adherence degree and response to previous pharmacological drugs, including side effects. It has been reported that up to 40% of newly diagnosed hypertensive patients will discontinue their antihypertensive medications during the first year, with only 40% of the remaining patients continuing their therapy over the next decade [18]. There was an inverse relationship between the likelihood of early treatment discontinuation and the frequency of the daily dosing regimen [19]. Several factors are able to improve medical adherence: (1) selection of agents with low side effects, (2) avoid complicated dosing schedules, (3) use of fixed-dose agents, (4) use of pill boxes or electronic systems with alarm or persons dedicated to assistance (nurses or familiar ones) to help patients with memory deficit, and (5) improve communication between the patient and physician and education of the patient regarding the regimen schedule, the achieving BP goals, the side effects of drugs, and the cost of this pathophysiological condition. One of the causes of pseudo-resistance is suboptimal doses of antihypertensive agents or inappropriate combinations of drugs. It has been shown that either increasing the dose or initiating or switching to the proper diuretic was the most common change that allowed achieving BP goal among patient classified as resistant hypertensives [20]. Another cause is the clinical inertia, defined as the conscious decision by a clinician to not adequately treat a condition despite knowing that it is present [21]. Despite efforts to translate evidence-based guidelines into practical recommendations, many physicians are reluctant to adhere to these guidelines due to lack of training and experience in the proper use of antihypertensive agents or an overestimation of care already provided [22].

Algorithms to identify pseudo-resistance have been proposed [8, 9] and consist in a two-step approach: (a) confirmation of true resistance and (b) identification of factors that contribute to treatment resistance (Table 37.1). The first step to rule out resistant hypertension is confirmation of the diagnosis not only with reliable office BP readings but also the determination of BP levels at home or with ambulatory measurements. Self-measured BP at home is much less affected by the so-called white coat effect and is more reproducible than clinic BP [23]. The use of ambulatory BP monitoring allows us to gain a large amount of important information on the behavior of the BP profile over the 24-h period, during the daytime, nighttime, or morning hours [24]. This technique allows us to gain also information on 24-h BP variability and its relationships with end-organ damage and cardiovascular events [25–27].

**Table 37.1** Factors contributing to resistant hypertension

| | |
|---|---|
| Drug induced | Nonsteroidal anti-inflammatory drugs |
| | Sympathomimetics |
| | Illicit drugs (cocaine, amphetamines, and others) |
| | Oral contraceptive hormones |
| | Adrenal steroids |
| | Erythropoietin |
| | Cyclosporine, tacrolimus |
| | Licorice |
| | Dietary herbal (ginseng) |
| Excessive alcohol intake | |
| Volume overload | Excess sodium intake |
| | Volume retention from kidney disease |
| | Inadequate diuretic therapy |
| Associated conditions | Obesity |
| | Diabetes mellitus |
| | Older age |
| Identifiable causes | Renal parenchymal disease |
| | Renovascular disease |
| | Primary aldosteronism |
| | Obstructive sleep apnea |
| | Pheochromocytoma |
| | Cushing |
| | Thyroid diseases |
| | Aortic coarctation |
| | Intracranial tumors |

## 37.4 Rationalization of the Three-Drug Treatment Regimen

Hypertension guidelines emphasize the need for combination treatment to be based on drugs with different and complementary mechanisms of the BP-lowering effect. They recommend a three-drug combination to make use of a diuretic, a blocker of the renin-angiotensin system (RAS), be it an ACE inhibitor or an angiotensin receptor antagonist, and a calcium channel blocker because this fulfills the above requirement and has been shown to markedly reduce BP (up to 30–40 mmHg reduction of systolic values) in hypertensive patients with a variety of clinical characteristics [28–30]. In resistant hypertensive patients under treatment with three drugs, a therapeutic option is thus to ensure that a diuretic/RAS blocker/calcium channel blocker combination is used, provided that (1) no contra indication to one or another of these drugs exists or (2) the clinical condition of the patient requires other drugs to be part of the combination, such as a beta-blocker in patients with a history of coronary disease or heart failure. Of special importance is the inclusion of a diuretic in the three-drug treatment regimen because diuretics enhance the antihypertensive effect of most antihypertensive agents and difficult-to-treat hypertensions may rarely not be associated with sodium and fluid retention as well as hypervolemia [31].

## 37.5 Increasing the Dose of the Prescribed Three Drugs

Drug underdosing is frequent in treated hypertensive patients, its high prevalence being one of the factors responsible for the low rate of BP control exhibited by the hypertensive population worldwide [32]. Careful checking of the drug doses prescribed (or assumed) is thus mandatory when dealing with a BP that remains uncontrolled under a three-drug therapeutic regimen, an adequate dose of each of them being indeed a prerequisite for patients' inclusion in the resistant hypertension category. Once this is established, however, a further increase in the dose of the prescribed drugs does not appear to be particularly helpful because (1) the shape of the dose/effect relationship can make the additional BP-lowering effect far from substantial and (2) there may be with a number of drug classes (e.g., calcium channel blockers) a more prominent increase in the drug-related side effects [33]. It should nevertheless be emphasized that this may not be entirely true for diuretics because, as shown in Fig. 37.1, increasing the dose of hydrochlorothiazide beyond the usual 25 mg daily has been associated with a clear-cut further BP reduction, this being the case also for an increase of the thiazide-like diuretic chlorthalidone beyond the usual 12.5 mg, daily [34]. Along this line several studies have shown an increase in

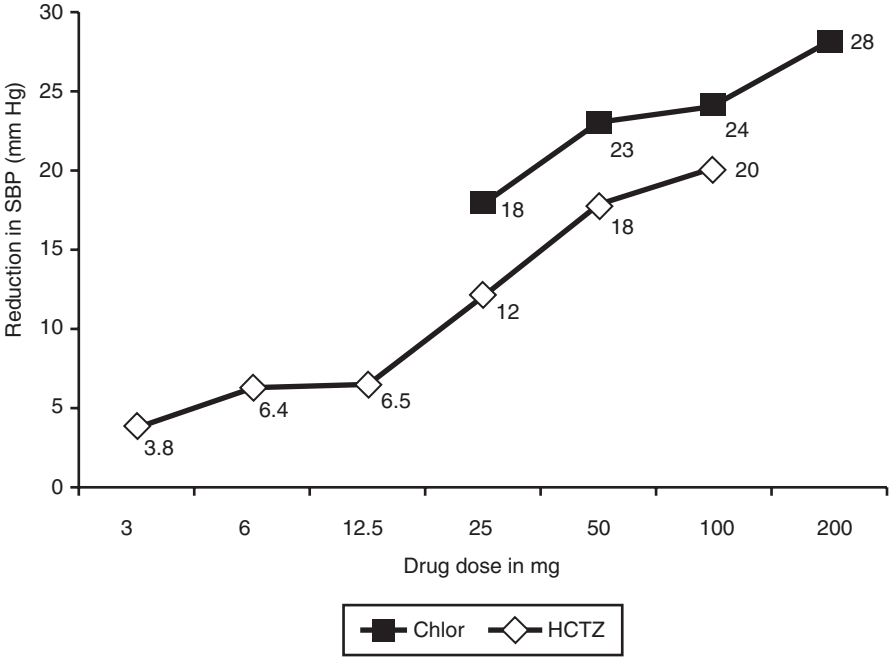



**Fig. 37.1** Effect of hydrochlorothiazide (HCTZ) and chlorthalidone (chlor) on systolic blood pressure (SBP) as a function of the daily dose (mg) (from [34], by permission)

the usual dose of diuretics to be accompanied by an increase in the number of resistant hypertensive patients reaching BP control. For example, in an American study on a cohort of about 150 resistant hypertensive patients, optimization of the existing treatment regimen that included an increase of the dose of diuretic was followed by BP control (<140/90 mmHg) in more than 50% of the cases [35].

## 37.6 Addition of a Fourth Drug

The drugs that are available as fourth step treatment of resistant hypertension have mechanisms of action that are only partly different from those of the drugs included in the background of three-drug treatment regimen. Beta-blockers, alpha-I blockers, and central agents, for example, share their sympatho-moderating influence with RAS blockers [36]. Beta-blockers and mineralocorticoid receptor antagonists share their opposition to the pressor and sodium-retaining effect of angiotensin II with RAS blockers. Direct vasodilators share their ability to reduce vasomotor tone with calcium channel blockers. Despite this potential mechanistic overlapping, however, addition of any fourth drug to the existing drug regimen stands a chance to lower BP and achieve control in a number of resistant hypertensive patients, which makes this approach the preferable one in this clinical condition.

Which drug to select among the available options is difficult to decide on an evidence basis because very few studies have addressed this issue by a randomized double-blind design, making the present fourth drug choice largely empiric. In this context, however, mineralocorticoid receptor antagonists and alpha-I blockers should probably be regarded as the preferred choice for pathophysiological considerations as well as for the extent of therapeutic data. Pathophysiological evidence leaves no doubt that hypertension is accompanied by (1) a sympathetic activation that increases with the degree of BP elevation [37] and is particularly pronounced in patients whose BP is resistant to treatment (Fig. 37.2) [38] and (2) a plasma and tissue elevation of aldosterone whose secretion by the adrenal glands escapes, for a variety of reasons, the inhibitory effect of RAS blockers even when combined to oppose the production or influence of angiotensin II more effectively [39] (Fig. 37.3). Therapeutic evidence shows that these two drug classes lower BP in patients in whom multidrug treatment did not achieve control. This is exemplified by the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) in which the addition of the alpha-I blocker doxazosin in a large number of hypertensives uncontrolled by combination of various drugs lowered systolic BP by about 13–14 mmHg, this being the case in a variety of clinical or demographic conditions (Fig. 37.4) [40]. Interestingly, the BP-lowering effect was associated with no major side effect and no increased risk of heart failure, at variance from what has been reported in the doxazosin-treated hypertensive patients of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [41]. It is further exemplified by the BP reduction observed in the same trial when a similarly large number of patients in whom multidrug treatment had failed to achieve BP control were given spironolactone (Fig. 37.5) [42].

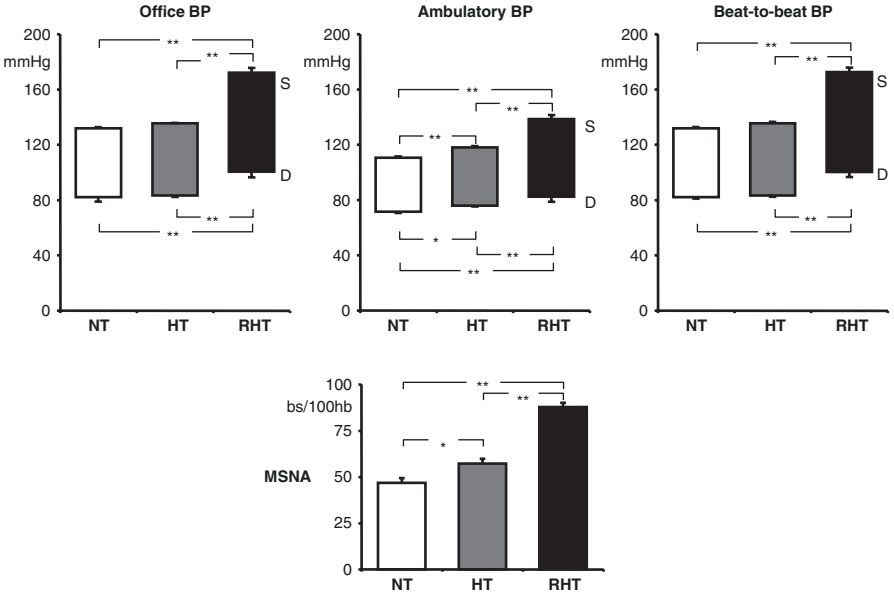



**Fig. 37.2** Office, ambulatory, and beat-to-beat (finger) blood pressure (BP) in normotensives (NT), nonresistant hypertensives (HT), and resistant hypertensives (RHT). Muscle sympathetic nerve traffic (MSNA) measured by microneurography in the three groups is also shown. $*P < 0.05$; $**P < 0.01$ (from [38], by permission)

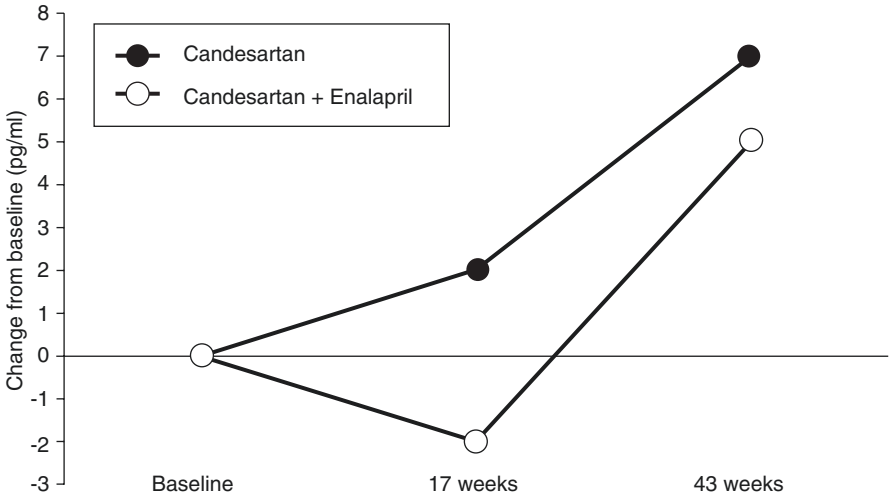



**Fig. 37.3** Escape of aldosterone (serum concentration) in patients under treatment with an angiotensin receptor antagonist or an angiotensin receptor antagonist/ACE inhibitor combination (from [39], by permission)

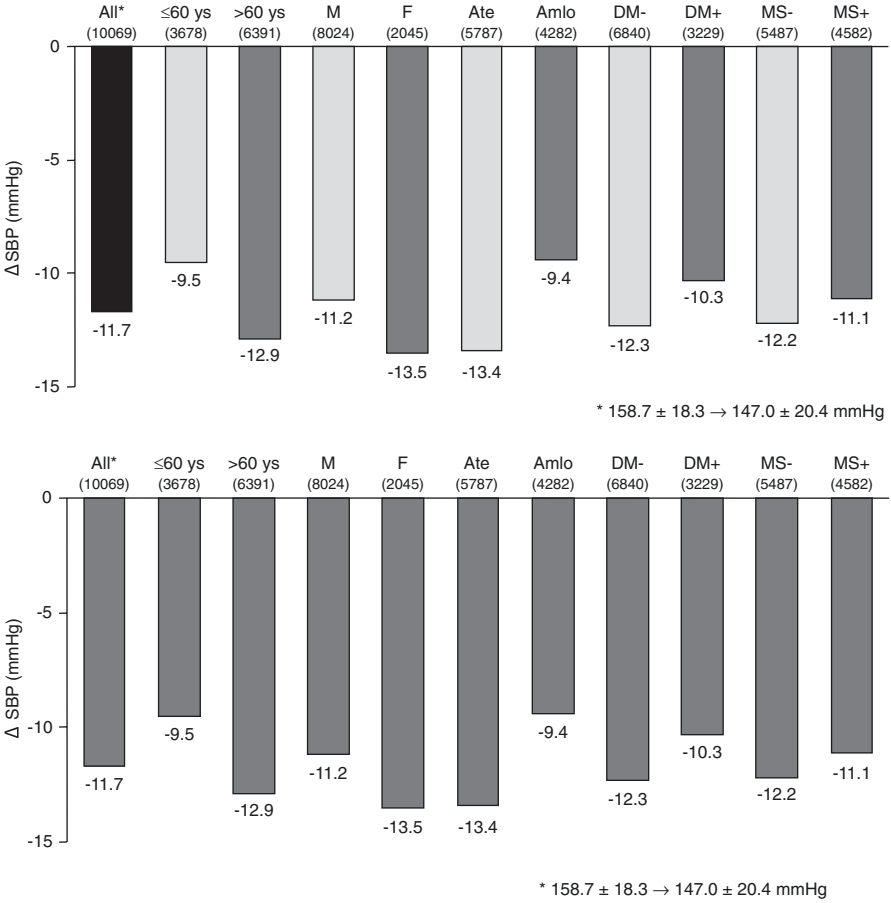



**Fig. 37.4** Systolic blood pressure (SBP) reduction induced by doxazosin administration in patients in whom SBP was not controlled by multiple drug treatment. Data for different patients subgroups. *Ys* years, *M* males, *F* females, *Ate* group initially treated with atenolol, *Amlo* group initially treated with amlodipine, *DM* diabetes mellitus, *MS* metabolic syndrome (from [40], by permission)

## 37.7 Mineralocorticoid Receptor Antagonists: Further Evidence

Support to the use of mineralocorticoid receptor antagonists as the fourth drug to be administered in resistant hypertension can be found in several other studies that have shown, in some instances via a randomized, placebo-controlled design, the BP-lowering ability of this class to include not only spironolactone but also eplerenone at adequate doses [43–50]. The most important documentation of the effectiveness of these drugs, however, comes from the recently published Prevention and Treatment of Hypertension with Algorithm-Based therapy (PATHWAY 2) study in

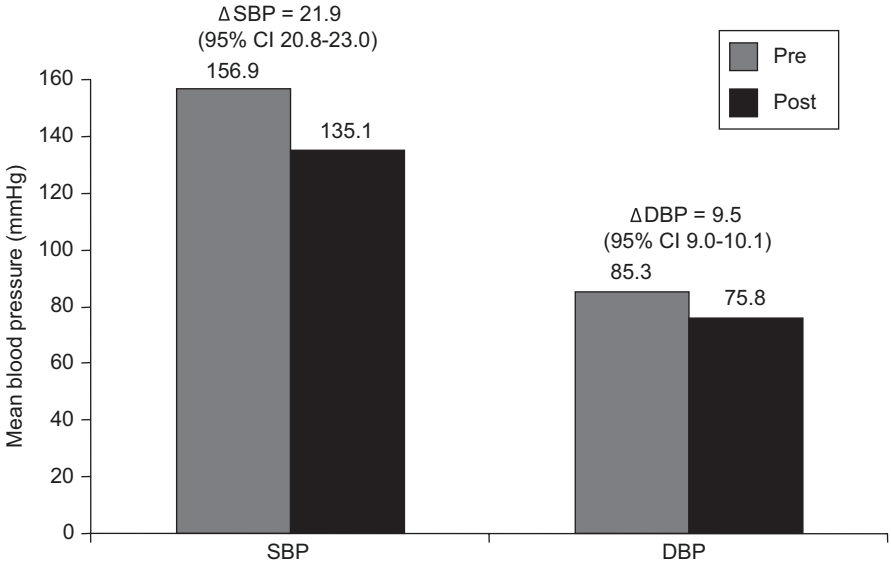



**Fig. 37.5** Systolic and diastolic blood pressure (SBP and DBP) before (pre) and after (post) administration of spironolactone in patients in whom BP was not controlled by multiple drug treatment. Treatment-induced changes are shown at the top of the histograms. *CI* confidence intervals (from [42], by permission)

which several hundred patients with a BP uncontrolled by the recommended three-drug treatment regimen were randomized to the addition of spironolactone, bisoprolol, doxazosin, or placebo. Following a few months of treatment, patients taking spironolactone showed a significantly greater BP reduction than patients taking doxazosin or bisoprolol, whose effect was modestly, albeit significantly, more evident than placebo. This was the case not only for office but also for home BP whose treatment-induced modification was the primary end point of the study (Fig. 37.6) [51]. This will probably lead future guidelines to privilege mineralocorticoid receptor antagonists over other drug options as the preferred fourth choice in resistant hypertension and perhaps also to define hypertension as resistant to treatment only after administration of a drug of this class has proven ineffective.

## 37.8 Unmet Needs

Although more effective than any other added drug currently available, mineralocorticoid receptor antagonists by no means take care of all the problems posed by treatment of resistant hypertension. First, these drugs are associated with a number of serious side effects, among which are hyperkalemia and reduction of renal function [42, 52]. Second, both hyperkalemia and reduction of renal function are more frequent and severe in patients with a seriously impaired glomerular filtration, a condition that was excluded in the patients enrolled for the PATHWAY 2 study, but

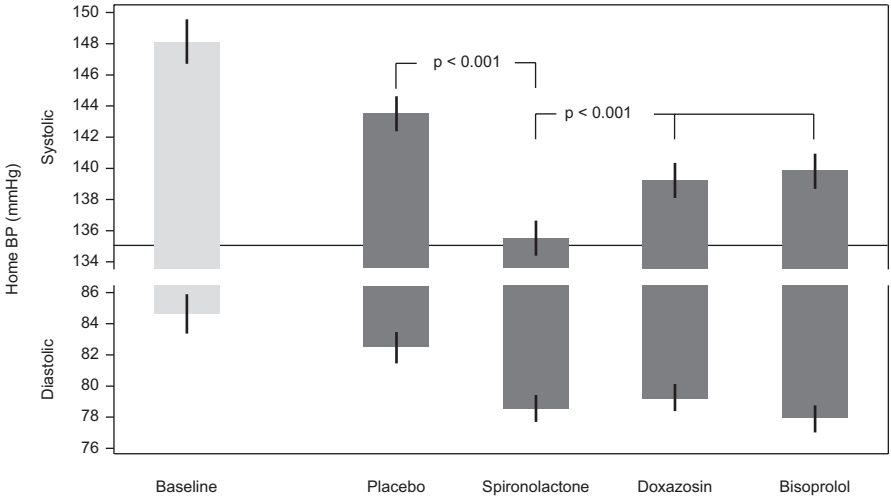



**Fig. 37.6** Home blood pressure (BP) values at baseline and during treatment with placebo, spironolactone, doxazosin, and bisoprolol (from [51], by permission)

that is not at all uncommon in resistant hypertension [53]. Third, despite the greater BP-lowering effect, in the PATHWAY 2 study, spironolactone failed to effectively lower BP in about 40% of the study population, i.e., those with a high renin level and perhaps a concomitant sympathetic hyperactivity (Fig. 37.7) [51]. Thus, more than a single drug class appears to be needed as fourth choice in order to extend effective treatment to the vast majority of resistant hypertensive individuals.

Future studies will have to address this issue by comparing the addition of a fourth drug with the combination of two or more additional agents, hopefully clarifying which combinations have the greatest potential to extend BP control. They may also, however, elect to address alternative possibilities, namely, whether (1) BP can be reduced in a larger number of resistant hypertensive patients by the use of drugs belonging to the same class but having a different site of action [54], an approach that sequential administration of a thiazide diuretic, a loop diuretic, and amiloride has proven effective [55], or (2) a more precise assessment of the resistant hypertension phenotype. The latter approach will mean to (1) identify as precisely as possible the nature and extent of the alterations of the structure and function of the organs (heart, brain, kidney, and vessels) targeted by the uncontrolled BP status and (2) determine which, among the multiple neural and humoral mechanisms controlling circulation, is more severely deranged, in order to try to individualize treatment and increase its success rate.

Finally, drug treatment of resistant hypertension may depend in the future count on new effective BP-lowering agents. In the past, use of endothelin antagonists has been disappointing because their BP-lowering effect turned out to be questionable and accompanied by an unfavorable side effect profile [56]. Drugs targeting arterial stiffening (a structural alteration majorly responsible for the difficulty of lowering

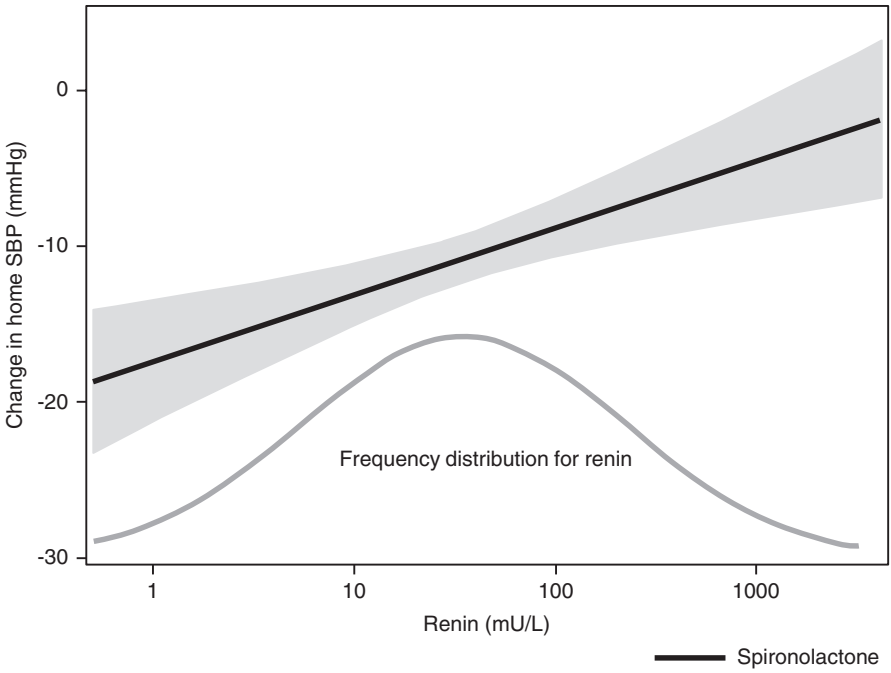



**Fig. 37.7** Relationship between the home systolic blood pressure (SBP) change induced by spironolactone and plasma renin activity in the PATHWAY 2 study (from [51], by permission)

systolic values) have also met with difficulties that have prevented their extensive testing in humans. New dual acting molecules as well as new powerful and better tolerated vasodilators, however, are promising medicaments that may allow to more successfully face therapeutic control of a condition that may have a prevalence greater than 5% of the overall hypertensive population [1], thereby involving in Europe several million individuals.

## References

1. G Mancia, R Fagard, K Narkiewicz et al; The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) (2013) 2013 ESH/ESC guidelines for the management of arterial hypertension. J. Hypertens 31:1281–1357
2. Burnier M, Pechere Bertschi A, Wuerzner G (2013) Treatment of resistant hypertension. Which additional antihypertensive drugs? In: Mancia G (ed) Resistant hypertension. Springer, Milan, pp 115–126
3. Schmieder RE, Redon J, Grassi G et al (2012) ESH position paper: renal denervation—an interventional therapy of resistant hypertension. J Hypertens 30:837–841
4. Bakris GL, Nadim MK, Haller H et al (2012) Baroreflex activation therapy provides durable benefit in patients with resistant hypertension: results of long-term follow-up in the Rheos Pivotal Trial. J Am Soc Hypertens 6:152–158

5. Florczak E, Prejbisz A, Szwench-Pietrasz E et al (2013) Clinical characteristics of patients with resistant hypertension: the RESIST-POL study. J Hum Hypertens 27:678–685
6. Pimenta E, Gaddam KK, Oparil S et al (2009) Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. Hypertension 54:475–481
7. Forman JP, Rimm EB, Curhan GC (2007) Frequency of analgesic use and risk of hypertension among men. Arch Intern Med 16:394–399
8. Moser M, Setaro JF (2006) Resistant or difficult-to-control hypertension. N Engl J Med 355:385–392
9. Calhoun DA, Jones D, Textor S et al (2008) Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension 51:1403–1419
10. Persell SD (2011) Prevalence of resistant hypertension in the United States, 2003-2008. Hypertension 57:1076–1080
11. Brambilla G, Bombelli M, Seravalle G et al (2013) Prevalence and clinical characteristics of patients with true resistant hypertension in central and Eastern Europe: data from the BP-CARE study. J Hypertens 31:2018–2024
12. Sarafidis PA, Georgianos P, Bakris GL (2013) Resistant hypertension—its identification and epidemiology. Nat Rev Nephrol 9:51–58
13. McAdam-Marx C, Ye X, Sung JC et al (2009) Results of a retrospective, observational pilot study using electronic medical records to assess the prevalence and characteristics of patients with resistant hypertension in an ambulatory care setting. Clin Ther 31:1116–1123
14. De la Sierra A, Segura J, Banegas JR et al (2011) Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension 57:898–902
15. Egan BM, Zhao Y, Axon RN et al (2011) Uncontrolled and apparent treatment resistant hypertension in the Unites States, 2003-2008. Circulation 124:1046–1058
16. Hajjar I, Kotchen TA (2003) Trends in prevalence, awareness, treatment and control of hypertension in the United States, 1988-2000. JAMA 290:199–206
17. Pierdomenico SD, Lapenna D, Bucci A et al (2005) Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension. Am J Hypertens 18:1422–1428
18. Mazzaglia G, Mantovani LG, Sturkenboom MC et al (2005) Patterns of persistence with antihypertensive medications in newly diagnosed hypertensive patients in Italy: a retrospective cohort study in primary care. J Hypertens 23:2093–2100
19. Corrao G, Zambon A, Parodi A et al (2008) Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. J Hypertens 26:819–824
20. Singer GM, Izhar M, Black HR (2002) Goal-oriented hypertension management: translating clinical trials to practice. Hypertension 40:464–469
21. Phillips LS, Branch WT, Cook CB et al (2001) Clinical inertia. Ann Intern Med 135:825–834
22. Trewet CL, Ernst ME (2008) Resistant hypertension: identifying causes and optimizing treatment regimens. South Med J101:166–173
23. Grassi G, Bombelli M, Seravalle G et al (2013) Role of ambulatory blood pressure monitoring in resistant hypertension. Curr Hypertens Rep 15:232–237
24. Mallion JM, Baguet JP, Mancia G (2006) European Society of Hypertension Scientific Newsletter: clinical value of ambulatory blood pressure monitoring. J Hypertens 24:2327–2330
25. Verdecchia P, Schillaci G, Guerrieri M et al (1990) Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. Circulation 81:528–536
26. Sega R, Corrao G, Bombelli M et al (2002) Blood pressure variability and organ damage in a general population: results from the PAMELA study (Pressioni Arteriose Monitorate E Loro Associazioni). Hypertension 39:710–714
27. Mancia G, Bombelli M, Facchetti R et al (2007) Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate E Loro Associazioni study. Hypertension 49:1265–1270

28. Tóth K; PIANIST Investigators (2014) Antihypertensive efficacy of triple combination perindopril/indapamide plus amlodipine in high-risk hypertensives: results of the PIANIST study (Perindopril-Indapamide plus AmlodipiNe in high rISk hyperTensive patients). Am J Cardiovasc Drugs 14:137–145
29. Calhoun DA, Lacourcière Y, Chiang YT, Glazer RD (2009) Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized clinical trial. Hypertension 54:32–39
30. Kjeldsen SE, Messerli FH, Chiang CE et al (2012) Are fixed-dose combination antihypertensives suitable as first-line therapy? Curr Med Res Opin 28:1685–1697
31. Rossi GP (2013) Resistant hypertension. Neurohumoral aspects. In: Mancia G (ed) Resistant hypertension. Springer, Milan, pp 11–21
32. Pereira M, Lunet N, Azevedo A, Barros H (2009) Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. J Hypertens 27:963–975
33. Law MR, Wald NJ, Morris JK, Jordan RE (2003) Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ 326:1427
34. Carter BL, Ernst ME, Cohen JD (2004) Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. Hypertension 43:4–9
35. Garg JP, Elliott WJ, Folker A, et al; RUSH University Hypertension Service (2005) Resistant hypertension revisited: a comparison of two university-based cohorts. Am J Hypertens 18:619–626
36. Saino A, Pomidossi G, Perondi R et al (1997) Intracoronary angiotensin II potentiates coronary sympathetic vasoconstriction in humans. Circulation 96:148–153
37. Mancia G, Grassi G (2014) The autonomic nervous system and hypertension. Circ Res 114:1804–1814
38. Grassi G, Seravalle G, Brambilla G et al (2014) Marked sympathetic activation and baroreflex dysfunction in true resistant hypertension. Int J Cardiol 177:1020–1025
39. McKelvie RS, Yusuf S, Pericak D et al (1999) Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. Circulation 100:1056–1064
40. Chapman N, Chang CL, Dahlöf B et al; ASCOT Investigators (2008) Effect of doxazosin gastrointestinal therapeutic system as third-line antihypertensive therapy on blood pressure and lipids in the Anglo-Scandinavian Cardiac Outcomes trial. Circulation 118:42–48
41. Davis BR, Kostis JB, Simpson LM et al; ALLHAT Collaborative Research Group (2008) Heart failure with preserved and reduced left ventricular ejection fraction in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Circulation 118:2259–2267
42. Chapman N, Dobson J, Wilson S et al; Anglo-Scandinavian Cardiac Outcomes Trial Investigators. (2007) Effect of spironolactone on blood pressure in subjects with resistant hypertension. Hypertension 49:839–845
43. Azizi M, Sapoval M, Gosse P et al; Renal Denervation for Hypertension (DENERHTN) Investigators (2015) Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. Lancet 385:1957–1965
44. Rosa J, Widimský P, Toušek P et al (2015) Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 study. Hypertension 65:407–413
45. Václavík J, Sedlák R, Plachy M et al (2011) Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomized, double-blind, placebo-controlled trial. Hypertension 57:1069–1075
46. Nishizaka MK, Zaman MA, Calhoun DA (2003) Efficacy of low-dose spironolactone in subjects with resistant hypertension. Am J Hypertens 16:925–930
47. Pitt B, Reichek N, Willenbrock R et al (2003) Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. Circulation 108:1831–1838

48. de Souza F, Muxfeldt E, Fiszman R, Salles G (2010) Efficacy of spironolactone therapy in patients with true resistant hypertension. Hypertension 55:147–152
49. Rodilla E, Costa JA, Pérez-Lahiguera F et al (2009) Spironolactone and doxazosin treatment in patients with resistant hypertension. Rev Esp Cardiol 62:158–166
50. Ramsay LE, Silas JH, Freestone S (1980) Diuretic treatment of resistant hypertension. Br Med J 281:1101–1103
51. Williams B, MacDonald TM, Morant S et al; British Hypertension Society's PATHWAY Studies Group (2015) Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 386:2059–2068
52. Bianchi S, Bigazzi R, Campese VM (2006) Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. Kidney Int 70:2116–2123
53. Daugherty SL, Powers JD, Magid DJ et al (2012) Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation 125:1635–1642
54. Mancia G (2012) Additional drug treatment in resistant hypertension: need for randomized studies. J Hypertens 30:1514–1515
55. Bobrie G, Frank M, Azizi M et al (2012) Sequential nephron blockade versus sequential renin-angiotensin system blockade in resistant hypertension: a prospective, randomized, open blinded endpoint study. J Hypertens 30:1656–1664
56. Weber MA, Black H, Bakris G et al (2009) A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trialLancet 374:1423-1431

# Accelerated/Malignant Hypertension

# 38

Alena Shantsila and Gregory Y.H. Lip

## 38.1 Introduction

Hypertension is a major cardiovascular risk factor. The most severe form of the hypertension is malignant or accelerated hypertension. Clinical diagnosis is usually based on the presence of very high blood pressure (BP) (office diastolic BP above 130 mmHg at the time of the diagnosis) accompanied by Grade III or IV hypertensive retinopathy according to the classification of Keith, Wagener and Barker [1, 2].

Recently it has been suggested to reclassify malignant hypertension to hypertension with multi-organ damage [3]. With this new definition, malignant hypertension described is one of the clinical presentations of hypertension with multi-organ damage. The diagnostic criteria of hypertension with multi-organ damage are an acute elevation of BP and an impairment of at least three different target organs (kidney, heart, brain, microangiopathy). Early diagnosis of the condition is paramount for the immediate start or adjustment of the treatment, to avoid worsening of the outcome. Indeed, while currently available antihypertensive agents provide adequate BP control in the majority of patients, malignant hypertension still represents an important clinical entity which would have significant consequences for the patient from stroke, myocardial infarction and renal failure, should the condition not be detected, investigated adequately, treated and managed.

A. Shantsila, M.D. • G.Y. H. Lip, M.D. (✉)
Institute of Cardiovascular Sciences, University of Birmingham, City Hospital, Birmingham, UK
e-mail: G.Y.H.LIP@bham.ac.uk



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_38

## 38.2 Clinical Features

Malignant hypertension phase is a hypertensive emergency characterised by severe elevation in systolic and out of range diastolic BP, usually appearing progressively over a period of several weeks to several months. In the West Birmingham Malignant Hypertension Registry, mean systolic and diastolic BP at presentation were 229 ± 30 mmHg and 142 ± 19 mmHg, respectively [4]. Over the 24 years of the registry, the average level of systolic and diastolic BP at the time of diagnosis has remained surprisingly similar (average BP 228/142 mmHg), despite improvements in antihypertensive therapy [4]. It is appropriate to note that although diastolic BP greater than 130 mmHg is a commonly referred diagnostic criterion of malignant hypertension, it should not be used rigidly. In certain cases malignant hypertension could occur with diastolic BP below this level in the presence of very high systolic BP (e.g. more 200 mmHg) and typical eye changes.

The main histological feature of malignant hypertension is fibrinoid necrosis of arterioles in various tissues, including the kidney. This could be accompanied by mucoid intimal proliferation in renal interlobular arteries and an ischemic dysfunction of the glomerular tufts. These changes trigger activation of the renin-angiotensin system, vasoconstriction and progression of hypertension.

The diagnosis of malignant hypertension diagnosis is often delayed as the patients tend to develop clinical symptoms only at a later stage of their disease [5, 6]. Malignant hypertension is commonly underdiagnosed in primate care settings, and up to 75% of patients with malignant hypertension would only by seen by a physician when they develop serious target organ damage and other complications [7, 8]. The usual first symptoms are visual disturbance (acute or subacute) that may be accompanied by a headache. The presence of these symptoms should always be treated with suspicion of possible malignant hypertension.

## 38.3 Retinopathy

Keith et al. classified hypertension-related retinal changes into four grades; clinical course and prognosis of such patients were characterised depending on the degree of retinopathy [1]. Accordingly, Grade 1 included only minimal constriction of the retinal arterioles with some tortuosity and typical of those with mild hypertension. In patients with more advanced hypertension, fundal changes usually included arteriovenous nipping (Grade 2). Patients with severe hypertension presented with Grade 3 (haemorrhages and exudates) and/or Grade 4 (papilloedema) fundal changes have worse prognosis. Ahmed et al. assessed survival in patient with accelerated and malignant hypertension in 200 consecutive patients with Grade 3–4 retinal changes. They have concluded that these two forms of hypertension were essentially the same disease with similar clinical presentation and prognosis [2].

Ophthalmological changes in hypertension can also be divided into Grade A and Grade B. Grade A reflects non-malignant changes of arteriolar narrowing and focal constriction. Grade B changes correspond to malignant hypertension, with linear

flame-shaped haemorrhages, and/or exudates, and/or cotton wool sports with or without papilloedema [9]. This approach offers simplification of the interpretation of fundoscopy, and it has direct implication for patient management.

Following the stabilisation of BP level, the specific malignant hypertension retinopathy gradually regresses, typically during 2–3 months [10]. The disappearance of retinal changes limits retrospective diagnosis of malignant hypertension [10]. That is why it is very important that evaluation of the retinal changes should be performed during the initial visit. There is an association between the development of irreversible ocular complications and very high BP at the time of diagnosis, prominent visual disturbance at presentation, and prolonged duration of the symptoms [11]. However, not all patients with extreme signs of malignant hypertension (i.e. hypertensive encephalopathy) would develop severe retinopathy and Grade 3–4 changes may be absent in some patients during initial examination thus reflecting the dynamic state of retinal changes [12]. However, not all patients have full recovery of vision and anterior ischemic optic neuropathy, or central retinal artery occlusion is a common complication of malignant hypertension [11, 13]. Even could lead to the retinal detachment of macula in patients with malignant hypertension [14]. To provide a timely diagnosis of this dangerous complication, repeated fundus examinations may be necessary, particularly if BP fluctuates substantially [15].

The signs of isolated bilateral papilloedema without haemorrhages could be present in patients with uncontrolled hypertension. Of note, patients with connective tissue disorders, infective endocarditis and severe anaemia also could have fundal haemorrhages and papilloedema [15]. Also, if patients develop diabetic retinopathy, the differential diagnosis of diabetic retinopathy might be problematic.

Data from the experimental animal models of malignant hypertension showed that retinopathy typically develops long time before the choroidopathy or optic neuropathy [16]. Additionally, focal intraretinal periarterial transudates have been described as the retinal changes specific to malignant hypertension [17].

The degree and dynamic of the retinal changes correspond to the changes of the renal system, thus emphasising the fact that patients with malignant hypertension develop microvascular dysfunction in a systemic pattern [13, 18, 19].

## 38.4 The Kidneys

The renal function is impaired in patients with malignant hypertension. Histological studies have shown that intrarenal fibrinoid necrosis of small arteries and arteriole is a characteristic lesion of malignant hypertension, although a myxoid intimal lesion is also not unusual [20–23]. Severe intrarenal vascular lesions are accompanied by signs of nephritis parallel with clinical manifestation of malignant hypertension [24].

Renin-angiotensin-aldosterone system is activated in patients with malignant hypertension. Indeed, marked elevation in plasma renin activity and aldosterone is evident in patients with malignant hypertension but not in patients with severe

hypertension despite small differences in BP [25]. Although the pathophysiological mechanisms leading to the elevation of renin in malignant hypertension are still a matter of debate, the activation of the renin-angiotensin-aldosterone system is usually attributed to juxtaglomerular ischaemia. In one case report of malignant hypertension, a massive increase in plasma renin activity and aldosterone was due to the neoplasm from the juxtaglomerular area [26]. Following the nephrectomy, potassium levels returned to normal range, and the concentrations of renin and aldosterone decreased. High plasma renin activity, features of microangiopathy and renal dysfunction in patients with malignant hypertension parallel the renin-mediated arteriolar damage and kidney dysfunction [27].

Acute renal failure in some cases was the first sign of malignant hypertension [22, 23, 28]. Renal damage evident by dipstick proteinuria marks raise in serum creatinine or urea. In the West Birmingham Malignant Hypertension Registry, at the time of diagnosis, dipstick proteinuria has been reported in 63%, and renal failure defined as serum creatinine 300 mmol/L or more was observed in 32% of patients [4]. The renal function often progressively deteriorates even in treated patients, with a significant rise in median serum urea and creatinine levels [29–31]. Elevated serum creatinine and urea independently predict occurrence of adverse outcomes on multivariable analyses [32]. Progressive renal function decline leading to end-stage renal disease remains a significant threat to patients with malignant hypertension. The optimal BP control during the follow-up is an important factor for preserved renal function [31, 33].

## 38.5 The Heart

In patients with malignant hypertension, cardiac structure and function are affected as well. In the West Birmingham Malignant Hypertension Registry, left ventricular hypertrophy on ECG was detected in 77% of patients [4]. In the same cohort of malignant hypertensive patients, 47% had signs of cardiomegaly on chest X-ray. At the time of the diagnosis, some patients could have signs of impaired systolic function, measured by global longitudinal strain [34]. However, the degree of the LV hypertrophy was still present after almost a year of treatment. Even with good long-term blood pressure control, malignant hypertension patients had an increased LV mass index and features of diastolic dysfunction, with preserved systolic function [35]. Although left ventricular hypertrophy may at least partly reflect an adaptive response to persistently raised BP, its presence is associated with unfavourable prognosis [32]. Of note, some patients do have normal radiographs, ECGs or echocardiograms despite very high BP, suggesting that hypertension may have been of acute onset before target organ damage occurred [4, 30, 36].

Clinically manifesting cardiac complications such as heart failure, angina or myocardial infarction develop in about 20% of patients with malignant hypertension. Hypertension causes heart failure by a number of mechanisms, including pressure overload on the heart due to the raised peripheral vascular resistance, reduced left ventricular compliance (e.g. in left ventricular hypertrophy), an increased risk for coronary artery disease and the precipitation of cardiac arrhythmias (such as atrial fibrillation). Severe hypertension results in a significant increase in afterload and may result in decompensation of the failing heart.

## 38.6 Vascular System

The key element of the vascular biology is the endothelium. Endothelium dysfunction on the macro- and microvascular level is one of the abnormalities seen in patients with malignant hypertension [37]. Excessive endothelial injury in malignant hypertension resulted in the development of thrombotic microangiopathies [38]. Small group study showed an association of thrombotic microangiopathies with elevation in plasma aldosterone level, but not with renin activity [38]. Thus, elevation of the aldosterone level could be a potential marker of the magnitude of organ damage, due to the thrombosis.

Extreme elevation of BP affects all cardiovascular beds, and multisystem complications are not uncommon. Features of target organ damage are often seen in these patients at presentation and could indicate prolonged history of BP elevation.

## 38.7 Hypertensive Encephalopathy

Hypertensive encephalopathy is a rare hypertensive emergency, and it clinically presents with symptoms of cerebral oedema, due to the severe BP elevation. The dysregulation of cerebral circulation leads to the high volume overload and impairment of blood-brain barrier function resulting in brain oedema. This all happens on the background of impaired macro- and microvascular function [37]. It is important to remember that encephalopathy in malignant hypertension is a genuine emergency, and it always requires hospital admission.

The main symptoms of malignant hypertension encephalopathy are sudden onset of headache, nausea and vomiting. Later these symptoms are followed by different visual disturbances, which might be accompanied by neurological symptoms (restlessness, confusion and, in extreme cases, seizures and coma) [39, 40]. The diagnosis of hypertensive encephalopathy can be facilitated by diagnostic tests such as increased pressure of the cerebrospinal fluid, evidence of white matter oedema on CT or MRI scans [40, 41]. In a recent retrospective analysis of the US data, the increasing trend for the hospital admission of patients with either hypertensive encephalopathy or malignant hypertension after 2007 has been observed, with no increase in morbidity [42]. These observations could reflect improved differential diagnoses of malignant hypertension with encephalopathy, as admissions for essential hypertension fell.

## 38.8 Epidemiological Insights

The prevalence of malignant hypertension is low in the general population and has an overall incidence of 5–6 patients per 100,000 of population per year in white and South Asian origin and 13–14 per 100,000 per year in the African-Caribbean [43, 44]. A higher rate of malignant hypertension in the black population may be due to their resistance to some antihypertensive medication as well as insufficient compliance with various treatments. The largest prospective of the West Birmingham Malignant Hypertension Registry maintained over the period of more than 40 years

has not demonstrated any noticeable reduction in the prevalence of malignant hypertension [45]. The condition appears to have similar prevalence in the developed and developing countries, where it constitutes a significant cause of end-stage renal failure [7, 8, 46].

Although most (about 95%) cases of the malignant hypertension can be considered an extreme form of essential hypertension, the secondary causes of malignant hypertension have also reported. Secondary forms of malignant hypertension are more common in young patients, especially in children. In fact, in children aged under 16 years, only 5% of malignant cases are due to essential hypertension with about two-thirds of occurrences being related to renal parenchymal disease and one-third to aortoarteritis and fibromuscular dysplasia [47–49]. Adults cases of neoplasm in the juxtaglomerular area and Takayasu's arteritis involving renal artery have been reported [26, 50, 51].

Interestingly, in women there is an association in the use of oral contraceptives and cigarette smoking and development of malignant hypertension [52]. It is hard to explain the pathophysiological mechanisms, and this association may exacerbate pre-existed hypertension than serves as isolated factor of malignant hypertension development per se.

Although the presence of distinct mechanisms of BP elevation in malignant hypertension has been suggested by experimental studies, there are common pathways shared with essential hypertension, such as endothelial dysfunction, platelet activation, elevated fibrinogen levels and lipid abnormalities [53–55]. Some data indicate that extreme elevation of BP predominantly occurs in poorly controlled essential hypertension patients with previous history of hypertension. The data from West Birmingham Malignant Hypertension Registry, based on the analysis of 350 patients, showed that 55.7% of them presented with de novo malignant hypertension, without any prior history of hypertension, and 41.7% had previous hypertension diagnosis [30]. The clinical presentation, BP and renal function at the time of diagnosis were not different between the two groups. Over the median 3-year follow-up, the survival time was not significantly different between two groups [30].

## 38.9 Prognosis

Characterisation of the hypertensive patient as 'malignant' reflects grim prognosis of the disorder in the past. Historically if malignant hypertension was left untreated, the mortality was around 80% within 2 years [1, 5]. Ethnicity is important, as it has been previously observed, black male patients with malignant hypertension had a worse prognosis, possibly reflecting more severe renal impairment and higher BP at presentation and follow-up [32, 56]. Following the development, the more efficient and tolerable antihypertensive drug therapy has meant that this prognosis is significantly improved. The demography and incidence of the new malignant hypertension cases have not significantly changed over the last decades, based on the registry including 5725 person-years of observation [45].

Also, the level of systolic BP at the time of diagnosis was not different between the patients seen before 1977 and between 1977 and 2006. Importantly the 5-year survival has increased dramatically from 32.0% before 1977 diagnosis to 91.0% for those patients with malignant hypertension diagnosed between 1997 and 2006. The independent predictors of survival on multivariable analyses were age, baseline creatinine and follow-up systolic BP (all $P < 0.0001$). Indeed, the tight BP control at follow-up significantly impacts prognosis in patients with malignant hypertension [32]. Despite this dramatic improvement in survival, compared to the hypertensive, with no history of malignant hypertensive phase, all-cause mortality was significantly higher ($p < 0.01$) with a higher prevalence of renal impairment [57]. The West Birmingham Malignant Hypertension Registry revealed that the kidney failure is the primary cause of death in patients with malignant hypertension.

**Conclusion**

Despite the improvements in the management of hypertension in general, there is no strong evidence to prove a reduction in the incidence of malignant hypertension. Moreover, this disorder may appear to become even more prevalent worldwide given the growing population in the developing countries with limited healthcare resources. Although the diagnostic criteria of malignant hypertension appear simple, the diagnosis is delayed in a substantial proportion of patients. As a result patients with malignant hypertension frequently present at the advanced stages of the disease. Furthermore, malignant hypertension and the accompanying ocular changes may gradually resolve to make retrospective diagnosis problematic, while persistent target organ damage can drive the development of complications and has an adverse prognosis in these patients. Certainly, malignant hypertension still presents a clinically relevant form of hypertension, and it should be kept in mind during the assessment of patients with poorly controlled hypertension.

## References

1. Keith NM, Wagener HP, Barker NW (1974) Some different types of essential hypertension: their course and prognosis. Am J Med Sci 268(6):336–345
2. Ahmed ME, Walker JM, Beevers DG, Beevers M (1986) Lack of difference between malignant and accelerated hypertension. Br Med J (Clin Res Ed) 292(6515):235–237
3. Cremer A, Amraoui F, Lip GY et al (2016) From malignant hypertension to hypertension-MOD: a modern definition for an old but still dangerous emergency. J Hum Hypertens 30:463–466
4. Lip GY, Beevers M, Beevers G (1994) The failure of malignant hypertension to decline: a survey of 24 years' experience in a multiracial population in England. J Hypertens 12(11):1297–1305
5. Leishman AW (1959) Hypertension: treated and untreated; a study of 400 cases. Br Med J 1(5134):1361–1368
6. Kincaid-Smith P (1991) Malignant hypertension. J Hypertens 9(10):893–899
7. Kadiri S, Olutade BO, Osobamiro O (2000) Factors influencing the development of malignant hypertension in Nigeria. J Hum Hypertens 14(3):171–174

8. Kadiri S, Olutade BO (1991) The clinical presentation of malignant hypertension in Nigerians. J Hum Hypertens 5(4):339–343
9. McGregor E, Isles CG, Jay JL, Lever AF, Murray GD (1986) Retinal changes in malignant hypertension. Br Med J (Clin Res Ed) 292(6515):233–234
10. Steinegger K, Bergin C, Guex-Crosier Y (2015) Malignant hypertension: clinical manifestations of 7 cases. Klin Monatsbl Augenheilkd 232(4):590–592. doi:10.1055/s-0034-1396333
11. Browning AC, Mengher LS, Gregson RM, Amoaku WM (2001) Visual outcome of malignant hypertension in young people. Arch Dis Child 85(5):401–403
12. Rodriguez MA, Kumar SK, De Caro M (2010) Hypertensive crisis. Cardiol Rev 18(2):102–107. doi:10.1097/CRD.0b013e3181c307b7
13. Balogh Z, Berta A, Pfliegler G, Nagy V (2011) Bilateral central retinal vein occlusion caused by malignant hypertension in a young patient. Clin Exp Hypertens 33(1):53–55. doi:10.3109/10641963.2010.503304
14. Shukla D, Ramchandani B, Vignesh TP et al (2010) Localized serous retinal detachment of macula as a marker of malignant hypertension. Ophthalmic Surg Lasers Imaging 1–7. doi:10.3928/15428877-20100215-74
15. Chen YH, Kuo HK, Kao ML (2003) Malignant hypertensive retinopathy-clinical and fundus manifestations in patients with new onset or acute exacerbation of chronic hypertension. Chang Gung Med J 26(9):669–677
16. Hayreh SS, Servais GE, Virdi PS et al (1986) Fundus lesions in malignant hypertension. III. Arterial blood pressure, biochemical, and fundus changes. Ophthalmology 93(1):45–59
17. Hayreh SS, Servais GE, Virdi PS (1986) Fundus lesions in malignant hypertension. IV. Focal intraretinal periarteriolar transudates. Ophthalmology 93(1):60–73
18. Heidbreder E, Huller U, Schafer B, Heidland A (1987) Severe hypertensive retinopathy. Increased incidence in renoparenchymal hypertension. Am J Nephrol 7(5):394–400
19. Cortina G, Hofer J, Giner T, Jungraithmayr T (2015) Severe visual loss caused by unrecognized malignant hypertension in a 15-year-old girl. Pediatr Int 57(2):e42–e44. doi:10.1111/ped.12525
20. Kadiri S, Thomas JO (1993) Kidney histology and clinical correlates in malignant hypertension. East Afr Med J 70(2):112–116
21. Pitcock JA, Johnson JG, Hatch FE et al (1976) Malignant hypertension in blacks. Malignant intrarenal arterial disease as observed by light and electron microscopy. Hum Pathol 7(3):333–346
22. Shavit L, Reinus C, Slotki I (2010) Severe renal failure and microangiopathic hemolysis induced by malignant hypertension—case series and review of literature. Clin Nephrol 73(2):147–152
23. Li X, Zhang W, Ren H et al (2009) Malignant hypertension complicated by acute renal failure. BMJ Case Rep 1–8. doi: 10.1136/bcr.10.2008.1116
24. Tao JL, Li H, Tang Y et al (2008) Lupus nephritis complicated with malignant hypertension: from renal vascular pathology to clinical relevance. Chin Med Sci J 23(2):81–87
25. Davies DL, Beevers DG, Briggs JD et al (1973) Abnormal relation between exchangeable sodium and the renin-angiotensin system in malignant hypertension and in hypertension with chronic renal failure. Lancet 1(7805):683–686
26. Leemingsawat C, Thongtang N (2012) Malignant hypertension due to a large reninoma: a case report. J Med Assoc Thai 95(Suppl 2):S251–S255
27. van den Born BJ, Koopmans RP, van Montfrans GA (2007) The renin-angiotensin system in malignant hypertension revisited: plasma renin activity, microangiopathic hemolysis, and renal failure in malignant hypertension. Am J Hypertens 20(8):900–906. doi:10.1016/j.amjhyper.2007.02.018
28. Gassanov N, Pollok M, Er F (2009) Acute renal failure associated with malignant hypertension. Dtsch Med Wochenschr 134(44):2224–2227. doi:10.1055/s-0029-1241930
29. Lip GY, Beevers M, Beevers DG (1997) Does renal function improve after diagnosis of malignant phase hypertension? J Hypertens 15(11):1309–1315
30. Lip GY, Beevers M, Beevers DG (2000) Do patients with de novo hypertension differ from patients with previously known hypertension when malignant phase hypertension occurs? Am J Hypertens 13(8):934–939

31. Amraoui F, Bos S, Vogt L, van den Born BJ (2012) Long-term renal outcome in patients with malignant hypertension: a retrospective cohort study. BMC Nephrol 13:71. doi:10.1186/1471-2369-13-71
32. Lip GY, Beevers M, Beevers DG (1995) Complications and survival of 315 patients with malignant-phase hypertension. J Hypertens 13(8):915–924
33. van der Merwe W, van der Merwe V (2013) Malignant hypertension: a preventable emergency. N Z Med J 126(1380):39–45
34. Gosse P, Coulon P, Papaioannou G et al (2011) Impact of malignant arterial hypertension on the heart. J Hypertens 29(4):798–802. doi:10.1097/HJH.0b013e3283430b12
35. Shantsila A, Dwivedi G, Shantsila E et al (2013) A comprehensive assessment of cardiac structure and function in patients with treated malignant phase hypertension: the West Birmingham Malignant Hypertension project. Int J Cardiol 167(1):67–72. doi:10.1016/j.ijcard.2011.11.077
36. Shapiro LM, Mackinnon J, Beevers DG (1981) Echocardiographic features of malignant hypertension. Br Heart J 46(4):374–379
37. Shantsila A, Dwivedi G, Shantsila E et al (2011) Persistent macrovascular and microvascular dysfunction in patients with malignant hypertension. Hypertension 57(3):490–496. doi:10.1161/HYPERTENSIONAHA.110.166314
38. Akimoto T, Muto S, Ito C et al (2011) Clinical features of malignant hypertension with thrombotic microangiopathy. Clin Exp Hypertens 33(2):77–83. doi:10.3109/10641963.2010.503303
39. Acelajado MC, Calhoun DA (2010) Resistant hypertension, secondary hypertension, and hypertensive crises: diagnostic evaluation and treatment. Cardiol Clin 28(4):639–654. doi:10.1016/j.ccl.2010.07.002
40. Vaughan CJ, Delanty N (2000) Hypertensive emergencies. Lancet 356(9227):411–417. doi:10.1016/S0140-6736(00)02539-3
41. Deguchi I, Uchino A, Suzuki H, Tanahashi N (2012) Malignant hypertension with reversible brainstem hypertensive encephalopathy and thrombotic microangiopathy. J Stroke Cerebrovasc Dis 21(8):915.e17–915.e20. doi:10.1016/j.jstrokecerebrovasdis.2012.02.005
42. Polgreen LA, Suneja M, Tang F et al (2015) Increasing trend in admissions for malignant hypertension and hypertensive encephalopathy in the United States. Hypertension 65(5):1002–1007. doi:10.1161/HYPERTENSIONAHA.115.05241
43. Shantsila A, Shantsila E, Lip GY (2010) Malignant hypertension: a rare problem or is it underdiagnosed? Curr Vasc Pharmacol 8(6):775–779
44. van den Born BJ, Koopmans RP, Groeneveld JO, van Montfrans GA (2006) Ethnic disparities in the incidence, presentation and complications of malignant hypertension. J Hypertens 24(11):2299–2304. doi:10.1097/01.hjh.0000249710.21146.38
45. Lane DA, Lip GY, Beevers DG (2009) Improving survival of malignant hypertension patients over 40 years. Am J Hypertens 22(11):1199–1204. doi:10.1038/ajh.2009.153
46. Seedat YK (1999) Improvement in treatment of hypertension has not reduced incidence of end-stage renal disease. J Hum Hypertens 13(11):747–751
47. Kanaheswari Y, Hamzaini AH, Wong SW, Zulfiqar A (2008) Malignant hypertension in a child with phakomatosis pigmentovascularis type II b. Acta Paediatr 97(11):1589–1591. doi:10.1111/j.1651-2227.2008.00971.x
48. Zgurzynski P, Manno M (1999) Coccygeal fracture, constipation, convulsion, and confusion: a case report of malignant hypertension in a child. Pediatr Emerg Care 15(6):425–428
49. Chaubey BS, Soni PH, Grover S (1984) Malignant hypertension in a young boy. J Assoc Physicians India 32(3):289–291
50. Liborio AB, Marques Fde O, Testagrossa L et al (2005) Malignant hypertension with intestinal ischemia secondary to juxtaglomerular cell tumor. Am J Kidney Dis 46(5):957–961. doi:10.1053/j.ajkd.2005.07.032
51. Moorthy N, Prasad BN, Kumar YC et al (2009) Malignant hypertension, dissection of aorta, cardiac tamponade and monoparesis—unusual presentation of Takayasu's arteritis: clinicopathological correlation. Int J Cardiol 133(3):e114–e117. doi:10.1016/j.ijcard.2007.12.042
52. Petitti DB, Klatsky AL (1983) Malignant hypertension in women aged 15 to 44 years and its relation to cigarette smoking and oral contraceptives. Am J Cardiol 52(3):297–298

53. Tadokoro K, Nishikimi T, Mori Y et al (2003) Altered gene expression of adrenomedullin and its receptor system and molecular forms of tissue adrenomedullin in left ventricular hypertrophy induced by malignant hypertension. Regul Pept 112(1–3):71–78
54. Lip GY, Edmunds E, Hee FL et al (2001) A cross-sectional, diurnal, and follow-up study of platelet activation and endothelial dysfunction in malignant phase hypertension. Am J Hypertens 14(8 Pt 1):823–828
55. Edmunds E, Landray MJ, Li-Saw-Hee FL et al (2001) Dyslipidaemia in patients with malignant-phase hypertension. QJM 94(6):327–332
56. Clough CG, Beevers DG, Beevers M (1990) The survival of malignant hypertension in Blacks, Whites and Asians in Britain. J Hum Hypertens 4(2):94–96
57. Amraoui F, Van Der Hoeven NV, Van Valkengoed IG et al (2014) Mortality and cardiovascular risk in patients with a history of malignant hypertension: a case-control study. J Clin Hypertens (Greenwich) 16(2):122–126. doi:10.1111/jch.12243

# Nocturnal Hypertension

# 39

Cesare Cuspidi, Carla Sala, Marijana Tadic, and Guido Grassi

## 39.1 Introduction

A growing body of evidence accumulated in the last decades underlines the clinical and prognostic values of circadian blood pressure (BP) variations and nocturnal BP levels [1]. In particular, two major lines of clinical research analyzed the impact and correlates of non-dipping status and nocturnal hypertension (NH) on cardiovascular disease [2]. At the end of 80′, O'Brien et al. were the first to show that an altered circadian BP pattern (i.e., reduced nighttime dipping) conveyed a higher risk of cerebrovascular events [3].

After this pioneering observation, the so-called non-dipping pattern (defined as nocturnal BP fall <10% of daytime value or nighttime/daytime BP ratio ≥ 0.90) has been reported to be associated with high-risk conditions such as diabetes [4], metabolic syndrome, obesity [5], sleep apnea [6], renal insufficiency [7], target organ damage [8, 9], and, more importantly, with an increased risk of fatal and nonfatal cardiovascular events in different clinical settings [10–12].

C. Cuspidi (✉)
Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

Istituto Auxologico Italiano, Milan, Italy
e-mail: cesare.cuspidi@unimib.it

C. Sala
Department of Clinical Sciences and Community Health, University of Milano and Fondazione Ospedale Maggiore Policlinico di Milano, Milan, Italy

M. Tadic
University Clinical Hospital Centre "Dragisa Misovic", Belgrade, Serbia

G. Grassi
Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

Istituto di Ricerche a Carattere Scientifico Multimedica, Sesto San Giovanni, Italy



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_39

These findings are still debated as a number of clinical investigations failed to demonstrate substantial differences in either intermediate [13, 14] or hard end points [15, 16] between dipping and non-dipping phenotypes after appropriate adjustments for confounders**.** In particular, it should be pointed out that a preserved BP fall at night may not result in normal nighttime BP values as defined by current cutoffs (i.e., <120/70 mmHg) recommended by guidelines [17, 18].

Clinical studies in different population settings suggest that nighttime BP is a stronger predictor of organ damage and cardiovascular events compared to daytime BP. Consequently, diagnostic and treatment strategies targeting nighttime BP have come into focus. This clinical perspective is well reflected in the European Society of Hypertension position paper on ambulatory BP monitoring (ABPM) where NH is listed among the prominent clinical indications for ABPM, in addition to white coat and masked hypertension [19]. In this chapter, current literature on NH, isolated NH, and chronotherapeutic management of hypertension will be discussed in separate sections.

## 39.2 Nocturnal Hypertension

ABPM offers the unique opportunity to assess day-night BP variability. This technique has consistently documented that nighttime BP values are 10–20% lower than daytime values in the vast majority of healthy subjects. The drop in nighttime BP is mostly related to reduced sympathetic and increased vagal tone during nocturnal bed rest period, leading to sustained decrease in heart rate, cardiac output, and peripheral resistances [20, 21].

The magnitude of 24-h BP variations in active subjects is related to a variety of factors such as age, level of physical activity, smoking habits, emotional state, and duration and quality of sleep. The mechanism(s) of impaired circadian BP pattern is multifactorial. A blunted BP fall at night in hypertensive patients has been shown to be highly prevalent in a wide array of conditions including secondary hypertension, chronic kidney diseases, types 1 and 2 diabetes mellitus, sleep apnea syndrome, autonomic nervous system dysfunction, and preeclampsia [22, 23].

Overall, a blunted decline in sympathetic tone and renin-angiotensin-aldosterone activity, endothelial dysfunction, impaired baroreflex sensitivity, and renal sodium excretion capacity have been associated to elevated nighttime BP [24] (Table 39.1).

**Table 39.1** Mechanisms and conditions involved in nocturnal hypertension

| |
|---|
| Increased sympathetic tone |
| Blunted vagal tone |
| Increased renin-angiotensin-aldosterone activity |
| Impaired baroreflex sensitivity |
| Impaired renal sodium excretion capacity |
| High dietary sodium intake |
| Endothelial dysfunction |
| Sleep apnea syndrome |
| Subclinical organ damage |

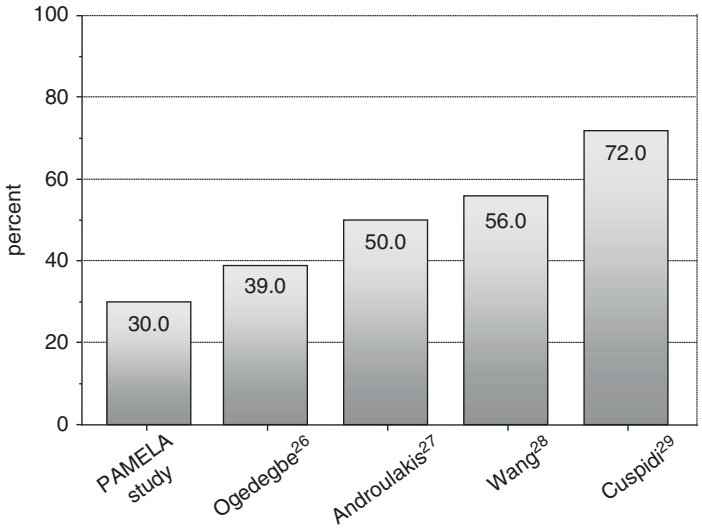



**Fig. 39.1** Prevalence rates of nocturnal hypertension in five studies published from 2011 to 2015

Clinical evidence pointing to the role of sodium in circadian BP rhythm is provided by the reversal of non-dipping status and NH after salt restriction or administration of thiazide diuretics [25]. It should be also pointed out that subclinical vascular damage itself has been hypothesized to attenuate the vasodepressor influence of sleep, thus contributing to maintenance of NH.

Prevalence rates of NH, as defined according to current guidelines (i.e., nighttime systolic BP > 120 mm Hg or diastolic BP > 70 mmHg), largely vary across studies, depending on demographic, clinical, and ethnical factors (Fig. 39.1). Among the 2021 subjects enrolled in the Pressioni Monitorate E Loro Associazioni (PAMELA) study, representative for gender and age decades of the population of Monza (a town in the northeast outskirts of Milan, Italy), 607 (30%) participants were found to fulfill ABPM diagnostic criteria for NH (unpublished data). In the Jackson Heart Study, a population-based cardiovascular epidemiologic study in African-Americans with high prevalence of obesity and type 2 diabetes, NH was documented in 152 out of 425 (39%) untreated participants [26]. In a study by Androulakis et al. [27] including 319 newly diagnosed hypertensive patients, NH was detected in approximately 50% of cases; NH subjects showed similar demographic and clinical characteristics (including metabolic profile) as their counterparts with normal nocturnal BP. In a Chinese cohort of 1322 patients with chronic kidney disease (56% with chronic glomerulonephritis), Wang et al. [28] found that systolic NH was present in 60% of the entire sample. Patients with NH were characterized by older age, prevalence of diabetes, higher levels of serum creatinine, cystatin C, calcium, uric acid, and homocysteine than nocturnal normotensive patients.

Although available information on NH prevalence across different clinical settings remains scanty, this condition appears highly prevalent in the hypertensive

population; genetic, demographic, lifestyle, and socioeconomic factors are conceivably responsible for the nighttime BP differences across studies. Of note, findings on NH in very elderly subjects are scarce, and no age-adjusted specific criteria for defining NH in this setting are provided by current hypertension guidelines.

The reproducibility of NH pattern has been investigated by a limited number of studies. Our group examined NH prevalence, correlates, and reproducibility in a cohort of 658 untreated hypertensives [29]: all subjects underwent two 24-h ABPMs at 1–4-week interval. A total of 477 subjects had NH in both ABPM sessions, and 62 subjects showed normal nighttime BP in both ABPMs. Overall, 119 subjects had a variable nocturnal pattern, as they changed their profile from one ABPM session to the other. Thus, 72.5% of subjects had a reproducible NH pattern, 18% a variable pattern, and 9.5% reproducible nocturnal normotension. In line with our results, Abdalla et al. [30] recently showed a satisfactory short-term reproducibility of NH pattern (kappa 0.65) in a community-based sample of 282 subjects.

As for asymptomatic target organ damage, a limited number of cross-sectional observations performed in general population and hypertensive cohorts suggest that NH combined to daytime BP elevation is associated with more advanced structural and functional alterations of the heart, ascending aorta, and carotid artery. Furthermore, a link between isolated NH (a condition characterized by BP elevation restricted to the nighttime period) and target organ damage has been demonstrated in recent years.

These findings are in keeping with available evidence that average nighttime BP values are superior to daytime ones in predicting subclinical cardiac and extracardiac organ damage and, more importantly, the risk of cardiovascular disease and mortality. We ourselves have shown that nighttime BP levels predicted the development of left ventricular hypertrophy (LVH) during a 12-year follow-up in subjects with normal LV mass at baseline evaluation; the same was not true for daytime BP and for the extent of nocturnal BP decline [31]. Again, in the PAMELA population, a 10-mmHg increase of nighttime systolic BP was associated with a higher risk of cardiovascular death than a 10-mmHg increase of daytime systolic BP, also after adjusting for several confounders [32].

One of the first contribution focusing on the relationship between NH and cardiac damage was provided by Perez-Lloret et al. [33]. In a group of 233 untreated and treated hypertensives, the authors were able to demonstrate that NH defined by fixed cutoff limits as recommended by the 2007 European Society of Hypertension/European Society of Cardiology Guidelines [17] was a better predictor of LVH (OR 11.1, CI 95% = 3.0–40.1, $p < 0.001$) than non-dipping pattern (OR 1.4, CI 95% = 0.4–5.5 $p$ = ns).

Considering the paucity of data linking NH to hypertensive organ damage, we performed a meta-analysis to investigate the relationship of NH with subclinical cardiac and carotid damage [34]. To this purpose, a pooled population including 3657 subjects (NH = 2083, nocturnal normotension = 1574) from 7 studies was analyzed. LV mass index was significantly higher in NH individuals than in normotensive ones (112 ± 4.7 g/m$^2$ versus 98 ± 4.8 g/m$^2$, $p < 0.01$). Similarly, common

carotid intima-media thickness was greater in NH subjects than in normotensive counterparts (751 ± 34 μm versus 653 ± 14 μm, $p < 0.01$).

As for the prognostic implications of NH, findings from a large meta-analysis including 25,856 hypertensive patients and 9641 individuals randomly recruited from population-based cohorts indicate that NH is a powerful risk factor for hard outcomes such as all-cause mortality and cardiovascular events [35]. In both groups nighttime BP was a stronger predictor of outcomes than daytime BP, day-night BP ratio, and non-dipping pattern.

In a retrospective study, Sun et al. [36] analyzed demographic/clinical characteristics and nocturnal BP circadian variability in 371 patients with hypertension (189 with spontaneous intracerebral hemorrhage and 182 controls). Multivariate logistic regression indicated that blood glucose, creatinine, and nocturnal mean arterial pressure were independent risk factors for intracerebral hemorrhage. More recently, the role of NH has been prospectively investigated in a large cohort of 859 diabetic subjects followed up for 5 years in the Dublin Outcome Study [12]. In this high-risk population, fully adjusted hazard ratio of cardiovascular mortality associated with nighttime BP was approximately 1.5-fold higher than daytime BP.

## 39.3 Isolated Nocturnal Hypertension (INH)

INH was defined in 2007 for the first time by Li et al. [37] to describe a novel clinical entity characterized by elevated nighttime BP (>120 and/or 70 mmHg) in the presence of normal daytime BP (<135/85 mmHg) in a rural Chinese population-based cohort. The authors investigated the prevalence and characteristics of this type of hypertension only detectable by 24-h ABPM and its association with arterial stiffness, a validated marker of target organ damage. Among 677 participants, 74 (10.9%) had INH, 310 (45.8%) were normotensive during both daytime and nighttime periods, 33 (4.9%) had isolated daytime hypertension, and 260 (38.4%) had day-night hypertension. Compared to subjects with ambulatory normotension, those with INH were characterized by older age, faster nighttime heart rate, higher serum levels of total cholesterol, and fasting glucose. From a retrospective analysis of a multiethnic international database [38], the same authors also reported that INH prevalence rates were higher in South Africans of black ancestry (10.5%) and in Japanese (10.4%) and Chinese subjects (10.9%) than in Western (6.0%) and Eastern Europeans (7.9%).

After this report, only few studies have prospectively investigated INH prevalence and clinical correlates (Fig. 39.2). In a Swedish study conducted in 414 patients with type 2 diabetes, Wijkman et al. [39] reported that INH was present in approximately 4.0% of patients. In the Jackson Heart Study, about one fifth of the entire cohort (19%) fulfilled clinic and ambulatory BP criteria for INH [26]. Participants with INH were characterized by older age, higher levels of total and LDL cholesterol, and higher prevalence of type 2 diabetes mellitus than normotensive counterparts (19% versus 10%). In the PAMELA population, elevated nighttime BP (>120/70 mmHg) and normal awake BP (<135/85 mmHg) was found in

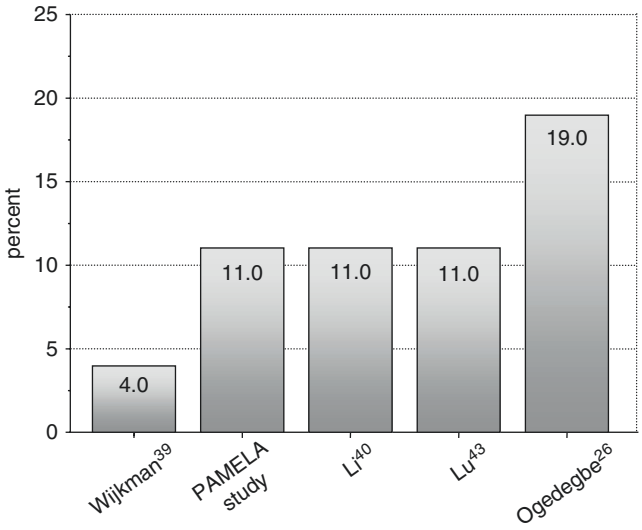



**Fig. 39.2** Prevalence rates of isolated nocturnal hypertension in five studies published from 2007 to 2013

approximately 11% of the participants. Compared to normotensive subjects, those with INH were older, more obese, and exhibited an unhealthy metabolic profile.

Reproducibility data on INH are very scanty. Li et al. [37] evaluated the long-term INH reproducibility over a 3.5-year follow-up in a group of 30 subjects. The persistence of INH pattern was documented only in ten subjects; two thirds of the sample, indeed, changed their ambulatory BP profile over time, as ten subjects developed day-night hypertension, two shifted to isolated daytime hypertension, and eight became sustained normotensives.

Pathophysiologic mechanism(s) of INH have been postulated to differ from those of isolated daytime and day-night hypertension [40]. Some line of evidence supports the hypothesis that INH is strongly related to altered sodium metabolism either due to increased dietary intake or impaired urinary sodium excretion. As previously underlined, INH is more common in Chinese and Japanese populations, characterized by higher sodium intake than European populations. In INH subjects studied by Li et al. [37], however, urinary sodium excretion was significantly lower than in other groups: this observation is more consistent with a disturbance of sodium excretion in the pathogenesis of increased nighttime BP.

Available evidence supports an association between sleep apnea syndrome with increased risk of hypertension and cardiovascular diseases; the relationship between INH and sleep apnea syndrome, however, remains unproven so far [41].

A recent narrative review by O'Flynn et al. [42] addressed the relationship between INH and subclinical organ damage. Only four studies, fulfilling inclusion predefined criteria (INH defined by ABPM according guidelines, assessment of recognized markers of target organ, and presence of normotensive control group) were

considered, and, because of heterogeneity of assessed outcomes, meta-analysis of results was not carried out.

Three out of four studies were conducted in population-based samples of Chinese [37, 43] and African-American ethnicities [26] and one in a diabetic setting [39]. In their pioneering study, Li et al. [37] found that four indices of arterial stiffness (i.e., central augmentation index, peripheral augmentation index, ambulatory arterial stiffness index, and brachial-ankle pulse wave velocity) were significantly increased in INH group compared with normotensive one. In a subsequent study, Lu et al. [43] failed to observe any difference in LVH prevalence (as assessed by Sokolow-Lyon and Cornell product indices) between INH and controls. Participants with INH belonging to Jackson Heart Study [26] exhibited higher absolute LV mass and LVH prevalence in unadjusted as well as age- and gender-adjusted models in comparison to normotensive controls. This was not the case for renal damage as assessed by proteinuria. Finally, Wijkman et al. [39] investigating the association of INH with cardiovascular damage in a small subset of diabetic patients reported no differences in central pulse pressure, central augmentation index, aortic pulse wave velocity, and LV mass index between cases and controls.

Thus, from the abovementioned studies, including a pooled population of 242 INH subjects, only inconclusive findings have been provided.

Available information on the prognostic value of INH is mostly derived from the International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome (IDACO) [44]. This large prospective database included 8711 individuals from 11 populations enrolled in Europe, Asia, and South America; during a mean follow-up period of 10.4 years, 577 subjects with INH showed a higher risk of all-cause mortality (HR 1.29, 95% CI 1.01–1.65, $p = 0.045$) and cardiovascular events (HR 1.38, 95% CI 1.02–1.87, $p = 0.037$), after adjusting for several confounders, including daytime BP.

## 39.4 Nocturnal Hypertension: Therapeutic Implications

Restoring normal circadian BP rhythm in hypertensive subjects is increasingly regarded as an effective therapeutic target to prevent/reduce organ damage and improve cardiovascular prognosis. Emerging evidence on treatment strategies targeting nighttime BP, such as bedtime administration of antihypertensive drugs, supports this approach as more protective against cardiovascular risk related to NH.

At the end of the 1990s, Uzu et al. [25] evaluated the effect of a short-term diuretic treatment (hydrochlorothiazide 25 mg daily for 4 weeks) in 21 hypertensive patients (10 dippers and 11 non-dippers). The extent of nocturnal BP fall was unaffected by treatment in dipper individuals; on the contrary it was markedly enhanced in non-dippers, mostly reverted to normal circadian rhythm.

In the Hypertension and Lipid Trial (HALT), the effect of bedtime administration of doxazosin on nighttime BP was tested in 118 hypertensive patients with different nocturnal BP patterns (18 extreme dippers, 46 dippers, 48 non-dippers, and 6 risers) [45]. The effect of doxazosin on mean nocturnal systolic BP varied depending on

dipping status: a 4-mmHg increase was observed in extreme dippers, whereas a decrease was documented in the remaining groups, in particular a decrement of 1 mmHg in dippers, 12 mmHg in non-dippers, and 18 mmHg in risers. Of note, approximately one third of non-dippers changed their status after therapy and became dippers.

In a prospective study aimed to compare the effect of valsartan (160 mg/day) administered either in the morning or at bedtime in 148 non-dipper hypertensive patients, similar reductions of office and 24-h BP were observed in both treatment arms after 3 months [46]. Diurnal/nocturnal BP ratio, however, was significantly increased only when valsartan was administered at bedtime (8% versus baseline, $p < 0.01$); as a result, 75% of patients in this group became dippers as compared to 24% of their counterparts. Of note, urinary albumin excretion was reduced only when valsartan was administered at bedtime.

Kario et al. [47] examined the effect of cilnidipine, a unique L-/N-type calcium channel blocker, on nocturnal BP in 615 Japanese hypertensive patients, classified according to their nocturnal dipping status as extreme dippers, dippers, non-dippers, and risers.

Cilnidipine induced BP decrements that were more pronounced at nighttime than daytime in risers, similar at nighttime as daytime in non-dippers, and more pronounced at daytime than nighttime in dippers. Restoration of circadian BP rhythm observed in this study may be ascribed to the dual antihypertensive effect of cilnidipine, a calcium blocker of both L- and N-type channels and the resulting inhibition of noradrenaline release and vasodilation.

The first therapeutic trial targeting NH was performed by Rossen et al. [48]: in an open-label crossover study including 41 patients with type 2 diabetes and NH, the authors investigated the effect of administration time of antihypertensive drugs. Patients were randomized to 8 weeks of either morning or bedtime once-daily administration of antihypertensive drugs, followed by 8 weeks of switched administration schedule. Bedtime administration of antihypertensive therapy resulted in a significant reduction in nighttime (7.5 mmHg; $p < 0.001$) and 24-h (3.1 mmHg; $p = 0.014$) systolic BP and a nonsignificant reduction in daytime (1.3 mm Hg; $P = 0.336$) systolic BP.

The potential benefit of improving nighttime BP control has been recently investigated in hypertensive subjects and in type 2 diabetic patients. The MAPEC study [49] tested the hypothesis that bedtime chronotherapy with ≥1 hypertensive drug may control BP and reduce cardiovascular risk more effectively than conventional therapy (i.e., all medications ingested in the morning). After a median follow-up of 5.6 years, subjects taking ≥1 BP-lowering medication at bedtime had a lower mean nighttime BP as well as reduced prevalence of non-dipping status (34% versus 62%; $p < 0.001$) than those taking all medications upon awakening; the difference in nocturnal BP was associated to a lower relative risk of total cardiovascular events (−60%).

Salles et al. [50] analyzed the prognostic impact of clinic and ambulatory BPs on cardiovascular morbidity and mortality in 565 type 2 diabetic subjects during a follow-up period of 5.7 years. They found that patients with persistent nighttime

systolic BP ≥120 mmHg experienced significantly more cardiovascular events as compared to those achieving nighttime systolic BP levels <110 mm Hg.

**Conclusions**

Consistent evidence from clinical studies supports the view that nocturnal BP is a strong predictor of intermediate and hard outcomes and points to the role of this out-of-office BP component only detectable by ABPM in improving cardiovascular risk stratification. In a practical perspective, targeting NH by correcting factors related to this condition and planning a chronotherapeutic approach may have important implications for public health.

**Disclosure** The authors report no conflicts of interest.

## References


1. Mancia G, Verdecchia P (2015) Clinical value of ambulatory blood pressure, evidence and limits. Circ Res 116:1034–1045
2. Tsioufis C, Andrikou I, Thomopoulos C et al (2011) Increased nighttime blood pressure or non dipping profile for prediction of cardiovascular outcomes? J Hum Hypertens 25:281–293
3. O'Brien E, Sheridan J, O'Malley K (1988) Dippers and non-dippers. Lancet 2(8607):397
4. Oh SW, Han SY, Han KH et al (2015) Morning hypertension and night non-dipping in patients with diabetes and chronic kidney disease. Hypertens Res 38:889–894
5. de la Sierra A, Redon J, Banegas JR et al (2009) Prevalence and factors associated with circadian blood pressure patterns in hypertensive patients. Hypertension 53:466–472
6. Cohen DL, Huan Y, Townsend RR (2013) Ambulatory blood pressure in chronic kidney disease. Curr Hypertens Rep 15:160–166
7. Wolf J, Hering D, Narkiewicz K (2010) Non-dipping pattern of hypertension and obstructive apnea syndrome. Hypertens Res 39:867–871
8. Pierdomenico SD, Lapenna D, Guglielmini LD et al (1997) Arterial disease in dipper and non-dipper hypertensive patients. Am J Hypertens 10:511–518
9. Cuspidi C, Meani S, Salerno M et al (2004) Cardiovascular target organ damage in essential hypertensives with or without reproducible nocturnal fall in blood pressure. J Hypertens 22:273–280
10. Ohkubo T, Hozawa A, Yamaguchi J et al (2002) Prognostic significance of nocturnal decline in blood pressure in subjects with and without high 24-hour blood pressure: the Ohasama study. J Hypertens 20:2183–2189
11. Fagard RH, Thijs L, Staessen JA et al (2009) Night-day blood pressure ratio and dipping pattern as predictors of death and cardiovascular events in hypertension. J Hum Hypertens 23:645–653
12. Draman MS, Dolan E, van der Poel L et al (2015) The importance of nighttime systolic blood pressure in diabetic patients: Dublin Outcome study. J Hypertens 33:1373–1377
13. Tsioufis C, Stefanadis C, Antoniadis D et al (2000) Absence of any significant effects of circadian blood pressure variations on carotid artery elastic properties in essential hypertensive subjects. J Hum Hypertens 14:813–818
14. Grandi AM, Broggi R, Jessula A et al (2002) Relation of extent of nocturnal blood pressure decrease to cardiovascular remodeling in never-treated patients with essential hypertension. Am J Cardiol 89:1193–1196
15. Bjorklund K, Lind L, Andren B, Lithell H (2002) The majority of nondipping men do not have increased cardiovascular risk: a population-based study. J Hypertens 20:1501–1506

16. Nakano S, Ito T, Furuya K et al (2004) Ambulatory blood pressure level rather than dipper/non dipper status predicts vascular events in type 2 diabetic subjects. Hypertens Res 27:647–656
17. Mancia G, De Backer G, Dominiczak A et al (2007) 2007 Guidelines for the Management of Arterial Hypertension. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 25:1105–1187
18. Mancia G, Fagard R, Narkiewicz K et al (2013) 2013 ESH/ESC Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 31:1281–1357
19. O'Brien E, Parati G, Stergiou G et al; European Society of Hypertension Working Group on Blood Pressure Monitoring (2013) European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens 31:1731–1768.
20. Pickering TG (1990) The clinical significance of diurnal blood pressure variations Dippers and non dippers. Circulation 81:700–702
21. Sherwood A, Steffen PR, Blumenthal JA et al (2002) Nighttime blood pressure dipping: the role of the sympathetic nervous system. Am J Hypertens 15:111–118
22. Kimura G (2008) Kidney and circadian blood pressure rhythm. Hypertension 51:827–828
23. Hermida RC, Chayan L, Ayala DE et al (2009) Association of metabolic syndrome and blood pressure non-dipping profile in untreated hypertension. Am J Hypertens 22:307–313
24. Grassi G, Seravalle G, Quarti-Trevano F et al (2008) Adrenergic, metabolic, and reflex abnormalities in reverse and extreme dipper hypertensives. Hypertension 52:925–932
25. Uzu T, Kimura G (1999) Diuretics shift circadian rhythm of blood pressure from non-dipper to dipper in essential hypertension. Circulation 100:1635–1638
26. Ogedegbe G, Spruill TM, Sarpong DF et al (2013) Correlates of isolated nocturnal hypertension and target organ damage in a population-based cohort of African Americans: The Jackson Heart Study. Am J Hypertens 26:1011–1016
27. Androulakis E, Papageorgiou N, Chatzistamatiou E et al (2015) Improving the detection of preclinical organ damage in newly diagnosed hypertension: nocturnal hypertension versus non-dipping pattern. J Hum Hypertens 29:689–695
28. Wang C, Deng WJ, Gong WY et al (2015) Nocturnal hypertension correlates better with target organ damage in patients with chronic kidney disease than a nondipping pattern. J Clin Hypertens 17:792–801
29. Cuspidi C, Sala C, Valerio C et al (2011) Nocturnal blood pressure in untreated essential hypertensives. Blood Press 20:335–341
30. Abdalla M, Goldsmith J, Muntner P et al (2016) Is isolated nocturnal hypertension a reproducible phenotype? Am J Hypertens 29:33–38
31. Cuspidi C, Facchetti R, Bombelli M et al (2013) Nighttime blood pressure and new-onset left ventricular hypertrophy: findings from the Pamela population. Hypertension 62:78–84
32. Sega R, Facchetti R, Bombelli M et al (2005) Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. Circulation 111:1777–1783
33. Perez-Lloret S, Tobbli JE, Cardinali DP et al (2008) Nocturnal hypertension defined by fixed cut-off limits is a better predictor of left ventricular hypertrophy than non-dipping. Int J Cardiol 127:387–389
34. Cuspidi C, Sala C, Tadic M et al (2016) Nocturnal hypertension and subclinical cardiac and carotid damage: an updated review and meta-analysis of echocardiographic studies. J Clin Hypertens (Greenwich) 18(9):913–920. doi:10.1111/jch.12790
35. Hansen TW, Li Y, Boggia J et al (2011) Predictive role of the night-time blood pressure. Hypertension 57:3–10
36. Sun J, Yang W, Zhu Y et al (2014) The relationship between nocturnal blood pressure and hemorrhagic stroke in Chinese hypertensive patients. J Clin Hypertens (Greenwich) 16:652–657

37. Li Y, Staessen JA, Lu L et al (2007) Is isolated nocturnal hypertension a novel clinical entity? Findings from a Chinese population study. Hypertension 50:333–339
38. Staessen JA, O'Brien ET, Amery AK et al (1994) Ambulatory blood pressure in normotensive and hypertensive subjects: results from an international database. J Hypertens 12(Suppl 7):S1–S12
39. Wijkman M, Länne T, Engvall J et al (2009) Masked nocturnal hypertension-a novel marker of risk in type 2 diabetes. Diabetologia 52:1258–1264
40. Li Y, Wang JG (2013) Isolated nocturnal hypertension a disease masked in the dark. Hypertension 61:278–283
41. Maeder MT, Schoch OD, Rickli H (2016) A clinical approach to obstructive sleep apnea as a risk factor for cardiovascular disease. Vasc Health Risk Manag 12:85–103
42. O'Flynn AM, Madden JM, Russell AJ et al (2015) Isolated nocturnal hypertension and subclinical target organ damage: a systematic review of literature. Hypertens Res 38:570–575
43. Lu L, Li Y, Huang QF (2008) The relationship between isolated nocturnal hypertension and left ventricular hypertrophy. Zhonghua Nei Ke Za Zhi 47:819–822
44. Fan HQ, Li Y, Thijs L et al (2010) Prognostic value of isolated nocturnal hypertension on ambulatory measurement in 8711 individuals from 10 populations. J Hypertens 28:2036–2045
45. Kario K, Schwartz JE, Pickering TG (2000) Changes of nocturnal blood pressure dipping status in hypertensives by nighttime dosing of alfa-adrenergic blocker, doxazosin. Results from the HALT study. Hypertension 35:787–794
46. Hermida RC, Calvo C, Ayala DE et al (2005) Treatment of non-dipper hypertension with bedtime administration of valsartan. J Hypertens 23:1913–1922
47. Kario K, Nariyama J, Kido H et al (2013) Effect of a novel calcium channel blocker on abnormal nocturnal blood pressure in hypertensive patients. J Clin Hypertens (Greenwich) 15:465–472
48. Rossen NB, Knudsen ST, Fleischer J et al (2014) Targeting nocturnal hypertension in type 2 diabetes mellitus. Hypertension 64:1080–1087
49. Hermida RC, Ayala DE, Mojón A, Fernández JR (2010) Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. Chronobiol Int 27:1629–1651
50. Salles GF, Leite NC, Pereira BB et al (2013) Prognostic impact of clinic and ambulatory blood pressure components in high-risk type 2 diabetic patients: the Rio de Janeiro Type 2 Diabetes Cohort Study. J Hypertens 31:2176–2186

# Salt and Hypertension

# 40

Andrew Smyth and Martin O'Donnell

## 40.1 Introduction

Hypertension is a leading global cause of death, more than tobacco use or physical inactivity or overweight and obesity [1]. Excess dietary sodium intake is associated with increased blood pressure [2, 3], cardiovascular disease, stroke, and other chronic diseases [4], and most current cardiovascular prevention guidelines recommend population-wide reductions in sodium intake [5]. As sodium intake is a population-wide exposure, it is an attractive target for the prevention and treatment of hypertension, as even small population-level reductions in blood pressure may result in large reductions in cardiovascular disease (CVD).

Sodium is an essential nutrient, is required for normal physiological function, and is tightly regulated (via multiple mechanisms) to maintain extracellular sodium concentrations [6], under the governance of numerous renal, endocrine, vascular, central, and immune systems. Excess dietary sodium intake is an important risk factor for hypertension, with marked interindividual variability in the pressor effect of increased dietary sodium attributed to both environmental (e.g., potassium intake) and genetic factors. Dietary sodium restriction for the management of hypertension dates back to 1948 when Kempner et al. introduced the rice diet [7]. Since then, epidemiologic studies have demonstrated a curvilinear increase in blood pressure with increasing sodium intake in populations, and clinical trials have shown that reducing sodium intake results in a reduction in blood pressure [8–10]. Findings from clinical trials of blood pressure have led to guidelines that recommend low sodium intake (e.g., <2.0 g/day of sodium, equivalent to <5 g/day of salt

A. Smyth • M. O'Donnell (✉)
Health Research Board Clinical Research Facility Galway, National University of Ireland Galway, Galway, Ireland

Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada
e-mail: andrew.smyth@nuigalway.ie; martin.odonnell@nuigalway.ie



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_40

recommended by WHO) [1] for the entire adult population. While modeling studies have projected large gains in the reduction of premature cardiovascular mortality, from reductions in sodium intake, based on an assumed linear relationship between sodium intake, blood pressure, and CVD, large prospective cohort studies have reported a J-shaped association between sodium intake and CVD/mortality, with a nadir of risk at moderate intake range (2.6–5.0 g/day) [11]. A recent pooled analysis of four studies ($n$ = 133,118) suggests the association between sodium intake and cardiovascular disease, and mortality was only significant in those with baseline hypertension [12]. Therefore, while the evidence supporting the reduction of high sodium intake (>4–5 g/day) is aligned, the evidence supporting a reduction from moderate to low intake is inconsistent and has led to controversy about whether low sodium intake should be recommended to the entire population.

The Global Burden of Disease (GBD) estimates mean global sodium intake at 3.95 g/day, based on meta-analyses of 24-h urine collection data from 187 countries [13], which means that achieving current low sodium intake targets will require a considerable reduction in mean intake of the population. The predominant dietary source of sodium is salt (sodium chloride), which accounts for approximately 95% of daily intake. Almost the entire (99.2%) adult population currently exceed recommendations [14, 15], and most consume between 3 and 6 g/day of sodium [13, 16].

Despite a large body of research on the effects of sodium intake and health, there are no large randomized controlled trials comparing low to moderate sodium intake for prevention CV events/mortality. The absence of definitive clinical trials has resulted in different perspectives about whether low or moderate sodium intake should be recommended in the general population, based on current evidence.

In this chapter, we review the relationship of dietary sodium intake with blood pressure and cardiovascular disease.

## 40.2 Measurement of Dietary Sodium Intake

There is no simple, accurate, and reliable method of estimating sodium intake in individuals. The reference standard for individual-level measurement of sodium intake is repeated 24-h urine sodium collection [17, 18], as about 95% of ingested sodium is thought to be excreted in urine (although this is dependent on amount of loss from other sources, such as sweat). Single measurements of sodium intake are problematic for individual-level estimation of sodium intake, because of day-to-day variability in intake and data suggesting infradian rhythmicity of interstitial sodium storage (especially the skin), independent of daily intake [19, 20]. A recent study suggested that at least seven 24-h urinary estimates would be required to achieve classification accuracy (within 3 g/day) of 92% for individual estimation of usual sodium intake [21]. A key limitation of 24-h urine collections is the high frequency of incomplete sample collection [22], which is also a particular challenge in estimating sodium intake in large populations. For population-level

estimates, single urine samples (e.g., fasting morning or spot urine samples) may also be used to estimate intake using various formulae (including the Kawasaki formula [23], Tanaka formula [24], INTERSALT formula [25], and Mage formula [26]). While these formula-based approaches are inaccurate for individual-level measurement, some have been validated (using standardized protocols) for population-level estimation of sodium intake, but the validity of using some approaches (e.g., Kawasaki formula) is dependent on timing and fasting status of urine capture [26, 27]. Dietary sodium intake may also be estimated using food frequency questionnaires or 24-h dietary recall; the main advantages of these techniques include convenience, the ability to carry out repeated measurements more conveniently, and the advantage of also being able to identify key dietary sources of excess sodium. However, these methods are limited by imprecision in estimating portion size, recall bias, variations in the sodium content of foods, and requirement for validation in different settings and countries. These issues are particularly important where the majority of sodium in the food chain is nondiscretionary [14, 28]. Taken together, the absence of feasible methods to accurately and reliably measure sodium intake in individuals contributes to difficulties in both the interpretation of studies and implementation of sodium reduction interventions in clinical practice.

## 40.3 Global Sodium Intake

A 2013 meta-analysis of cross-sectional studies including 187 countries reported mean global intake at 3.95 g/day, with significant regional variations [13]. Intakes were highest in East Asia, Central Asia, and Eastern Europe (mean >4.2 g/day) and in Central Europe and Middle East/North Africa (3.9–4.2 g/day). Mean intakes in North America, Western Europe, and Australia/New Zealand ranged from 3.4 to 3.8 g/day. Between 1990 and 2010, there was a suggestion of slight increases in overall sodium intakes. Among individual studies, the INTERSALT study was the first international studies that reported estimates of sodium intake, based on 24-h urine collections from 52 populations in 32 countries ($n = 10{,}079$), and found wide variations in 24-h sodium excretion from 0.46 g/day (Yanomami Indians in Brazil) up to 6.0 g/day (Tianjin, Northern China) [29]. The INTERMAP study, based in Japan, China, the UK, and the USA, that used two consecutive 24-h dietary recalls and one 24-h urine collection to estimate sodium intake confirmed that highest mean sodium excretion was in Northern China [30, 31]. The largest study to report global variations in sodium intake is the Prospective Urban Rural Epidemiological Study (PURE Study), which included 628 communities in 18 countries and reported a mean intake of 4.9 g/day [16].

Dietary sources of sodium intake may be discretionary (added during cooking or at the table) or nondiscretionary (processed or preprepared foods) [32]. The ratio of discretionary to nondiscretionary use varies significantly between regions [33]. For example, in the USA, mean sodium intake per day is 3660 mg with 29% from added salt, compared to Japan with a mean sodium intake per day of 4651 mg with 9.5% from added salt [33].

## 40.4 Sodium Intake and Blood Pressure (Physiology)

Sodium is essential to mammalian physiology [34], and our appetite for sodium, in low sodium intake settings, is controlled by neural mechanisms in response to peripheral hormonal signals (principally angiotensin II and aldosterone). Sodium is required to maintain osmotic pressure and retain water in the extracellular space [6], achieved by balancing dietary sodium intake, storage, and excretion. The relationship of sodium intake with blood pressure spans a continuum from physiologic role in maintenance of blood pressure to pathologic determinants of hypertension and cardiovascular disease. Our understanding of how excess sodium intake causes increases blood pressure and risk of cardiovascular disease continues to evolve, as does our understanding of the effects of low sodium intake on physiologic and clinical outcomes.

*Sodium Intake and Blood Pressure*: A change in blood pressure with high sodium intake is observed in a proportion of the population and is termed 'salt sensitivity'. Although arbitrarily defined in a binary manner (10% increase in blood pressure with high sodium load compared to low sodium intake), salt sensitivity is more accurately considered a continuous characteristic [35]. Salt sensitivity is more common in blacks than whites and with increasing age, but not significantly associated with obesity or gender [36]. Sodium intake may also modify the circadian pattern, and individuals may be more or less salt sensitive depending on the time of day that sodium was consumed [37].

Traditional theories propose that the key mechanism underlying the pressor effect in salt-sensitive individuals is impaired renal sodium excretion leading to expanded extracellular fluid volume and resultant hypertension [35], and salt-resistant individuals rapidly excrete sodium in response to a sodium load [38]. In the setting of higher sodium intake, sodium retention is proposed to arise due to increases in the activity of sodium transporters and Na/K/ATPase activity [39], sympathetic activity (through effects on the Na/H exchanger) [40], and angiotensin II, which increases the activity of epithelial sodium channels (ENaC) [41]. ENaC activity is also increased by aldosterone, which physiologically leads to vasodilatation through nitric oxide generation in the endothelium. However, hypertension may lead to endothelial dysfunction and denudation, promoting sodium entry into vascular smooth muscle causing vasoconstriction [42]. Animal studies also suggest that higher sodium intake leads to upregulated expression of serum- and glucocorticoid-inducible kinase 1 (SGK1) which further mediates mineralocorticoid receptors and its effect on ENaC [43].

The central role of the kidney in blood pressure regulation is supported by animal experiments which report increased blood pressure in a normotensive rat after transplantation of a kidney from a salt sensitive hypertensive rat [44, 45] and increased activity of the Na/H exchanger [46]. Genome-wide association studies (GWAS) have also identified variants in the promoter of the UMOD gene, which encodes uromodulin (a protein commonly secreted in normal urine), which increase susceptibility to salt sensitivity, hypertension, and kidney disease [47]. High sodium intake prompts the release of a "digitalis-like factor," a stereoisomer of ouabain, from the adrenal glands and brain, increasing expression of activity of the renal sodium pump leading to increases in blood pressure [48, 49].

Sodium retention may also increase intracellular fluid sodium concentration [48, 50], stimulating the sodium-calcium exchanger type 1 driving calcium into vascular smooth muscle cells, membrane depolarization, and further intracellular calcium entry [51], leading to vasoconstriction, compounded by reduced nitric oxide synthesis and increased asymmetric dimethyl L-arginine (an inhibitor of nitric oxide production) [52].

Modifications in dietary sodium intake may result in parallel changes in plasma sodium in both normotensive and hypertensive individuals [53]. This may contribute to hypertension by promoting intracellular to extracellular fluid transfer, stimulating thirst, inducing pressor effects on the hypothalamus and RAAS [54], altered smooth muscle tension [55, 56], cellular hypertrophy of both arterial smooth muscle and cardiac myocytes [57], stiffened endothelium, and reducing nitric oxide release [58]. Although a UK study reported a 1 mmol/L increase in plasma sodium is associated with a 1 mmHg increase in systolic blood pressure, this was not confirmed in an analysis of normotensive participants from the Framingham Heart Study [59].

The effects of sodium are also dependent on the associated counter anion, as only sodium chloride ingestion is associated with hypertension [60]. In addition, the hypertensive effect of increased sodium intake may be attenuated by increased potassium intake, due to increased serum potassium which stimulates the sodium pump and opens potassium channels, leading to hyperpolarization of the endothelial cell and vasodilatation [61, 62]. This subsequently leads to decreased cytosolic calcium in vascular smooth muscle, further promoting vasodilatation. In the kidney, higher potassium intake inhibits sympathetic activity and angiotensin II activity, reducing the reabsorption of sodium [39]. The importance of the sodium/potassium balance is also highlighted by a study which reported reduced muscle potassium in participants with hypertension compared to healthy normotensive controls [63].

Although most research focuses on daily sodium intake, based on the assumption that the majority of consumed sodium is excreted, total body sodium and sodium storage may play a significant role in hypertension, calling traditional theories of the association between sodium and hypertension into question [64]. Blood pressure and blood volume remained essentially unchanged in salt-resistant normotensive individuals in response to significant sodium loading, despite significant sodium retention [65, 66]. A study of 32 healthy male test subjects in a metabolic ward with varied sodium intake (50–550 mmol/day) reported large amounts of sodium retention but minimal change in blood pressure [67]. Subsequent studies report that total body sodium fluctuates independently of intake, body weight, or extracellular water [19], as even at fixed dietary sodium intake, an infradian or circaseptan rhythmicity is observed in 24-h urine collections for sodium [20, 21].

Animal and human studies demonstrate a capacity to retain large amounts of sodium, without the associated amount of water, due to an ability to store sodium in an osmotically inactive form in the interstitium [67, 68]. A major site of sodium storage is the skin, where sodium binds to negatively charged glycosaminoglycans [69]. The skin acts as a buffering compartment for sodium, which may be accessed by monocyte phagocytic system cells that sense sodium via tonicity-responsive enhancer binding protein (TonBEP), which signals vascular endothelial growth

factor-C (VEGF-C) to increase the lymph capillary network to clear sodium from skin storage [70]. Importantly, others propose that the storage of osmotically inactive sodium may also occur in the glycocalyx of endothelial linings, limiting the ability of plasma sodium ions to enter the endothelium, triggering other mechanisms of hypertension [71, 72], which may be exaggerated by endothelial dysfunction seen with arterial hypertension.

Acute sodium loading in normotensive salt-resistant individuals is associated with increased stroke volume, cardiac output, and blood volume, with minimal change in blood pressure [64]. Similar findings were observed with chronic sodium loading in salt-resistant subjects, but not in salt-sensitive subjects. Importantly, sodium loading in normal subjects has been associated with increases in stroke volume, cardiac output, and blood volume, without increases in blood pressure in salt-sensitive and salt-resistant normotensives [64]. This suggests that an important determinant is peripheral vascular resistance, not dependent on renal or extrarenal sodium handling, where sodium loading results in a reduction in peripheral resistance in those who do not have an increase in blood pressure (salt resistant), whereas those experiencing a rise in blood pressure (i.e., salt sensitive) have a muted response [73]. A study of 21 normotensive human volunteers reported that those with salt sensitivity had higher blood pressure in response to sodium loading, due to increased total peripheral resistance [74]. Importantly, those with salt sensitivity were found to be unable to modulate total peripheral resistance in response to salt depletion and an inability to vasodilate during salt loading, proposed to be due to differences in sodium storage in the interstitium.

*Other Physiologic Effects of Low Sodium Intake*: While low sodium intake is associated with lower blood pressure, it may also result in RAAS activation (increases renin 3.6-fold and stimulates aldosterone secretion 3.2-fold [75, 76]) and may have adverse effects on the lipid profile [77] or other biomarkers (including C-reactive protein (CRP), interleukin (IL-6), troponin, B-natriuretic peptide (BNP), and uromodulin [47, 78–80]).

Reductions in the dietary intake of sodium have also been associated with sympathetic activation—specifically increases in urinary norepinephrine levels and plasma norepinephrine concentrations—as well as norepinephrine spillover and increased efferent postganglionic sympathetic nerve activity [81]. This may also lead to impaired baroreceptor modulation of vagal and sympathetic cardiovascular outflow (i.e., lack of restrained sympathetic tone) [82]. A study of 11 patients with untreated mild to moderate essential hypertension reported that a reduction in urinary sodium excretion (from a mean of 221 mmol/day to 75 mmol/day) was accompanied by increases in plasma renin activity, aldosterone, and muscle sympathetic nerve traffic activity (MSNA), as well as a reduction in baroreflex modulation of MSNA [81], which persisted beyond the initial period of sodium reduction. Indeed, increased sodium intake is recommended in patients with symptomatic orthostatic hypotension. An animal study, where apolipoprotein E mice were given a low-salt diet for 6 weeks, results in a fourfold increase in plaque accumulation, in addition to activation of RAAS and increased vascular expression of inflammatory cytokines and adhesion molecules, which was attenuated with a high-salt diet [83].

## 40.5 Sodium Intake and Blood Pressure (Epidemiology)

INTERSALT [2] included randomly sampled participants aged 20–50 years from 52 centers in 39 countries ($n$ = 10,079) who provided a 24-h urine collection for sodium. Sodium excretion was positively associated with systolic blood pressure (recorded as the mean of two readings) in 39 of the 52 centers, but a negative association was observed in 2 centers. There was a significant linear association between median 24-h urinary sodium excretion for all 52 centers and the slope of systolic blood pressure; however, four isolated populations with both low sodium excretion and low median blood pressure (Yanomami Indians in Brazil and Xingu in Brazil, Papua New Guinea, and Kenya) strongly influenced the observed associations. When these four populations were excluded, there was loss of statistical significance between sodium excretion and blood pressure.

INTERMAP [30] was an international cooperative multi-sample cross-sectional population study of men and women aged 40–50 years from China, Japan, the UK, and the USA ($n$ = 4680) where each participant provided four 24-h dietary recalls and two timed 24-h urine samples. Estimated dietary sodium intake was positively associated with blood pressure [84]. INTERMAP also reported that other dietary components may have important blood pressure effects, specifically sugar sweetened beverages, whose effects were further exaggerated in those with the highest estimated sodium intake [85].

The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) study included community-dwelling adults aged 45–79 years that were unselectively recruited from general practice age-sex registers in the UK. Participants completed health and lifestyle questionnaires and provided casual urine specimens, 7-day diet diaries, and 24-h urine collections (in a subset). Increases in urinary sodium to creatinine ratio were positively associated with blood systolic and diastolic blood pressure in men and women, independent of hypertension, age, and sex [86].

The Prospective Urban Rural Epidemiology (PURE) study included 102,216 adults from 18 countries where the Kawasaki formula [23] was applied to results from fasting morning urine samples to estimate 24-h sodium excretion. These analyses reported a positive association between sodium excretion and systolic and diastolic blood pressure in all regions [16]. The slope of the association was less steep in the Middle East than other regions, and the observed association was nonlinear with a steeper slope seen at sodium excretion >5 g/day. The magnitude of association between sodium intake and blood pressure was largest in older individuals, those with high sodium intake, those with hypertension, and those with low potassium intake.

## 40.6 Sodium Intake and Blood Pressure (Clinical Trials)

Dietary sodium restriction for the management of hypertension was first reported in 1948 when Kempner et al. introduced the rice diet [7]. Since then, multiple clinical trials have been performed with the objective of providing robust data about the role of dietary modification in the treatment of blood pressure, with TONE and TOHP

trials being the longest in duration and the DASH-Sodium trial exerting most influence on target sodium intake recommended by guidelines.

*Short-Term Trial*: The Dietary Approaches to Stop Hypertension (DASH) trial was a crossover trial that included adults (≥22 years old) with blood pressure >120/80 mmHg up to stage 1 hypertension (defined as systolic blood pressure up to 159 mmHg or diastolic blood pressure up to 95 mmHg). Participants were randomized to three levels of dietary salt intake (low, intermediate, or high) on two different diets (the normal American diet or the DASH diet which is rich in fruits, vegetables, and low-fat dairy products). Participants completed a 2-week run-in period where all consumed a high-sodium control diet and were then randomized to one of the diets and one of the salt targets for 30 consecutive days. A 24-h urine collection was completed during the screening period and during the last week of each intervention period, and dietary adherence was determined by reviewing food diaries or eating meals on site. For those randomized to the high salt intake, achieved dietary sodium intake was 144 mmol/day (DASH diet) and 141 mmol/day (control diet); for the intermediate salt intake, achieved dietary sodium intake was 107 mmol/day (DASH diet) and 106 mmol/day (control diet); and for the low salt intake, achieved dietary sodium intake was 67 mmol/day (DASH diet) and 64 mmol/day (control diet). Reduction in dietary sodium intake was associated with a reduction in blood pressure, but the effects were greater in those on the DASH diet and in those of African origin and older participants [87]. A reduction in dietary sodium intake and the DASH diet resulted in a decrease in systolic blood pressure of 7.1 mmHg in participants who were normotensive at baseline and a reduction of 11.5 mmHg in participants with hypertension at baseline [88].

*Longer-Term Clinical Trials*: The Trials of Hypertension Prevention (TOHP) trials included participants aged 30–54 years who had high-normal diastolic blood pressure (80–89 mmHg) and not taking antihypertensive medications for the preceding 2 months and tested multiple interventions ($n$ = 2142). Lifestyle interventions were provided by nutritionists, psychologists, or other counselors who focused on shopping, cooking, and food selection behaviors to reduce caloric intake (weight reduction) or sodium intake (sodium reduction) or provided education on stress management. The sodium reduction intervention reduced urinary sodium excretion by 50 mmol/day at 6 months and by 40 mmol/day at 36 months; at 6 months, blood pressure had reduced by 2.9/1.6 mmHg but only 1.3/0.9 mmHg at 36 months [89]. Therefore, trials with longer term follow-up are needed to determine if sodium reduction results in clinically meaningful reductions in blood pressure.

The Trial of Non-Pharmacological Interventions in the Elderly (TONE) included participants aged 60–80 years with an average of nine blood pressure measurements with average systolic blood pressure <145 mmHg and diastolic blood pressure <85 mmHg, on a single antihypertensive agent or a single combination regimen (consisting of a diuretic and a non-diuretic agent). Participants were excluded if they had a history of recent cardiovascular disease (heart attack, stroke, angina, heart failure) or diabetes. Interventions included sodium reduction (target sodium intake of 80 mmol/day measured by 24-h urine collection) and weight reduction

(goal of >4.5 kg [10 lb] sustained weight loss) delivered by nutritionists and exercise counselors through a combination of small group and individual meetings. The primary endpoint of the trial was the occurrence of high blood pressure at one or more TONE study visits following attempted withdrawal of antihypertensive medications. Sodium reduction intervention resulted in a decrease in urinary sodium excretion of 45.2 mmol/day at 9 months, 44.6 mmol/day at 18 months, and 39.8 mmol/day at 30 months. Sodium reduction led to a reduction in blood pressure of 3.4/1.9 mmHg [4].

A cluster randomized trial of 29 primary schools ($n$ = 279 children and $n$ = 832 family members) in urban China tested an educational intervention highlighting the harmful effects of sodium intake and included strategies to reduce sodium intake over three and a half months. Sodium intake was reduced by a mean of 0.8 g/day (from a baseline of 4.7 g/day) with an overall increase in blood pressure, although significantly less of an increase was observed in the intervention group [90].

Multiple meta-analyses of clinical trials testing the ability of dietary sodium reduction to reduce blood pressure have been completed, reporting variable magnitudes of blood pressure reduction with reduction in dietary sodium intake (Tables 40.1 and 40.2). Clinical trials have also tested if salt substitutes (i.e., replacing a proportion sodium chloride with potassium chloride or magnesium sulfate) can reduce blood pressure. Meta-analyses of five trials ($n$ = 1974) reports a mean blood pressure reduction of 4.9/1.5 mmHg [91]. Subsequently, the China Rural Health Initiative Sodium Reduction Study randomized 120 Chinese villages to community health education and salt substitution (with a subsidy in some villages) vs. controls [92]. Those randomized to intervention had a 0.3 g reduction in daily sodium intake, but there was no significant difference in blood pressure.

Clinical trials of dietary sodium reduction have also been completed in other populations. A pilot study of 38 patients with heart failure randomized participants to low (1500 mg/day) or moderate (2300 mg/day) sodium intake and after 6 months showed sodium reduction to be feasible and accompanied by a reduction B-type natriuretic peptide in the low sodium group [93]. A crossover trial of 20 participants with hypertensive chronic kidney disease (CKD) showed that low sodium intake (mean 75 mmol/day) resulted in lower blood pressure and proteinuria than high sodium intake (mean 168 mmol/day); however low sodium intake also resulted in increases in plasma renin and aldosterone [94].

## 40.7 Ongoing Clinical Trials

The China Salt Substitute and Stroke Study (SSaSS) is a large cluster randomized trial of >21,000 participants in 600 villages that has completed recruitment and tests the effect of salt substitution on stroke risk over 5 years of follow-up [95]. The Prevent Adverse Outcomes in Heart Failure by Limiting Sodium (PROHIBIT) Study is currently recruiting participants with heart failure and will test the effect of a 12-week dietary intervention where participants receive food with either 1500 or

**Table 40.1** Meta-analyses of sodium trials

| Author | Included trials | Outcome |
|---|---|---|
| Law et al., 1991 [115] | 68 crossover trials<br>10 randomized trials | SBP reduction of 5 mmHg overall, but reduction of 7 mmHg in hypertensives |
| Midgley et al., 1996 [116] | 56 trials monitored by timed sodium excretion | Mean reduction in 24-h urinary sodium excretion of 95 mmol in hypertensives ($n$ = 1131) and 125 mmol in normotensives ($n$ = 2374). Per 100 mmol reduction in urinary sodium excretion per day, a reduction in BP of 3.7/0.9 mmHg in hypertensives and by 1.0/0.1 mmHg in normotensives |
| Cutler et al., 1997 [117] | 32 trials with outcome data for 2365 subjects | Reducing sodium resulted in blood pressure reduction of 4.8/2.5 mmHg in hypertensives and 1.9/1.1 mmHg in normotensives. Per 100 mmol reduction, BP reduction of 5.8/2.5 mmHg in hypertensives and 2.3/1.4 mmHg in normotensives |
| Graudal et al., 1998 [75] | 59 trials of hypertensives and 56 trials of normotensives | In hypertensives, mean reduction of sodium intake of 118 mmol/day reduced BP by 3.9/1.9 mmHg. In normotensives, mean reduction of sodium intake of 160 mmol/day reduced blood pressure by 1.2/0.3 mmHg |
| Alam et al., 1999 [118] | 11 trials of ≥ 9-week duration of high/low sodium diets | A chronic high sodium diet increased BP by 5.6/3.5 mmHg, with increase in BP of 5.5/2.6 mmHg in trials of participants ≥60 years and 3.3/2.7 mmHg in participants with mean age close to 60 years |
| Hooper et al., 2002 [119] | 11 trials of interventions of ≥6-month duration | With sodium reduction of 35.5 mmol/day blood pressure was reduced by 1.1/0.6 mmHg at 13–60 months |
| He et al., 2002 [120] | 28 trials (17 in hypertensives and 11 in normotensives) with modest reduction in salt intake and a duration of ≥4 weeks | In hypertensives, the mean reduction in sodium was 78 mmol/day with a BP reduction of 5.0/2.7 mmHg. In normotensives, the mean reduction in sodium was 74 mmol/day with a BP reduction of 2.0/1.0 mmHg. For a 100 mmol reduction in sodium, BP was predicted to fall by 7.1/3.9 mmHg in hypertensives and by 3.6/1.7 mmHg in normotensives |
| He et al., 2013 [10] | 34 trials of duration of ≥4 weeks | Reduction in urinary sodium of 75 mmol/day was associated with a BP reduction of 4.28/2.06 mmHg. BP reduced by 5.39/2.82 mmHg in hypertensives and by 2.42/1.00 mmHg in normotensives |

3000 mg/day of sodium [96]. The SODIUM-HF trial is also currently recruiting participants with heart failure to test the effect of a low sodium diet (1500 mg/day) vs. usual care on a composite outcome of all-cause mortality, cardiovascular hospitalization, and cardiovascular emergency department visits over 12-month follow-up [97]. The Sodium Intake in Chronic Kidney Disease Study (STICK) is also currently recruiting participants with chronic kidney disease (eGFR 30–60 mL/min/1.73m$^2$) to test if sodium reduction (<2300 mg/day) vs. general healthy eating guidelines reduces progression of kidney disease over 2 years [98].

**Table 40.2** Estimates of effect of reduced sodium on systolic and diastolic blood pressure in adults overall and by subgroup (Adapted [28])

| Subgroup | No. of studies | No. of participants[a] | Systolic blood pressure | | Diastolic blood pressure | |
|---|---|---|---|---|---|---|
| | | | $I^2$ | Effect estimate: mean difference (95% CI)[b,c] | $I^2$ | Effect estimate: mean difference (95% CI) |
| Overall | 36 | 6736 | 65 | −3.39 (−4.31 to −2.46) | 60 | −1.54 (−2.11 to −0.98) |
| Blood pressure status at baseline: | | | | | | |
| No hypertension | 7 | 3067 | 61 | −1.38 (−2.74 to −0.02) | 38 | −0.58 (−1.29 to 0.14) |
| Hypertension | 24 | 2273 | 13 | −4.06 (−5.15 to −2.96) | 29 | −2.26 (−3.02 to −1.50) |
| Relative sodium reduction in intervention group: | | | | | | |
| <1/3 of control | 8 | 3995 (4001) | 46 | −1.45 (−2.29 to −0.60) | 38 | −0.74 (−1.28 to −0.19) |
| ≥1/3 of control | 30 | 3521 | 55 | −3.79 (−4.82 to −2.75) | 55 | −1.68 (−2.34 to −1.02) |
| Trial duration (months): | | | | | | |
| <3 | 31 | 3351 | 51 | −4.07 (−5.12 to −3.02) | 49 | −1.67 (−2.33 to −1.02) |
| 3–6 | 5 | 2817 | 67 | −1.91 (−3.60 to −0.23) | 67 | −1.33 (−2.50 to −0.15) |
| >6 | 3 | 2862 | 59 | −0.88 (−2.00 to 0.23) | 56 | −0.45 (−1.25 to 0.34) |
| Sex: | | | | | | |
| Male[d] | 2 | 53 | 0 | −9.10 (−16.63 to −1.57) | 0 | −4.83 (−8.98 to −0.68) |
| Mixed | 34 | 6749 | 65 | −3.34 (−4.25 to −2.42) | 60 | −1.50 (−2.07 to −0.94) |
| Study design: | | | | | | |
| Parallel | 16 | 4147 | 44 | −2.47 (−3.51 to −1.43) | 52 | −1.33 (−2.04 to −0.62) |
| Crossover | 22 | 2849 | 63 | −4.04 (−5.27 to −2.81) | 54 | −1.70 (−2.43 to −0.97) |

[a]Values in brackets relate to diastolic blood pressure. $I^2$ is a measure of heterogeneity with higher values suggesting higher heterogeneity
[b]Inverse variance, random effects model
[c]Negative means differences represent greater decreases in intervention versus control
[d]No studies reported results for women only

## 40.8 Generalizability of Sodium Reduction

Reducing dietary sodium intake in the population to levels achieved in longer-term clinical trials (TOHP and TONE trials) may be difficult in the general population, as the nature of dietary counseling interventions are resource intensive. Participants in

nutrition clinical trials are likely to be those most receptive to dietary counseling and as such represent the ideal population to test a dietary intervention. Efforts to reduce sodium content of manufactured and preprepared foods may be challenging for some participants as they cannot directly control the sodium added to foods and will require the involvement of the food industry, which will vary significantly around the world. A recent systematic review reported an increasing number of countries with national sodium reduction strategies, which includes industry engagement, sodium content targets for foods, education of consumers, labeling, taxation on high-sodium-containing foods, and interventions targeting public institutions [99]. In addition, there is a paucity of data on sodium reduction in low- or middle-income countries and limited activity of sodium reduction strategies.

## 40.9 Effects of Reduced Sodium Intake on Mortality and Cardiovascular Events

Current guidelines advocating low sodium diets assume that reductions in blood pressure will lead to reductions in cardiovascular morbidity and mortality, as hypertension is a significant modifiable risk factor for cardiovascular disease. However, no large long-term clinical trial has definitively shown that long-term sodium reduction results in reductions in cardiovascular disease. Meta-analyses of clinical trials, mostly designed to determine the effects of reduced sodium intake on blood pressure, have been completed. A recent Cochrane review concluded that there was insufficient power to determine a treatment effect of reducing sodium intake, although one analysis did report a 14% relative risk reduction in cardiovascular events in participant randomized to reduced sodium intake. However, one trial exerted a large effect on the estimate; a cluster randomized controlled trial of kitchens in Taiwanese veteran retirement homes, where potassium-enriched salt was used to replace sodium, reported a reduction in cardiovascular mortality (HR 0.59, 95% CI 0.37–0.95) in those receiving potassium-enriched salt [100]. In that trial, sodium intake was reduced from high to moderate range, rather than achieving low sodium intake, and potassium intake was increased, which meant that determining the independent effects of sodium reduction was not possible. Also included in that meta-analysis was an extended observational follow-up analysis of the TOHP trials, which independently reported a nonsignificant trend toward a reduction in cardiovascular morbidity and mortality with low sodium (<2.3 g/day excreted sodium), compared to excretion of 3.6–4.8 g/day [18]. However, there was a high rate of loss to follow-up (23%), and data was unavailable for a further one third of participants, meaning that half of the participants of the trials were excluded from these analyses which were based on 193 cardiovascular events or deaths.

Prospective cohort studies are the largest studies to evaluate the association between sodium intake and health outcomes, such as mortality and major cardiovascular events. Analyses of the ONTARGET and TRANSCEND trial cohorts ($n = 28{,}880$ at high cardiovascular risk) revealed a J-shaped association between sodium intake and cardiovascular mortality, with an increased risk in those consuming <3 or >6 g/

day [101]. The PURE study, a prospective cohort ($n$ = 101,945), reported similar results, where an increased risk of death or major cardiovascular event was seen with sodium excretion of <3 or >7 g/day [102]. A European prospective cohort study ($n$ = 3681) reported that lower sodium excretion was associated with reductions in systolic (but not diastolic) blood pressure, but lower sodium excretion was associated with increased cardiovascular mortality [103]. Similarly, a prospective cohort study of patients with type 1 diabetes mellitus ($n$ = 2807) reported a nonlinear association between urinary sodium excretion and mortality, with an increased risk of mortality in those with either the lowest or highest sodium excretion [104]. A French, prospective cohort study ($n$ = 1439) of participants with type 2 diabetes reported a J-shaped association between sodium excretion and cardiovascular mortality [105], and EPIC-Norfolk ($n$ = 19,857) reported a J-shaped association between estimated 24-h urinary sodium excretion and heart failure [106]. The Health, Aging, and Body Composition (Health ABC) study ($n$ = 2642) also reported that sodium intake was not associated with mortality, cardiovascular disease, or heart failure [107]. High sodium intake has also been associated with adverse renal outcomes, but there were inconsistent findings from studies comparing low to moderate sodium intake [108].

The association between dietary sodium intake and cardiovascular disease is not uniform in all populations. Analysis of the Prevention of Renal and Vascular End-stage Disease (PREVEND) study of adults without cardiovascular or kidney disease ($n$ = 7453) reported that high sodium intake was associated with an increased risk of cardiovascular events only in those with hypertension [109]. Similarly, an increased cardiovascular risk with higher sodium intake was seen only in those with hypertension from the PURE study, but the increased risk in those with low sodium intake was independent of hypertension [102]. Adjusted for hypertension and/or baseline blood pressure have been included in multiple studies, without materially changing observations, suggesting that the association is only partly mediated by blood pressure. Although diabetes mellitus does not appear to act as an effect modifier for the association with clinical outcomes, obesity may further increase the risk [110]. In addition, other dietary factors, including fruit and vegetable intake and overall diet quality, are important effect modifiers, likely mediated by dietary potassium intake [111–113]. Taken together, the body of observational studies indicate a J-shaped association between sodium intake and cardiovascular disease [9, 114], despite reducing blood pressure.

## Conclusion

High sodium intake is an important determinant of hypertension, mediated by numerous mechanisms. A reduction in high sodium intake (>5 g/day) lowers blood pressure and is consistently associated with a reduced risk of mortality and cardiovascular events. While reducing sodium intake from moderate intake range (3–5 g/day) to low intake levels (<2 g/day) also lowers blood pressure, there is no convincing evidence that it translates into lower rates of cardiovascular events, although definitive clinical trials are lacking. Therefore, reducing high sodium intake is an important public health target, and definitive clinical trials are required to determine whether moderate or low sodium intake is optimal for

cardiovascular health. Future research is required to identify simple and valid methods of estimating sodium intake in individuals and further evolution of our understanding of the mechanism through which differing levels of sodium intake affect cardiovascular health.

## References


1. World Health Organization (2012) Guideline: sodium intake for adults and children. World Health Organization, Geneva
2. INTERSALT (1988) Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. BMJ 297(6644):319–328
3. He FJ, MacGregor GA (2009) A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. J Hum Hypertens 23(6):363–384
4. Whelton PK (2011) Urinary sodium and cardiovascular disease risk: informing guidelines for sodium consumption. JAMA 306(20):2262–2264
5. Aburto NJ, Hanson S, Gutierrez H et al (2013) Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. BMJ 346:f1378
6. Kotchen TA, Cowley AW Jr, Frohlich ED (2013) Salt in health and disease—a delicate balance. N Engl J Med 368(13):1229–1237
7. Kempner W (1948) Treatment of hypertensive vascular disease with rice diet. Am J Med 4(4):545–577
8. Frost CD, Law MR, Wald NJ (1991) By how much does dietary salt reduction lower blood pressure? II—analysis of observational data within populations. BMJ 302(6780):815–818
9. Graudal N, Hubeck-Graudal T, Jurgens G, McCarron DA (2015) The significance of duration and amount of sodium reduction intervention in normotensive and hypertensive individuals: a meta-analysis. Adv Nutr 6(2):169–177
10. He FJ, Li J, Macgregor GA (2013) Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. BMJ 346:f1325
11. Graudal N, Jurgens G, Baslund B, Alderman MH (2014) Compared with usual sodium intake, low- and excessive-sodium diets are associated with increased mortality: a meta-analysis. Am J Hypertens 27(9):1129–1137
12. Mente A, O'Donnell M, Rangarajan S et al (2016) Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. Lancet 388(10043):465–475
13. Powles J, Fahimi S, Micha R et al (2013) Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. BMJ Open 3(12):e003733
14. Dietary Guidelines Advisory Committee (2010) Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines of Americans 2010, to the Secretary of Agriculture and the Secretary of Health and Human Services. Department of Agriculture, Agricultural Research Service, Washington DC
15. Mozaffarian D, Fahimi S, Singh GM et al (2014) Global sodium consumption and death from cardiovascular causes. N Engl J Med 371(7):624–634
16. Mente A, O'Donnell MJ, Rangarajan S et al (2014) Association of urinary sodium and potassium excretion with blood pressure. N Engl J Med 371(7):601–611
17. Whelton PK, Appel LJ, Sacco RL et al (2012) Sodium, blood pressure, and cardiovascular disease: further evidence supporting the American Heart Association Sodium Reduction Recommendations. Circulation 126(24):2880–2889
18. Cook NR, Appel LJ, Whelton PK (2014) Lower levels of sodium intake and reduced cardiovascular risk. Circulation 129(9):981–989
19. Titze J, Dahlmann A, Lerchl K et al (2014) Spooky sodium balance. Kidney Int 85(4):759–767

20. Rakova N, Juttner K, Dahlmann A et al (2013) Long-term space flight simulation reveals infradian rhythmicity in human Na(+) balance. Cell Metab 17(1):125–131
21. Lerchl K, Rakova N, Dahlmann A et al (2015) Agreement between 24-hour salt ingestion and sodium excretion in a controlled environment. Hypertension 66(4):850–857
22. Pfeiffer CM, Hughes JP, Cogswell ME et al (2014) Urine sodium excretion increased slightly among U.S. adults between 1988 and 2010. J Nutr 144(5):698–705
23. Kawasaki T, Itoh K, Uezono K, Sasaki H (1993) A simple method for estimating 24 h urinary sodium and potassium excretion from second morning voiding urine specimen in adults. Clin Exp Pharmacol Physiol 20(1):7–14
24. Tanaka T, Okamura T, Miura K et al (2002) A simple method to estimate populational 24-h urinary sodium and potassium excretion using a casual urine specimen. J Hum Hypertens 16(2):97–103
25. Brown IJ, Dyer AR, Chan Q et al (2013) Estimating 24-hour urinary sodium excretion from casual urinary sodium concentrations in western populations: the INTERSALT study. Am J Epidemiol 177(11):1180–1192
26. Cogswell ME, Wang CY, Chen TC et al (2013) Validity of predictive equations for 24-h urinary sodium excretion in adults aged 18-39 y. Am J Clin Nutr 98(6):1502–1513
27. Mente A, O'Donnell MJ, Dagenais G et al (2014) Validation and comparison of three formulae to estimate sodium and potassium excretion from a single morning fasting urine compared to 24-h measures in 11 countries. J Hypertens 32(5):1005–1014. discussion 15
28. Aburto NJ, Ziolkovska A, Hooper L et al (2013) Effect of lower sodium intake on health: systematic review and meta-analyses. BMJ 346:f1326
29. Stamler J (1997) The INTERSALT study: background, methods, findings, and implications. Am J Clin Nutr 65(2 Suppl):626S–642S
30. Zhou BF, Stamler J, Dennis B et al (2003) Nutrient intakes of middle-aged men and women in China, Japan, United Kingdom, and United States in the late 1990s: the INTERMAP study. J Hum Hypertens 17(9):623–630
31. Dennis B, Stamler J, Buzzard M et al (2003) INTERMAP: the dietary data—process and quality control. J Hum Hypertens 17(9):609–622
32. Shimazu T, Kuriyama S, Hozawa A et al (2007) Dietary patterns and cardiovascular disease mortality in Japan: a prospective cohort study. Int J Epidemiol 36(3):600–609
33. Anderson CA, Appel LJ, Okuda N et al (2010) Dietary sources of sodium in China, Japan, the United Kingdom, and the United States, women and men aged 40 to 59 years: the INTERMAP study. J Am Diet Assoc 110(5):736–745
34. Takahashi H, Yoshika M, Komiyama Y, Nishimura M (2011) The central mechanism underlying hypertension: a review of the roles of sodium ions, epithelial sodium channels, the renin-angiotensin-aldosterone system, oxidative stress and endogenous digitalis in the brain. Hypertens Res 34(11):1147–1160
35. Coffman TM (2014) The inextricable role of the kidney in hypertension. J Clin Invest 124(6):2341–2347
36. Weinberger MH (1996) Salt sensitivity of blood pressure in humans. Hypertension 27(3 Pt 2):481–490
37. Kawasaki T, Itoh K, Cugini P (1994) Influence of reapportionment of daily salt intake on circadian blood pressure pattern in normotensive subjects. J Nutr Sci Vitaminol (Tokyo) 40(5):459–466
38. Hall JE (2015) Guyton and Hall textbook of medical physiology. Elsevier, Philadelphia
39. Adrogue HJ, Madias NE (2007) Sodium and potassium in the pathogenesis of hypertension. N Engl J Med 356(19):1966–1978
40. Liu J, Yan Y, LIU L et al (2011) Impairment of Na/K-ATPase signaling in renal proximal tubule contributes to Dahl salt-sensitive hypertension. J Biol Chem 286(26):22806–22813
41. Amin MS, Reza E, El-Shahat E et al (2011) Enhanced expression of epithelial sodium channels in the renal medulla of Dahl S rats. Can J Physiol Pharmacol 89(3):159–168
42. Ritz E, Tomaschitz A (2009) Aldosterone, a vasculotoxic agent—novel functions for an old hormone. Nephrol Dial Transplant 24(8):2302–2305

43. Farjah M, Roxas BP, Geenen DL, Danziger RS (2003) Dietary salt regulates renal SGK1 abundance: relevance to salt sensitivity in the Dahl rat. Hypertension 41(4):874–878
44. Dahl LK, Heine M, Thompson K (1972) Genetic influence of renal homografts on the blood pressure of rats from different strains. Proc Soc Exp Biol Med 140(3):852–856
45. Dahl LK, Heine M, Thompson K (1974) Genetic influence of the kidneys on blood pressure. Evidence from chronic renal homografts in rats with opposite predispositions to hypertension. Circ Res 34(1):94–101
46. Meneton P, Jeunemaitre X, de Wardener HE, MacGregor GA (2005) Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. Physiol Rev 85(2):679–715
47. Trudu M, Janas S, Lanzani C et al (2013) Common noncoding UMOD gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression. Nat Med 19(12):1655–1660
48. Blaustein MP, Zhang J, Chen L, Hamilton BP (2006) How does salt retention raise blood pressure? Am J Physiol Regul Integr Comp Physiol 290(3):R514–R523
49. Ferrari P, Ferrandi M, Valentini G, Bianchi G (2006) Rostafuroxin: an ouabain antagonist that corrects renal and vascular Na+−K+− ATPase alterations in ouabain and adducin-dependent hypertension. Am J Physiol Regul Integr Comp Physiol 290(3):R529–R535
50. Dolson GM, Wesson DE, Adrogue HJ (1995) Vascular relaxation probably mediates the antihypertensive effect of a high-potassium diet: a role for enhanced vascular Na, K-ATPase activity. J Hypertens 13(12 Pt 1):1433–1439
51. Iwamoto T (2006) Vascular Na+/Ca2+ exchanger: implications for the pathogenesis and therapy of salt-dependent hypertension. Am J Physiol Regul Integr Comp Physiol 290(3):R536–R545
52. Fujiwara N, Osanai T, Kamada T, Katoh T, Takahashi K, Okumura K (2000) Study on the relationship between plasma nitrite and nitrate level and salt sensitivity in human hypertension : modulation of nitric oxide synthesis by salt intake. Circulation 101(8):856–861
53. He FJ, MacGregor GA (2010) Reducing population salt intake worldwide: from evidence to implementation. Prog Cardiovasc Dis 52(5):363–382
54. de Wardener HE, He FJ, MacGregor GA (2004) Plasma sodium and hypertension. Kidney Int 66(6):2454–2466
55. Friedman SM, McIndoe RA, Tanaka M (1990) The relation of blood sodium concentration to blood pressure in the rat. J Hypertens 8(1):61–66
56. Friedman SM (1990) The relation of cell volume, cell sodium and the transmembrane sodium gradient to blood pressure. J Hypertens 8(1):67–73
57. Gu JW, Anand V, Shek EW et al (1998) Sodium induces hypertrophy of cultured myocardial myoblasts and vascular smooth muscle cells. Hypertension 31(5):1083–1087
58. Oberleithner H, Riethmuller C, Schillers H et al (2007) Plasma sodium stiffens vascular endothelium and reduces nitric oxide release. Proc Natl Acad Sci U S A 104(41):16281–16286
59. Lago RM, Pencina MJ, Wang TJ et al (2008) Interindividual variation in serum sodium and longitudinal blood pressure tracking in the Framingham Heart Study. J Hypertens 26(11):2121–2125
60. Adrogue HJ, Madias NE (2014) Sodium surfeit and potassium deficit: keys to the pathogenesis of hypertension. J Am Soc Hypertens 8(3):203–213
61. Haddy FJ, Vanhoutte PM, Feletou M (2006) Role of potassium in regulating blood flow and blood pressure. Am J Physiol Regul Integr Comp Physiol 290(3):R546–R552
62. Amberg GC, Bonev AD, Rossow CF, Nelson MT, Santana LF (2003) Modulation of the molecular composition of large conductance, Ca(2+) activated K(+) channels in vascular smooth muscle during hypertension. J Clin Invest 112(5):717–724
63. Ericsson F (1984) Potassium in skeletal muscle in untreated primary hypertension and in chronic renal failure, studied by X-ray fluorescence technique. Acta Med Scand 215(3):225–230
64. Kurtz TW, DiCarlo SE, Pravenec M et al (2016) An alternative hypothesis to the widely held view that renal excretion of sodium accounts for resistance to salt-induced hypertension. Kidney Int 90(5):965–973

65. Wedler B, Brier ME, Wiersbitzky M et al (1992) Sodium kinetics in salt-sensitive and salt-resistant normotensive and hypertensive subjects. J Hypertens 10(7):663–669
66. Schmidlin O, Sebastian AF, Morris RC Jr (2007) What initiates the pressor effect of salt in salt-sensitive humans? Observations in normotensive blacks. Hypertension 49(5):1032–1039
67. Heer M, Baisch F, Kropp J et al (2000) High dietary sodium chloride consumption may not induce body fluid retention in humans. Am J Physiol Renal Physiol 278(4):F585–F595
68. Titze J, Bauer K, Schafflhuber M et al (2005) Internal sodium balance in DOCA-salt rats: a body composition study. Am J Physiol Renal Physiol 289(4):F793–F802
69. Titze J, Shakibaei M, Schafflhuber M et al (2004) Glycosaminoglycan polymerization may enable osmotically inactive Na+ storage in the skin. Am J Physiol Heart Circ Physiol 287(1):H203–H208
70. Machnik A, Neuhofer W, Jantsch J et al (2009) Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. Nat Med 15(5):545–552
71. Kusche-Vihrog K, Jeggle P, Oberleithner H (2014) The role of ENaC in vascular endothelium. Pflugers Arch 466(5):851–859
72. Olde Engberink RH, Rorije NM, Homan van der Heide JJ, van den Born BJ, Vogt L (2015) Role of the vascular wall in sodium homeostasis and salt sensitivity. J Am Soc Nephrol 26(4):777–783
73. Kurtz TW, Dominiczak AF, DiCarlo SE et al (2015) Molecular-based mechanisms of Mendelian forms of salt-dependent hypertension: questioning the prevailing theory. Hypertension 65(5):932–941
74. Laffer CL, Scott RC 3rd, Titze JM et al (2016) Hemodynamics and salt-and-water balance link sodium storage and vascular dysfunction in salt-sensitive subjects. Hypertension 68(1):195–203
75. Graudal NA, Galloe AM, Garred P (1998) Effects of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride: a meta-analysis. JAMA 279(17):1383–1391
76. Alderman MH (2007) Dietary sodium and cardiovascular disease: the J-shaped relation. J Hypertens 25(5):903–907
77. Graudal NA, Hubeck-Graudal T, Jurgens G (2011) Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. Cochrane Database Syst Rev 11:CD004022
78. Oudot C, Lajoix AD, Jover B, Rugale C (2013) Dietary sodium restriction prevents kidney damage in high fructose-fed rats. Kidney Int 83(4):674–683
79. Damgaard M, Goetze JP, Norsk P, Gadsboll N (2007) Altered sodium intake affects plasma concentrations of BNP but not proBNP in healthy individuals and patients with compensated heart failure. Eur Heart J 28(22):2726–2731
80. Yilmaz R, Akoglu H, Altun B et al (2012) Dietary salt intake is related to inflammation and albuminuria in primary hypertensive patients. Eur J Clin Nutr 66(11):1214–1218
81. Grassi G, Dell'Oro R, Seravalle G et al (2002) Short- and long-term neuroadrenergic effects of moderate dietary sodium restriction in essential hypertension. Circulation 106(15):1957–1961
82. Mancia G, Grassi G, Ferrari AU (1997) Reflex control of the circulation in experimental and human hypertension. In: Zanchetti A, Mancia G (eds) Handbook of hypertension, Pathophysiology of hypertension, vol 17. Elsevier Science, Amsterdam, pp 568–601
83. Tikellis C, Pickering RJ, Tsorotes D et al (2012) Activation of the renin-angiotensin system mediates the effects of dietary salt intake on atherogenesis in the apolipoprotein E knockout mouse. Hypertension 60(1):98–105
84. Stamler J, Elliott P, Appel L et al (2003) Higher blood pressure in middle-aged American adults with less education-role of multiple dietary factors: the INTERMAP study. J Hum Hypertens 17(9):655–775
85. Brown IJ, Stamler J, Van Horn L et al (2011) Sugar-sweetened beverage, sugar intake of individuals, and their blood pressure: international study of macro/micronutrients and blood pressure. Hypertension 57(4):695–701

86. Khaw K-T, Bingham S, Welch A et al (2004) Blood pressure and urinary sodium in men and women: the Norfolk Cohort of the European Prospective Investigation into Cancer (EPIC-Norfolk). Am J Clin Nutr 80(5):1397–1403
87. Vollmer WM, Sacks FM, Ard J et al (2001) Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. Ann Intern Med 135(12):1019–1028
88. Sacks F, Svetkey L, Vollmer W et al (2001) The sodium-restricted DASH diet lowers blood pressure. CMAJ 164(11):1613
89. TOHP Collaborative Research Group (1997) Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The trials of hypertension prevention, phase II. The Trials of Hypertension Prevention Collaborative Research Group. Arch Intern Med 157(6):657–667
90. He FJ, Wu Y, Feng XX et al (2015) School based education programme to reduce salt intake in children and their families (school-EduSalt): cluster randomised controlled trial. BMJ 350:h770
91. Peng YG, Li W, Wen XX et al (2014) Effects of salt substitutes on blood pressure: a meta-analysis of randomized controlled trials. Am J Clin Nutr 100(6):1448–1454
92. Li N, Yan LL, Niu W et al (2013) A large-scale cluster randomized trial to determine the effects of community-based dietary sodium reduction—the China Rural Health Initiative Sodium Reduction Study. Am Heart J 166(5):815–822
93. Colin-Ramirez E, McAlister FA, Zheng Y et al (2015) The long-term effects of dietary sodium restriction on clinical outcomes in patients with heart failure. The SODIUM-HF (Study of Dietary Intervention Under 100 mmol in Heart Failure): a pilot study. Am Heart J 169(2):274–281. e1
94. McMahon EJ, Bauer JD, Hawley CM et al (2013) A randomized trial of dietary sodium restriction in CKD. J Am Soc Nephrol 24(12):2096–2103
95. Neal B, Wu Y, Labarthe D et al (2016) .China Salt Substitute and Stroke Study (SSASS) NCT02092090. https://clinicaltrials.gov/ct2/show/NCT02092090. Accessed 2016/08/14
96. Butler J, Papadimitriou L, Georgiopoulou V et al (2015) Comparing sodium intake strategies in heart failure: rationale and design of the Prevent Adverse Outcomes in Heart Failure by Limiting Sodium (PROHIBIT) Study. Circ Heart Fail 8(3):636–645
97. Colin E, Ezekowitz JE (2016) .SODIUM-HF: Study of dietary intervention under 100mml in heart failure (NCT02012179). https://clinicaltrials.gov/ct2/show/NCT02012179. Accessed 2016/08/14
98. Smyth A, O'Donnell M (2016) Sodium Intake in Chronic Kidney Disease (STICK). https://clinicaltrials.gov/ct2/show/NCT02458248. Accessed 2016/08/24
99. Trieu K, Neal B, Hawkes C et al (2015) Salt reduction initiatives around the world—a systematic review of progress towards the global target. PLoS One 10(7):e0130247
100. Chang H-Y, Hu Y-W, Yue C-SJ et al (2006) Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. Am J Clin Nutr 83(6):1289–1296
101. O'Donnell MJ, Yusuf S, Mente A et al (2011) Urinary sodium and potassium excretion and risk of cardiovascular events. JAMA 306(20):2229–2238
102. O'Donnell M, Mente A, Rangarajan S et al (2014) Urinary sodium and potassium excretion, mortality, and cardiovascular events. N Engl J Med 371(7):612–623
103. Stolarz-Skrzypek K, Kuznetsova T, Thijs L et al (2011) Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. JAMA 305(17):1777–1785
104. Thomas MC, Moran J, Forsblom C et al (2011) The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. Diabetes Care 34(4):861–866
105. Saulnier PJ, Gand E, Hadjadj S, Group SS (2014) Sodium and cardiovascular disease. N Engl J Med 371(22):2135–2136
106. Pfister R, Michels G, Sharp SJ et al (2014) Estimated urinary sodium excretion and risk of heart failure in men and women in the EPIC-Norfolk study. Eur J Heart Fail 16(4):394–402

107. Kalogeropoulos AP, Georgiopoulou VV, Murphy RA et al (2015) Dietary sodium content, mortality, and risk for cardiovascular events in older adults: The Health, Aging, and Body Composition (Health ABC) Study. JAMA Intern Med 175(3):410–419
108. Smyth A, O'Donnell MJ, Yusuf S et al (2014) Sodium intake and renal outcomes: a systematic review. Am J Hypertens 27(10):1277–1284
109. Joosten MM, Gansevoort RT, Mukamal KJ et al (2014) Sodium excretion and risk of developing coronary heart disease. Circulation 129(10):1121–1128
110. He J, Ogden LG, Vupputuri S et al (1999) Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. JAMA 282(21):2027–2034
111. Morris RC Jr, Schmidlin O, Frassetto LA, Sebastian A (2006) Relationship and interaction between sodium and potassium. J Am Coll Nutr 25(3 Suppl):262S–270S
112. Khaw KT, Barrett-Connor E (1987) Dietary potassium and stroke-associated mortality. A 12-year prospective population study. N Engl J Med 316(5):235–240
113. Bazzano LA, He J, Ogden LG et al (2001) Dietary potassium intake and risk of stroke in US men and women: National Health and Nutrition Examination Survey I epidemiologic follow-up study. Stroke 32(7):1473–1480
114. Smyth A, O'Donnell M, Mente A, Yusuf S (2015) Dietary sodium and cardiovascular disease. Curr Hypertens Rep 17(6):559
115. Law MR, Frost CD, Wald NJ (1991) By how much does dietary salt reduction lower blood pressure? III—analysis of data from trials of salt reduction. BMJ 302(6780):819–824
116. Midgley JP, Matthew AG, Greenwood CM, Logan AG (1996) Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. JAMA 275(20):1590–1597
117. Cutler JA, Follmann D, Allender PS (1997) Randomized trials of sodium reduction: an overview. Am J Clin Nutr 65(2 Suppl):643S–651S
118. Alam S, Johnson AG (1999) A meta-analysis of randomised controlled trials (RCT) among healthy normotensive and essential hypertensive elderly patients to determine the effect of high salt (NaCl) diet of blood pressure. J Hum Hypertens 13(6):367–374
119. Hooper L, Bartlett C, Davey Smith G, Ebrahim S (2002) Systematic review of long term effects of advice to reduce dietary salt in adults. BMJ 325(7365):628–632
120. He FJ, MacGregor GA (2002) Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials. Implications for public health. J Hum Hypertens 16(11):761–770

# Diabetes Mellitus and Hypertension

# 41

Luke J. Laffin and George L. Bakris

## 41.1 Introduction

Primary hypertension is a complex polygenic condition that is highly modifiable via environmental influences such as salt intake and obesity. Greater than 60% of the US population above the age of 60 has hypertension and 19% of the population between 18 and 59 years of age [1]. However, only half have their hypertension controlled [2, 3]. Hypertension is exceedingly common among patients with type 1 and type 2 diabetes mellitus. When diagnosed with type 2 diabetes mellitus (DM2), 39% of individuals already have hypertension [4]. Among patients with type 1 diabetes mellitus (DM1), the incidence of hypertension increases significantly every decade after diagnosis, with a third of patients being hypertensive 20 years after a diagnosis of DM1 [5].

Diabetes mellitus, hypertension, and metabolic syndrome are a constellation of environmental and hormonal interactions that result in increased risk for macrovascular and microvascular complications. Early treatment of hypertension in the diabetic population leads to improvement in both sets of complications. Modification of risk factors in diabetic patients is crucial given they are at elevated risk of stroke, myocardial infarction, and heart failure. This is even more essential when acknowledging the fact that no substantial randomized clinical trial of glucose-lowering therapy demonstrates a significant decrease in major adverse cardiovascular events (although glucose-lowering therapy clearly decreases microvascular events such as nephropathy and retinopathy) [6].

The following chapter will address the pathogenesis of hypertension and diabetes mellitus. The controversial question of what level of blood pressure (BP) control should be targeted in patients with diabetes will then be discussed, with a focus on

L.J. Laffin, M.D. • G.L. Bakris, M.D. (✉)
Department of Medicine, ASH Comprehensive Hypertension Center, University of Chicago Medicine, 5841 S. Maryland Ave, MC 1027, Chicago, IL 60637, USA
e-mail: laffinlj@gmail.com; gbakris@gmail.com



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_41

the clinical trial data that supports these targets. In addition, the authors will offer data to support certain pharmacotherapy choices in patients with coexisting hypertension and diabetes mellitus.

## 41.2 Pathophysiology

Contributing factors in the pathogenesis of hypertension in diabetes mellitus are multifactorial. For many years, it is been recognized that hypertension is common to both obese and non-insulin-dependent diabetic subjects [7–9]. There are likely four significant pathogenic contributors to the high coincidence of diabetes and hypertension. The development of diabetic nephropathy is clearly a factor. In patients with DM1, the development of hypertension strongly correlates with the degree of albuminuria and progression of diabetic kidney disease [10]. This differs from DM2 where moderate albuminuria does not necessarily serve as a prelude to the development of hypertension [4].

Other principal factors include volume expansion, hyperinsulinemia, and increased arterial stiffness. The contribution of volume expansion is likely due to sodium retention induced via insulin and an increase in filtered glucose load due to hyperglycemia [10, 11]. In the setting of moderate hyperglycemia, excess glucose is reabsorbed in the proximal tubule of the kidney by a sodium-glucose cotransporter and contributes to a rise in sodium reabsorption [11]. Lowering dietary sodium intake can attenuate this reabsorption. Elevated serum levels of insulin, due to exogenous insulin or insulin resistance in DM2, can also cause a significant hypertensive response although this has not been noted in all studies [12]. It may in fact be caused by concurrent weight gain with insulin treatment.

Finally, in patients with diabetes, evidence suggests they have increased vascular stiffness that produces a reduction in arterial distensibility, which likely contributes to a rise in systolic BP and ultimately an increased risk of death [13].

## 41.3 Goal Blood Pressure in Diabetic Patients

The benefits of treating hypertension within a diabetic population are clear; macrovascular complications are prevented and progression of nephropathy and retinopathy are slowed with early treatment [14]. Before recent guideline updates, the prevailing theory when treating hypertensive patients with diabetes mellitus was to treat to a BP goal of 130 mmHg systolic over 80 mmHg diastolic. This was noted in widely distributed guidelines such as the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) [2] and subsequently in numerous sets of guidelines, such as those set forth by the American Diabetes Association [15]. These recommendations originated from retrospective data analyses that suggested an association of lower blood pressure with slower decline in chronic kidney disease and more significant cardiovascular risk reduction among diabetic patients. More recent clinical trials, and continued analytical appraisal of higher quality

**Table 41.1** Recent guidelines for treatment of hypertension in diabetes mellitus

| Guideline | BP goal (mmHg) | Initial antihypertensive agent | BP for initial combo therapy | Beta-blockers—first-line drug |
|---|---|---|---|---|
| JNC 8 | <140/90 | RAS blockers, CCB, or diuretic | ≥160/100 | No |
| ADA 2014 | <140/80 | RAS blockers | Not addressed | Not addressed |
| ESH/ESC 2013 | <140/85 | RAS blockers, CCB, or diuretic | Patients with marked BP elevation | Yes |
| ASH/ISH 2014 | <140/90 | RAS blockers, CCB, or diuretic | ≥160/100 | No (step 4) |

*RAS* renin-angiotensin system blockers, i.e., ACE inhibitor or angiotensin receptor blockers; *CCB*, calcium channel blockers, *BP*, blood pressure

evidence, have shifted this paradigm. It is not well established that lower blood pressure goals in patients with DM, when compared to the nondiabetic population goals of <140/90 mmHg, improve outcomes. Given this shift, major society and guideline statements, such as the Eighth Joint National Committee (JNC 8) [3] and the American and International Societies of Hypertension (ASH/ISH) (16), have updated their position and now recommend a BP goal of <140/90 mmHg in patients with diabetes (see Table 41.1).

There are numerous randomized clinical trials that demonstrate the benefits of treating hypertension within a diabetic population to a goal of less than 140/90 mmHg. Further a recent meta-analysis also demonstrated the substantial benefits of blood pressure lowering in patients with diabetes [17]. The most relevant of these trials include the United Kingdom Prospective Diabetes Study (UKPDS) trial [18], the Hypertension Optimal Treatment (HOT) trial [19], and the ADVANCE trial [20] (see Table 41.2).

Published in 1998, UKPDS was a trial studying 1148 subjects with DM2 and randomized them (2:1) to a "tight" BP goal of <150/85 mmHg or a BP of <180/105 mmHg. BP control was attained using captopril and atenolol primarily. Subjects entered the study at a mean age of 56 years and BP of 160/94 mmHg. During a median follow-up of 8.4 years, the "tight" BP control group was able to achieve a BP of 144/82 mmHg, whereas the other achieved a BP of 154/87 mmHg. The <150/85 mmHg BP group demonstrated a 24% reduction in all DM-related endpoints, 32% reduction in deaths related to DM, and 44% reduction in strokes.

Also published in 1998 was data from the HOT trial. Studying almost 19,000 patients, with approximately 3000 having diabetes, subjects were randomized to one of three target diastolic BPs, <80, <85, or <90 mmHg. The separation between the actual attained BPs of the three groups was minimal (144/85 mmHg, 141/83 mmHg, and 140/81 mmHg, respectively) and the overall trial outcome was negative. However, in a post hoc analysis of a small subset of patients that was not prespecified, the relative risk of a cardiovascular event among patients with diabetes in the lowest BP target group was significantly reduced compared to the highest target group.

The ADVANCE trial, published in 2007, is the only major placebo-controlled randomized trial that explicitly examined treatment with antihypertensive agents in DM2. Enrolled subjects were long-standing diabetics deemed at high risk for

**Table 41.2** Key randomized trials of blood pressure control in diabetes mellitus

| Trial | Follow-up (years) | No. of subjects | BP goal (mmHg) | BP achieved (mmHg) | Main results |
|---|---|---|---|---|---|
| UKPDS (1998) | 8.4 | 1148<br>758 "tight"<br>390 control | <150/85 (tight) vs. <180/105 (control) | 144/82 (tight) and 154/87 (control) | Tight control resulted in risk reduction in diabetes related endpoints and strokes |
| ACCORD (2010) | 1 | 4733<br>2362 "intensive"<br>2371 control | <120 sys (intensive) vs. <140 sys (control) | 119 sys (intensive) and 134 sys (control) | No reduction in fatal and nonfatal cardiovascular events |
| ADVANCE (2007) | 4.3 | 11,140<br>5569 "intervention"<br>5571 placebo | None | 135/74 (intervention) and 40/76 (control) | Intervention reduced risk of major vascular events, including death |
| SANDS (2008) | 3 | 499<br>252 "aggressive"<br>247 "standard" | <115 sys (aggressive) vs. <130 sys (standard)[a] | 117 sys (aggressive) and 129 sys (standard) | No difference in clinical cardiovascular events |
| Normotensive ABCD (2002) | 5.3 | 480<br>237 "intensive"<br>243 placebo | 10 mmHg below baseline dia (intensive) vs. 80–89 dia (moderate) | 128/75 (intensive) and 137/81 (moderate) | No significant improvement in composite cardiovascular events |

*BP* blood pressure, *sys* systolic, *dia* diastolic
aAlso included low-density lipoprotein cholesterol goals

cardiovascular disease. The trial compared a fixed combination of perindopril/indapamide to placebo in more than 11,000 subjects. The mean baseline BP was 145/81 mmHg, and subjects were followed for a mean of 4.3 years. There was no targeted BP to guide protocol therapy. The primary endpoints were macrovascular or microvascular events. The intervention group (i.e., those that received perindopril and indapamide) demonstrated a significantly lower rate of events, a significant decrease in mean BP (5.6/2.2 mmHg), and a lower rate of cardiovascular, as well as all-cause mortality. The mean BP achieved in the intervention arm was 135/74 mmHg versus 140/76 mmHg in the control arm. Lower BPs in the ADVANCE trial were clearly associated with improved cardiovascular outcomes. Of note, this trial was not considered in the JNC 8 recommendations given that it was not based on targeted BP goals, and there was not a prespecified minimum baseline blood pressure [3].

In addition to the above studies demonstrating benefit of BP lowering to less than 140 mmHg, randomized trials specifically address the issue of whether even lower BPs should be targeted in patients with diabetes (see Table 41.2). The most

noteworthy of these trials (and the trial that drove the recommendation to relax BP control guidelines in diabetics) is the Action to Control Cardiovascular Risk in Diabetes blood pressure trial (ACCORD BP) [21], discussed below.

Previous BP treatment guidelines advocating treatment to a systolic BP of <130 mmHg were common; however there are no randomized control trials that support this level of control in preference to a systolic BP of <140 mmHg. With respect to diastolic BP, recommendations were to treat to a diastolic BP <80 mmHg; however again there are no good- or fair-quality randomized control trials that demonstrate this greater need for more aggressive control [3, 16]. As such, BP goals of <140/90 mmHg, consistent with goals in the treatment of the general population of 60 years of age or less, can be applied to diabetic patients as well.

Trials specifically addressing whether lower BPs should be targeted in patients with DM demonstrate no difference in primary outcomes with more intensive blood pressure lowering. This includes the smaller normotensive Appropriate Blood pressure Control in Diabetes (ABCD) trial of 480 patients with DM2 that were randomly assigned to moderate diastolic BP control (80–89 mmHg) via placebo or intensive control (10 mmHg below the patient's baseline diastolic BP) via either enalapril or nisoldipine [22]. The intervention group achieved a BP of 128/75 mmHg and the control achieved a BP of 137/81. No difference in the primary endpoint of renal function as measured by creatinine clearance was seen, but certain secondary microvascular endpoints were significantly reduced. The intervention group did not demonstrate a reduction in the composite cardiovascular events with the lower diastolic BP goal; however there was a significant reduction in stroke.

Another smaller randomized trial was the SANDS trial published in 2008. It studied approximately 500 American Indian subjects with DM2 and no prior cardiovascular disease, targeting a systolic BP and LDL cholesterol (<130 mmHg for systolic BP) and more intensive control (<115 mmHg) [23]. BPs attained after 3 years of follow-up were 117 and 129 mmHg, respectively. No significant difference in clinical cardiovascular events was demonstrated, and aggressive therapy had significantly more adverse events related to antihypertensive medications.

As noted above, likely the major evidence driving the recent change in BP goals in patients with diabetes is the ACCORD BP trial [21]. Published in 2010, this randomized study of 4733 subjects with DM2 and a baseline BP of 139/76 mmHg targeted systolic BP of <120 mmHg in the intensive control group and <140 mmHg in the standard therapy group. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes, with mean follow-up of 4.7 years. Both groups achieved the desired BP (119 and 133 mmHg). There was no significant difference in the annual rate of the primary endpoint and no difference in all-cause mortality. The lower BP goal was associated with significant reductions in total and nonfatal strokes; however significantly more serious adverse events occurred in the intensive therapy group.

Aside from randomized trials, post hoc analyses of trials that had large subgroups of patients with DM2 such as the International Verapamil SR-Trandolapril (INVEST) [24] and the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) [25] also failed to

demonstrate a cardiovascular outcome benefit at a blood pressure below 130/80 mmHg.

The finding that stroke risk is attenuated at lower BPs in the ACCORD trial is consistent with other studies such as ADVANCE [20], INVEST [24], and the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) [26]. INVEST and ONTARGET were both large international clinical trials of blood pressure-lowering therapies of greater than 20,000 subjects, with diabetics comprising 37% and 28% of the study, respectively. Both demonstrated a systolic below 130 mmHg that is associated with stroke reduction but no other CV risk reduction below that level of BP. In ACCORD, the most definitive study in the diabetic population to date, it is important to take note that the risk of serious adverse events (hypotension, syncope, arrhythmia, hyperkalemia, angioedema, and renal failure) associated with more aggressive BP control (3.3% intensive vs. 1.3% in the standard arm). When coupled with the small absolute benefit in stroke reduction (1 in 89 patients at 5 years), the finding does not compel the authors of this article or recent guidelines to recommend a lower BP goal [3, 16, 21].

## 41.4 Diabetes, Hypertension, and Chronic Kidney Disease

The progression of diabetic nephropathy is clearly accelerated by uncontrolled BP. Patients with diabetic nephropathy and overt proteinuria (at least 500 mg/day) is the one subset of diabetic patients where evidence, although still not of high quality, reasonably suggests a lower systolic BP goal of <130/80 mmHg. This is due to data from a post hoc analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT) [27]. This was published in 2005 and examined the cardiovascular outcomes in patients with DM, hypertension, and overt proteinuria when treated with irbesartan, amlodipine, or placebo (among other BP medications) to achieve a BP of <135/85 mmHg. Progressively lower systolic BP to 120 mmHg predicted a decrease in cardiovascular mortality and heart failure, but not myocardial infarction. A systolic BP <120 mmHg was associated with increased risk for CV deaths and heart failure events. Patients with diabetes and moderate albuminuria/no proteinuria should be treated to the same guidelines as those patients without renal dysfunction as there is no adequate data to support lower targets.

## 41.5 What About SPRINT-BP Results?

The landscape of hypertension management changed in late 2015 with the release of data from the National Institutes of Health funded Systolic Blood Pressure Intervention Trial (SPRINT) [28]. Performed after the similar NIH-funded aforementioned ACCORD trial, this trial was performed in nondiabetic patients at high risk for cardiovascular events.

It demonstrated a clear cardiovascular and mortality benefit in nondiabetics with tighter blood pressure control (goal of <120 mmHg).

The question then becomes, why were similar results not seen in an unquestionably higher cardiovascular risk group of subjects in ACCORD? Multiple factors may account for this discrepancy, yet no one answer is applicable. SPRINT enrolled almost double the number of subjects than ACCORD, suggesting that ACCORD may have been underpowered to detect any differences. SPRINT included the clinical endpoint of heart failure that was not used in ACCORD. Interestingly, heart failure was the main driver of positive results with respect to the primary composite endpoint in SPRINT. SPRINT subjects were prescribed chlorthalidone as a diuretic when applicable, rather than hydrochlorothiazide, which was used more frequently in ACCORD. It is well established that hydrochlorothiazide is not as effective at lowering BP over 24 h as chlorthalidone [29].

Thus, with currently available evidence, patients should be treated to a goal BP of <140/90 mmHg if they have DM.

## 41.6 Choice of Pharmacotherapy

Similar to patients without DM, nonpharmacological treatments should be the first consideration for all clinicians when managing hypertension in patients with diabetes mellitus. Weight loss, exercise, healthy dietary choices, smoking cessation, salt restriction, and alcohol moderation among other lifestyle modifications are critical. However, if goal BP is not reached within 3 months of implementing lifestyle modifications, treatment with antihypertensive pharmacotherapy should commence.

Choosing an antihypertensive agent(s) in patients with diabetes mellitus is nuanced. It is well established that the amount of blood pressure reduction is the major determinant of cardiovascular risk reduction in all patients with hypertension, including those with diabetes [30]. The class or choice of blood pressure-lowering medication is considerably less important. This was the conclusion of multiple meta-analyses and the 2013 European Societies of Hypertension and Cardiology guideline [30]. However, if the clinician is given the opportunity to select antihypertensive therapy, one should choose the most effective medications to reduce the patient's risk of mortality, adverse cardiovascular events, and prevent progression of renal disease if present. Interestingly, choice of BP medication likely does not affect the progression of retinopathy given that comparative studies have not demonstrated superiority of one agent over another.

The recent Expert Panel Report (JNC 8) report does not clearly address the ideal choice of antihypertensive therapy in diabetic patients [3]. It suggests that in all nonblack patients, without chronic kidney disease, treatment can consist of a thiazide-type diuretic, angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or calcium channel blocker (CCB). Alternatively, in black patients without chronic kidney disease, a thiazide-type diuretic or CCB is recommended. Naturally, patients with severely increased albuminuria (i.e., renal disease) should be treated with an ACE inhibitor or an ARB. Further, a strong argument can be made that in those patients with microalbuminuria, diabetes, and hypertension, an ACE or ARB should be first-line therapy as well.

The results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [31] help inform our choice of antihypertensive therapy in patients with and without DM. Results from the subgroup of DM patients were no different from the trial population as a whole. Amlodipine, lisinopril, and chlorthalidone all produced equivalent rates of the primary cardiovascular endpoint of nonfatal myocardial infarction and coronary heart disease death. However, chlorthalidone did result in significantly higher blood glucose levels in study subjects, which is consistent with findings of thiazide diuretics, and should be a consideration when trying to meet BP goals.

Beta-blockers and alpha-blockers are not appropriate first-line drug therapy in hypertensive diabetic patients (unless other significant factors such as recent myocardial infarction or systolic dysfunction are present). Alpha-blockers, although as effective as CCBs and ACE inhibitors in lowering BP, should not be prescribed as initial or primary therapy for hypertension given their side effects and results of the ALLHAT trial that demonstrated an increased rate of heart failure with doxazosin compared to chlorthalidone [31]. The use of beta-blockers in hypertensive diabetics is slightly more nuanced. UKPDS demonstrates that atenolol is as effective as captopril with respect to BP lowering and protection against microvascular disease [18]. However, multiple studies have demonstrated that beta-blockers such as metoprolol may result in worsening of glycemic control or increased incidence of new-onset diabetes [32]. Carvedilol is a well-studied beta-blocker that is advantageous to use, if needed for heart rate and BP control, in diabetic patients. The GEMINI trial randomized 1235 diabetic hypertensive patients (already taking an ACE inhibitor or ARB) to carvedilol or metoprolol [33]. Carvedilol did not increase hemoglobin A1C, whereas metoprolol did, and resulted in an increase in a patient's insulin sensitivity, whereas metoprolol did not. Thus, if beta-blocker therapy is needed in a diabetic patient, carvedilol is likely the best pharmacological therapy.

One of the newest classes of glucose-lowering agents are sodium-glucose cotransporter 2 (SGLT2) inhibitors. They act by suppressing the cotransport of glucose and sodium from the tubular lumen of renal proximal tubules to the blood and enhance the glucose excretion into urine. They ultimately result in actions similar to a loop diuretic and lower blood pressure. Larger-scale studies are needed to demonstrate their effectiveness in reducing cardiovascular events and mortality; however recent data demonstrates a clear decrease in 24-h ambulatory BP with use of an SGLT2 inhibitor [34]. This class of medication may ultimately serve a dual purpose of controlling BP and blood glucose.

## Conclusion

Diabetes mellitus and hypertension will continue to contribute to cardiovascular morbidity and mortality if not treated appropriately. With the currently available evidence, aside from patients with overt proteinuria, patients with diabetes mellitus and hypertension should be treated to a goal BP of less than 140/90 mmHg. Based on the results of the SPRINT trial in late 2015 in nondiabetic patients, further thoughtful study and discourse about BP treatment goals and agents in patients with diabetes mellitus is warranted.

## References


1. Navar-Boggan AM, Pencina MJ, Williams K, Sniderman AD, Peterson ED (2014) Proportion of US adults potentially affected by the 2014 hypertension guideline. JAMA 311(14):1424–1429
2. Chobanian AV, Bakris GL, Black HR et al (2003) The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 289(19):2560–2572
3. James PA, Oparil S, Carter BL et al (2014) 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 311(5):507–520
4. (1993) Hypertension in Diabetes Study (HDS): I. Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. J Hypertens 11(3):309–317
5. Parving HH, Hommel E, Mathiesen E et al (1988) Prevalence of microalbuminuria, arterial hypertension, retinopathy and neuropathy in patients with insulin dependent diabetes. Br Med J (Clin Res Ed) 296(6616):156–160
6. Hemmingsen B, Lund SS, Gluud C et al (2013) Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. Cochrane Database Syst Rev 11:CD008143
7. Modan M, Halkin H, Almog S et al (1985) Hyperinsulinemia. A link between hypertension obesity and glucose intolerance. J Clin Invest 75(3):809–817
8. Stamler R, Stamler J, Riedlinger WF et al (1978) Weight and blood pressure. Findings in hypertension screening of 1 million Americans. JAMA 240(15):1607–1610
9. Havlik RJ, Hubert HB, Fabsitz RR, Feinleib M (1983) Weight and hypertension. Ann Intern Med 98(5 Pt 2):855–859
10. Epstein M, Sowers JR (1992) Diabetes mellitus and hypertension. Hypertension 19(5):403–418
11. Nosadini R, Sambataro M, Thomaseth K et al (1993) Role of hyperglycemia and insulin resistance in determining sodium retention in non-insulin-dependent diabetes. Kidney Int 44(1):139–146
12. Randeree HA, Omar MA, Motala AA, Seedat MA (1992) Effect of insulin therapy on blood pressure in NIDDM patients with secondary failure. Diabetes Care 15(10):1258–1263
13. Cruickshank K, Riste L, Anderson SG et al (2002) Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation 106(16):2085–2090
14. Gaede P, Vedel P, Parving HH, Pedersen O (1999) Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. Lancet 353(9153):617–622
15. American Diabetes Association (2014) Standards of medical care in diabetes--2014. Diabetes Care 37(Suppl 1):S14–S80
16. Weber MA, Schiffrin EL, White WB et al (2014) Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. J Clin Hypertens 16(1):14–26
17. Emdin CA, Rahimi K, Neal B et al (2015) Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 313(6):603–615
18. (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 317(7160):703–713
19. Hansson L, Zanchetti A, Carruthers SG et al (1998) Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 351(9118):1755–1762
20. Patel A; ADVANCE Collaborative Group, MacMahon S (2007) Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 370(9590):829–840

21. ACCORD Study Group, Cushman WC, Evans GW et al (2010) Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 362(17):1575–1585
22. Schrier RW, Estacio RO, Esler A, Mehler P (2002) Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 61(3):1086–1097
23. Howard BV, Roman MJ, Devereux RB et al (2008) Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial. JAMA 299(14):1678–1689
24. Cooper-DeHoff RM, Gong Y, Handberg EM et al (2010) Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. JAMA 304(1):61–68
25. Weber MA, Bakris GL, Jamerson K et al (2010) Cardiovascular events during differing hypertension therapies in patients with diabetes. J Am Coll Cardiol 56(1):77–85
26. Investigators ONTARGET, Yusuf S, Teo KK et al (2008) Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 358(15):1547–1559
27. Berl T, Hunsicker LG, Lewis JB et al (2005) Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan diabetic nephropathy trial. J Am Soc Nephrol 16(7):2170–2179
28. SPRINT Research Group, Wright JT Jr, Williamson JD et al (2015) A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 373(22):2103–2116
29. Sternlicht H, Bakris GL (2016) Hydrochlorothiazide as the diuretic of choice for hypertension: time to kick the habit. J Am Coll Cardiol 67(4):390–391
30. Mancia G, Fagard R, Narkiewicz K et al (2013) 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 31(7):1281–1357
31. ALLHAT Officers, ALLHAT Collaborative research Group Coordinators (2002) Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 288(23):2981–2997
32. Messerli FH, Bangalore S, Julius S (2008) Risk/benefit assessment of beta-blockers and diuretics precludes their use for first-line therapy in hypertension. Circulation 117(20):2706–2715. discussion 2715
33. Bakris GL, Fonseca V, Katholi RE et al (2004) Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. JAMA 292(18):2227–2236
34. Townsend RR, Machin I, Ren J et al (2016) Reductions in mean 24-hour ambulatory blood pressure after 6-week treatment with canagliflozin in patients with type 2 diabetes mellitus and hypertension. J Clin Hypertens 18(1):43–52

# Obesity and Metabolic Syndrome Hypertension

# 42

Michael E. Hall, Zhen Wang, Jussara do Carmo, Daisuke Kamimura, and John E. Hall

## 42.1 Introduction

The worldwide prevalence of obesity has more than doubled since 1980. In the United States, more than one-third of adults and almost 20% of children are obese [1]. Obesity is a major cause of cardiovascular and renal diseases through several mechanisms including hypertension, dyslipidemia, impaired glucose homeostasis, and inflammation which together have been referred to as the "metabolic syndrome." However, it is clear that visceral adiposity, not just increased body mass index (BMI), is the driving force for all of these disorders. Data from the Framingham Heart Study indicate that obesity accounts for approximately three-fourths of the risk for primary hypertension [2].

M.E. Hall (✉)
Department of Medicine, University of Mississippi Medical Center, Jackson, MS 39216, USA

Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS 39216, USA

Mississippi Center for Obesity Research, University of Mississippi Medical Center, Jackson, MS 39216, USA

Mississippi Center for Heart Research, University of Mississippi Medical Center, Jackson, MS 39216, USA
e-mail: mehall@umc.edu

Z. Wang • J. do Carmo • J.E. Hall
Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS 39216, USA

Mississippi Center for Obesity Research, University of Mississippi Medical Center, Jackson, MS 39216, USA

D. Kamimura
Department of Medicine, University of Mississippi Medical Center, Jackson, MS 39216, USA



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_42

The importance of obesity as a cause of hypertension is supported by (1) animal studies showing that excess weight gain raises blood pressure (BP), (2) clinical studies showing that weight loss is effective in reducing BP in most hypertensive patients [3, 4], and (3) epidemiological studies showing that excess weight gain is one of the best predictors for development of hypertension. While not every obese person is "hypertensive" by current classifications (BP ≥ 140/90 mmHg), there is a linear relationship with body weight and BP, and weight loss reduces BP in most obese individuals. Excess weight gain shifts the BP frequency distribution to higher levels of BP so that obese individuals with "normotensive" BP have a higher BP than they would if they weighed less (Fig. 42.1.). Therefore, weight loss generally lowers BP in normotensive as well as in hypertensive obese subjects [5, 6].

Although some obese individuals have been classified as "metabolically healthy," this may be a misnomer; compared to normal weight individuals, obese subjects who are metabolically healthy have higher prevalence of cardiometabolic risk factors including hypertension. Data from the Atherosclerosis Risk in Communities (ARIC) study showed that weight gain over a 3-year period was associated with larger increases in systolic and diastolic BP in metabolically healthy obese compared to normal weight participants [7]. In the Look AHEAD trial of intensive lifestyle interventions in diabetics [mean body mass index (BMI) = 36 kg/m$^2$], even small reductions in body weight (~6%) led to significant reductions in systolic BP (~5 mmHg) [8]. Over a 10-year follow-up period in the Swedish Obese Subjects (SOS) study [9] (mean BMI 40.9 kg/m$^2$ at baseline), weight loss (>10 kg, either

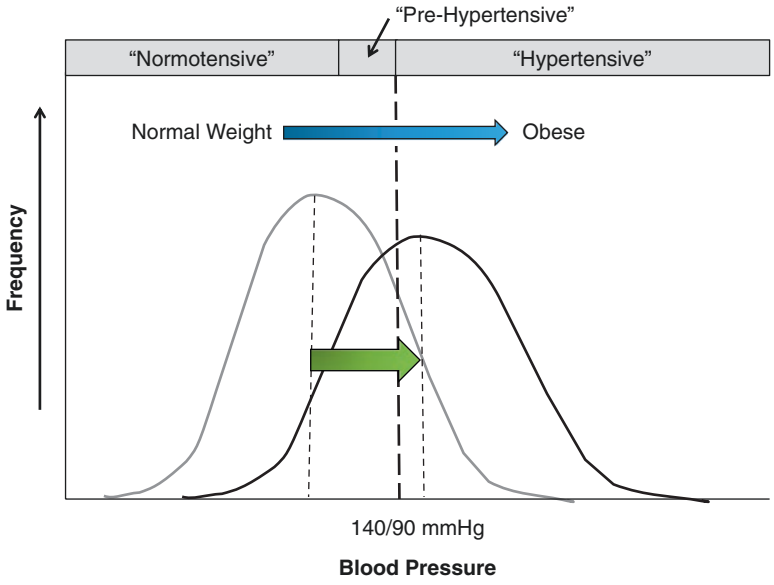



**Fig. 42.1** Effect of excess weight gain to shift the frequency (*y*-axis) distribution of blood pressure (*x*-axis) to higher levels so that obese individuals with "normotensive" BP have a higher BP than they would if they weighed less

surgically or with lifestyle interventions) was required to significantly attenuate aging-associated increases in BP.

Emerging evidence suggests that low birth weight followed by excess weight gain in early childhood may increase risk for higher future throughout life. A recent prospective study examining linear growth in early life of almost 1000 children showed that rapid gains in BMI during the first 6 months of life and in preschool years may lead to higher systolic BP in mid-childhood, regardless of birth size [10]. These findings suggest that excess weight gain in early childhood may cause pathophysiological changes that later lead to chronic hypertension.

Obesity is also a major risk factor for development of chronic kidney disease (CKD) through hypertension and diabetes. However, obesity may also cause renal dysfunction independent of diabetes and hypertension. Activation of neurohormonal systems and increased renal sodium reabsorption after excessive weight gain rapidly elevate BP and may initiate a vicious cycle that, in turn, leads to renal injury and increasingly severe, treatment resistant hypertension [11]. Here we discuss some of the mechanisms by which obesity may lead to hypertension and impaired renal function.

## 42.2 High BMI Versus Visceral Adiposity as a Risk Factor for Hypertension

While increases in body weight are associated with increased BP, differences in body composition, particularly visceral adiposity, appear to play a more important role. BMI is often used to describe a patient's overweight/obesity status due to ease of measurement. However, it is clear that BMI has its limitations. For example, a 220 pound muscular, well-trained athlete who is 6 ft tall would have a BMI in the "obese" range although the percentage of body fat might be lower than normal. While linear relationships between BMI and BP [12] exist on a population basis, other measures such as waist circumference or waist-to-hip ratio are better markers of visceral adiposity and cardiovascular risk [13]. Direct measures of visceral adiposity with magnetic resonance imaging (MRI) or computed tomography (CT) imaging provide even better assessment of hypertension risk.

Clinical and experimental animal studies suggest that specific fat depots such as renal sinus fat or perinephric fat are associated with increased BP and renal dysfunction, independent of BMI, or overall adiposity. The specific mechanisms by which fat depots in and around the kidneys contribute to the pathogenesis of hypertension may include activation of the renin-angiotensin-aldosterone system (RAAS), lipotoxicity, or increased renal sodium reabsorption due to physical compression of the kidneys [11, 14].

## 42.3 Hemodynamic and Vascular Changes in Obesity

Experimental studies have provided mechanistic insights into the hemodynamic and renal structural and functional changes that occur in obesity. In dogs and rabbits, obesity induced by a high-fat diet raises BP in less than 5 weeks [15, 16] and the

metabolic, cardiovascular, and renal changes that occur are similar to those observed in obese humans. Obesity is associated with increased extracellular volume expansion and increased tissue blood flow which increases venous return to the heart and cardiac output [15, 17]. Some of the increased tissue blood flow is due to secondary growth of these tissues as body weight and metabolic demands of these tissues increase. However, blood flow to some organs, namely, the kidneys, is increased even when expressed per gram of tissue weight, suggesting functional vasodilation [16, 17]. This may be related to increased metabolic rates in tissues such as the heart, skeletal muscle, and kidneys, resulting in increased tissue oxygen consumption.

Even though resting tissue blood flow may be increased in obese individuals, blood flow "reserve" and exercise-induced increases in blood flow are reduced. This may be due partly to obesity-induced endothelial dysfunction and arterial stiffness [18]. Aortic stiffness, a characteristic of aging, is an independent risk factor for incident hypertension and cardiovascular disease and has been independently correlated with measures of adiposity. A longitudinal study of over 5000 older individuals demonstrated that multiple measures of adiposity (BMI, waist circumference, waist-to-hip ratio, and fat mass by impedance) were independently associated with increased aortic stiffening after adjustment for age, sex, ethnicity, and BP [19]. Arterial thickening and stiffness have also been observed in adolescents and young adults with severe obesity independent of changes in BP. Some of these early vascular changes may be related to increased inflammation, oxidative stress, and endothelial dysfunction. Markers such as C-reactive protein or IL-6 are commonly elevated in obese individuals with early vascular dysfunction [20].

## 42.4 Renal Structural and Functional Changes in Obesity

Obesity causes structural and functional changes in the kidneys that lead to increased sodium reabsorption and ultimately elevated BP and renal injury (Table 42.1). In experimental animals or humans, excess weight gain increases renal sodium reabsorption which, in turn, leads to compensatory renal vasodilation and increased glomerular filtration rate (GFR) [15]. With prolonged obesity and hypertension, the glomerular hyperfiltration eventually lessens, and there is a gradual decline in GFR associated with renal injury and nephron loss.

Structural changes in the kidneys occur rapidly after excess weight gain. In dogs placed on a high-fat diet for only 7–9 weeks, there was increased glomerular cell proliferation and enlargement of Bowman's space, increased mesangial matrix, and thicker glomerular basement membranes [21]. These changes occurred despite modest increases in BP and no evidence of diabetes. Early in obesity, structural changes such as mesangial matrix deposition may protect against glomerular capillary overstretching in the setting of increased glomerular hydrostatic pressure due to renal vasodilation and mildly elevated BP. Over time, however, these changes could ultimately reduce renal filtration leading to further increases in BP and renal injury.

Metabolic and neurohumoral derangements, including hyperglycemia, oxidative stress, and activation of the SNS and RAAS, may exacerbate renal

**Table 42.1** Renal structural and functional changes in obesity

| |
|---|
| *Structural changes* |
| Increased renal sinus and perinephric fat |
| Increased mesangial matrix deposition |
| Glomerular cell proliferation |
| Enlargement of Bowman's space |
| Basement membrane thickening |
| Glomerulosclerosis |
| Increased renal medullary matrix |
| *Functional changes* |
| Increased renal interstitial hydrostatic pressure |
| Renal vasodilation |
| Impaired renal-pressure natriuresis |
| Increased renal tubular sodium reabsorption |
| Increased renin secretion |
| Early—Glomerular hyperfiltration |
| Late—Reduced glomerular filtration rate |

dysfunction and injury in obesity. Common markers of renal injury such as GFR or serum creatinine may be misleading since GFR is likely to be increased in the early stages of obesity [22]. Other markers such as proteinuria may detect earlier stages of obesity-induced renal dysfunction in obesity even in the absence of hypertension or diabetes.

## 42.5 Physical Compression of the Kidneys

Abdominal obesity is associated with hypertension and CKD independently of overall adiposity or increased BMI, although there is generally a good association between BMI and visceral obesity. In a longitudinal study of normotensive participants enrolled in the Dallas Heart Study and followed for 7 years, BMI was associated with incident hypertension, but after adjusting for multiple covariates including visceral and subcutaneous adiposity measured by MRI, only visceral adiposity remained independently associated with incident hypertension [23]. Furthermore, other clinical studies quantitating specific visceral fat depots have demonstrated detrimental effects of fat in and around the kidneys. For example, in middle-aged and elderly individuals, renal sinus fat was independently associated with increased risk of Stage II hypertension (systolic BP $\geq$ 160 or diastolic BP $\geq$ 100 mmHg) and use of more antihypertensive medications [24]. In the Framingham Heart Study, individuals characterized as having "fatty kidneys" (increased perinephric fat) had a higher risk of hypertension (odds ratio 2.12) even after adjusting for BMI and total visceral fat [25]. Participants with "fatty kidneys" also had a 2.3-fold increased risk for incident CKD after adjustment for BMI and visceral fat.

The mechanisms by which visceral, perinephric, and renal sinus fat may lead to hypertension and renal injury are not completely understood. Physical compression of the kidneys by fat in and around the kidneys is one hypothesized mechanism (Fig. 42.2.). Intra-abdominal pressures correlate directly with sagittal abdominal diameter and are increased to as high as 40 mmHg in morbidly obese individuals

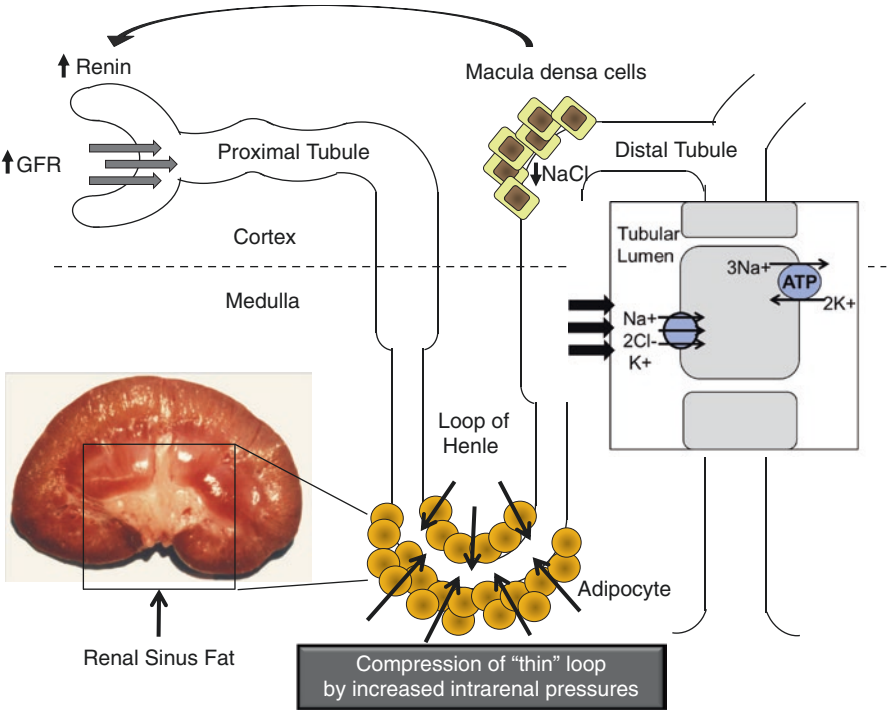



**Fig. 42.2** Renal compression as a mechanism of obesity hypertension. Compression of the thin loop of Henle by renal sinus fat may lead to increased sodium reabsorption in the thick ascending loop of Henle. This would lead to reduced sodium chloride delivery to the macula densa cells which (through a tubuloglomerular feedback mechanism) would increase secretion of renin and glomerular filtration, both of which are observed in obese individuals prior to nephron injury

[26]. High intrarenal pressures may tend to reduce renal tubular flow in general, but the most compressible tubule segment is the thin loop of Henle in the renal medulla. Reduced renal tubular flow would cause more complete sodium reabsorption in the thick ascending loop (via the sodium-potassium-2chloride co-transporter), leading to reduced macula densa sodium chloride delivery. This, in turn, would increase GFR and renin secretion (via tubuloglomerular feedback) and angiotensin II formation which would further increase renal sodium reabsorption and BP [11]. Small increases (3–4 mmHg) in renal interstitial hydrostatic pressure may inhibit renal sodium reabsorption, but large increases of the magnitude observed in obese dogs (to around 19 mmHg) would increase sodium reabsorption [27].

## 42.6 Renin-Angiotensin-Aldosterone System

### 42.6.1 Role of Angiotensin II

Evidence from experimental and clinical studies suggests that the RAAS is activated in obesity and contributes to increased BP [28]. In humans, obesity is associated with

increases in plasma renin activity (PRA), angiotensinogen, angiotensin II (Ang II), and aldosterone. Activation of the RAAS in obesity occurs despite sodium retention and elevated BP which would normally suppress renin secretion and decrease Ang II production.

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) attenuate sodium reabsorption, volume expansion, and increased BP in obese dogs fed a high-fat diet [29, 30]. RAAS blockade in obese Zucker rats lowers BP more than in lean rats despite lower than normal PRA, suggesting increased sensitivity to the BP effects of Ang II [31].

Ang II stimulates renal sodium reabsorption by three major mechanisms [28]: (1) activating multiple nephron epithelial sodium chloride transporters in proximal, loop of Henle, distal, and collecting tubules, (2) stimulating secretion of aldosterone which increases sodium chloride reabsorption in the late distal and collecting tubules, and (3) efferent arteriolar constriction which increases peritubular capillary reabsorption, renal tubular sodium reabsorption, and glomerular hydrostatic pressure. Each of these mechanisms contributes to the chronic BP effects of Ang II.

Ang II-mediated efferent arteriolar constriction, when combined with afferent arteriolar dilation and increased BP, also increases glomerular hydrostatic pressure in obesity. Although it is likely that increased glomerular capillary pressure is an important contributor to glomerular injury, the relative importance and interactions of hemodynamic and metabolic abnormalities in obesity-induced kidney injury are still unclear.

In clinical trials, ACEIs or ARBs reduce proteinuria in obese diabetic patients with kidney disease and decrease the incidence of kidney failure. In the TROPHY study, the ACEI lisinopril was more effective than hydrochlorothiazide at achieving a diastolic BP goal of less than 90 mmHg in obese hypertensives. Additionally, lisinopril treatment had more favorable metabolic profiles, including lower plasma glucose [32]. Unfortunately, large clinical trials comparing the effectiveness of RAAS antagonists in lean versus obese hypertensive patients are still lacking.

### 42.6.2 Mineralocorticoid Receptor Activation

Obesity is sometimes associated with inappropriately increased aldosterone which is synthesized in the zona glomerulosa of the adrenal glands in response to Ang II or increased plasma potassium levels as well as other stimuli. Adipose tissue may also produce components of the RAAS such as angiotensinogen, Ang II, and aldosterone which have autocrine or paracrine functions [33]. However, it remains unclear whether adipocyte-derived components of the RAAS play a major role in chronic control of BP. There is evidence from experimental animals that RAAS antagonism plays a role in adipocyte differentiation and growth; however, there is little evidence in humans that RAAS antagonists have major effects on adiposity.

In a small clinical study of hypertensive patients with visceral adiposity, treatment with the mineralocorticoid receptor (MR) antagonist spironolactone significantly reduced BP and creatinine clearance (attenuated glomerular hyperfiltration)

and improved endothelial function [34] independent of lipid or glucose effects. In obese dogs, MR antagonism significantly reduced renal sodium retention, glomerular hyperfiltration, and BP [35]. Importantly, amelioration of glomerular hyperfiltration may have implications for obesity-induced renal injury.

Plasma aldosterone levels are often mildly elevated in obese hypertensives and may be partially responsible for resistant hypertension that is often encountered in these individuals. In treated essential hypertensive patients, a BMI > 35 kg/m$^2$ was associated with increased plasma aldosterone levels even in those treated with ACEIs or ARBs [36]. MR antagonism has a significant antihypertensive effect in obese-resistant hypertensive patients even though there are no significant correlations between plasma aldosterone concentrations and BP responses. In obese patients with resistant hypertension, reduced BP with MR antagonists occurred despite concomitant therapy with ACEIs or ARBs, suggesting that MR activation in obesity may occur independently of Ang II-mediated stimulation of aldosterone release.

It is not clear why MR blockade is so effective in lowering BP and improving renal function in obese subjects. Obesity may increase sensitivity to aldosterone-mediated MR activation, or the MR may be activated by non-aldosterone mechanisms. For example, Rac1, a small guanosine triphosphate (GTP)-binding protein member of the Rho family of GTPases, may activate MR in obese subjects [37]. Another potential mechanism is glucocorticoid activation of MR in obesity. The glucocorticoid cortisol binds to the MR with high affinity; however, the kidneys are normally protected by the enzyme 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) which converts cortisol to cortisone which does not readily bind to the MR. If renal tubular 11β-HSD2 is downregulated in obesity, this may provide an additional mechanism for increased MR activation.

## 42.7 Sympathetic Nervous System

Visceral obesity is generally associated with decreased parasympathetic tone in the heart and increased SNS activity in many tissues, including the kidneys [17, 38]. These changes in autonomic activity are associated with increases in HR, decreased HR variability, reduced baroreflex sensitivity, and hypertension [39]. The importance of increased SNS activity in the pathogenesis of obesity hypertension has been demonstrated in experimental animals and in humans [17, 38]. Administration of α/β-adrenergic blockers greatly attenuates BP increases in obese animals and obese hypertensive patients [17, 40]. Renal denervation also markedly reduces BP and sodium retention in obese animals and obese patients with resistant hypertension [38, 41, 42].

The mechanisms that link obesity, especially excess visceral adiposity, to hypertension are still uncertain although several mediators have been suggested including (1) impaired baroreceptor reflexes, (2) activation of chemoreceptor-mediated reflexes associated with sleep apnea and intermittent hypoxia, (3) Ang II, (4) hyperinsulinemia, (5) cytokines such as leptin released from adipocytes, and (6) the CNS proopiomelanocortin (POMC) pathway [38, 39].

### 42.7.1 Baroreceptor Dysfunction

Studies in experimental animals and in humans have shown that baroreflex control of SNS activity is impaired in obesity hypertension, in parallel with elevated BP and metabolic abnormalities such as hyperglycemia, dyslipidemia, hyperleptinemia, and hyperinsulinemia [43–45]. However, the importance of these mechanisms and of baroreceptor dysfunction in contributing to elevated BP in obesity is unclear.

The arterial baroreceptors provide powerful moment-to-moment control of BP, but their roles in long-term BP regulation and obesity hypertension are not as well appreciated. Impaired baroreflex function in hypertension may be secondary to resetting of arterial baroreceptors to higher BPs. However, some studies suggest that baroreceptors may not completely reset in hypertension and therefore may buffer increases in BP [46]. To the extent that baroreceptor dysfunction occurs in obesity hypertension, the buffering effect to attenuate increases in BP would be lost. Currently, it is still unclear whether baroreflex dysfunction merely alters the time course for onset of hypertension or plays an important role in long-term BP regulation.

Consistent with the concept that arterial baroreceptor activation can cause long-term reductions in BP is the finding that strong electrical stimulation of the carotid sinus nerves causes sustained reductions in SNS activity and BP in obese dogs and in treatment resistant obese humans [47, 48]. In contrast, chronic carotid sinus nerve stimulation does not cause sustained decreases in BP in dogs infused chronically with aldosterone, a form of hypertension that is not associated with increased SNS activity [49]. Although these observations support the concept that strong activation of carotid sinus nerves can lower BP when SNS activity is increased, they do not necessarily indicate that baroreceptor dysfunction actually causes obesity hypertension.

Even if baroreceptor dysfunction does not play a major role in initiating obesity hypertension, increased BP variability caused by impaired baroreflexes may eventually contribute to target organ injury and exacerbate hypertension. Large swings in BP, even in the absence of changes in average daily BP, have been shown to cause cardiac hypertrophy and renal injury. Therefore, baroreceptor dysfunction may play a significant role in promoting injury to the kidneys, heart, and blood vessels.

### 42.7.2 Chemoreceptors, Intermittent Hypoxia, and Sleep Apnea

Obstructive sleep apnea (OSA) is common in obese individuals and has been associated with resistant hypertension in cross-sectional and longitudinal studies [50]. Intermittent hypoxia triggers release of catecholamines and endothelin that cause vasoconstriction. Furthermore, alternating hypoxia and reoxygenation may lead to increased reactive oxygen species.

One of the primary mechanisms by which OSA may contribute to obesity hypertension is through SNS activation. Activation of carotid body chemoreceptors by hypoxia, even when intermittent, leads to SNS activation and increased respiratory drive. Leptin and other circulating factors associated with obesity may also cause hypersensitivity of these receptors as well as CNS chemoreceptors to hypoxic and hypercapnic stimuli [51, 52].

In an experimental model of obesity hypertension where dogs were fed a high-fat diet for 5 weeks, significant increases in BP were abolished by carotid baroreflex activation (electrical stimulation of the carotid sinus) [53]. Surgical denervation of the carotid sinus, including afferent nerves of the carotid body, caused sustained reductions in arterial partial pressure of oxygen and hypercapnia as well as a 50% reduction in the obesity-induced increase in BP. These findings suggest that in obesity, chronic intermittent hypoxia may cause stimulation of peripheral chemoreceptors which contributes to SNS activation and hypertension. Clinical studies in obese patients with metabolic syndrome have shown that modest reductions in body weight (~5 kg), induced by diet and exercise, improve chemoreflex sensitivity and reduce apnea-hypopnea episodes [54] as well as muscle SNS activity and BP.

### 42.7.3 Leptin-Melanocortin System-Induced SNS Activation in Obesity

Leptin is an adipokine that has powerful effects on the central nervous system (CNS) to regulate energy balance by reducing appetite and increasing energy expenditure. Rodent models (ob/ob or db/db mice or obese Zucker rats) and humans that have impaired leptin signaling pathways develop severe obesity yet are not usually hypertensive despite morbid obesity and associated metabolic derangements such as insulin resistance and hyperglycemia [39]. Chronic intravenous infusions of leptin increased BP and renal sympathetic nerve activity. Similar findings are observed when leptin was administered directly into the brain. This rise in BP occurs despite significant reductions in body weight which would normally reduce BP.

The chronic effects of leptin to increase BP are mediated via activation of the SNS as combined α- and β-adrenergic blockade completely blocked hypertension during leptin infusion. A role for endogenous leptin in mediating obesity hypertension is supported by the finding that administration of a leptin receptor antagonist in obese rabbits on a high-fat diet reduced BP and renal SNS activity [55].

Leptin's effects to activate the SNS and raise BP appear to be mediated through stimulation of the proopiomelanocortin (POMC) pathway. POMC neurons located in the arcuate nucleus and brain stem send projections to second-order neurons in the hypothalamus and hindbrain where they release α-melanocyte-stimulating hormone which activates melanocortin 3 (MC3R) and melanocortin 4 receptors (MC4R). Chronic activation of MC4R in rats increases BP while reducing appetite and body weight [56]. Alpha- and β-adrenergic blockade abolishes this rise in BP due to activation of MC4R demonstrating the role of the SNS [57]. Conversely, MC4R antagonism lowers BP especially when the SNS is activated, such as in spontaneously hypertensive rats (SHR) [58].

The POMC/melanocortin pathway appears to be an important link between obesity, SNS activation, and hypertension. Genetic deletion of leptin receptors specifically on POMC neurons or blockade of MC4R completely abolished the BP effect of leptin [59, 60]. Humans and rodents with POMC or MC4R mutations have early-onset morbid obesity and many characteristics of the metabolic syndrome, including insulin resistance and dyslipidemia, but do not have increased SNS activity or

hypertension [61, 62]. Also, chronic administration of an MC4R agonist caused significant increases in BP in humans as well as in rodents. Thus, in humans and rodents, chronic activation of the POMC-MC4R pathway raises BP, and the presence of a functional MC4R system appears to be necessary for obesity and hyperleptinemia to increase SNS activity and BP.

### 42.7.4 Role of the Renal Nerves

There is substantial evidence that the chronic hypertensive effects of SNS activation in obesity are mediated by renal sympathetic nerves. Renal SNS activation stimulates renin secretion and renal sodium reabsorption which contribute to the development and maintenance of obesity hypertension. In obese dogs, renal denervation (RDN) markedly attenuated sodium retention and hypertension in response to a high-fat diet and in established obesity hypertension [41, 42] (Fig. 42.3.). This BP

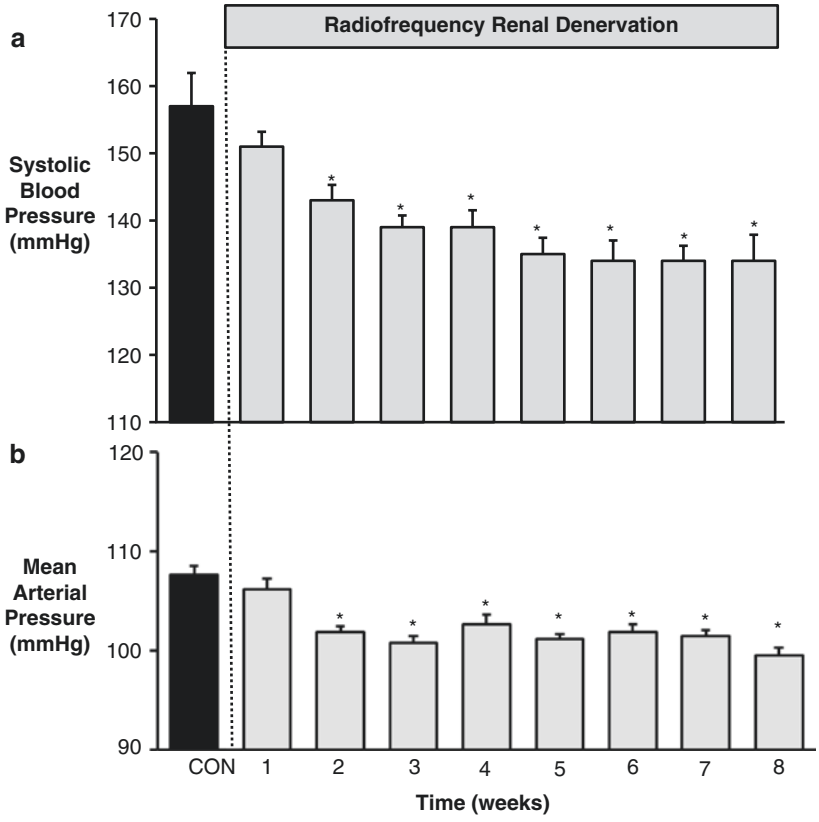



**Fig. 42.3** Mean systolic blood pressure and mean arterial pressure during control (CON) and for 8 weeks following renal denervation in obese dogs. Each *bar* represents the average of 7 days of blood pressure measurements in (**a**) and the average daily blood pressure in (**b**), measured 18 h a day, in bursts of 12 s each minute at a rate of 500 samples per second. *$p < 0.05$ vs. CON

reduction was observed even when less than 50% of the renal nerves were ablated. In obese, resistant hypertensive patients, percutaneous radiofrequency RDN lowered office-based systolic BP by up to 30 mmHg [63]. However, follow-up studies evaluating the effects of RDN procedures on 24-hour ambulatory BP did not demonstrate a significant reduction in BP compared to a sham procedure [64]. Of note, control patients were on three or more antihypertensive medications (including RAAS antagonists) which may mitigate the antihypertensive effects of ablating the renal nerves.

The specific roles of the renal afferent versus efferent nerves in obesity hypertension are unclear. Both (to some degree) are ablated during RDN procedures. The afferent nerves carry information from renal mechano- and chemoreceptors to the brain. Their role in pathogenesis of hypertension has been controversial. We assessed the role of renal afferent nerves in obesity hypertension by surgical denervation via dorsal root ganglionectomies from T10 to L2. This did not attenuate development of hypertension in obese dogs fed a high-fat diet suggesting that the BP-lowering effect of RDN was due to removal of renal efferent, rather than afferent, nerves [65]. However, further studies are needed, particularly in obese humans.

## 42.8 Treatment of Obesity Hypertension with Lifestyle Modification, Medications, and Bariatric Surgery

Therapeutic strategies for treating obesity have focused mainly on treatment of the associated metabolic derangements although strategies targeting obesity prevention have been widely disseminated. Lifestyle modification with diet and exercise are obvious first-line recommendations for obese individuals, particularly those with hypertension. There is abundant evidence that weight loss achieved through diet and exercise improves many of the cardiovascular, renal, and metabolic abnormalities associated with obesity. Mean 4-year follow-up data from the Look AHEAD (Action for Health in Diabetes) trial demonstrated that intensive lifestyle interventions significantly lowered BP (−5.3 mmHg systolic and −2.9 mmHg diastolic) in diabetic participants with a mean reduction of only 5.3% in body weight [8].

Unfortunately, weight losses with lifestyle changes are difficult to maintain and obese individuals who lose large amounts of weight are at high risk for regaining weight. A systematic review of 18 studies of diet-only versus diet-plus-exercise interventions for a minimum of 6 months showed that exercise in addition to diet resulted in a small reduction in body weight (1.64 kg) [66]. Although significant, these relatively small reductions in body weight may not normalize BP, and there is a lack of long-term studies examining these effects on chronic BP control.

Other strategies for long-term weight loss have been developed including weight loss pharmacotherapies. Orlistat inhibits pancreatic and gastric lipases and blocks gastrointestinal uptake of approximately 30% of ingested fats. In a 2-year randomized controlled trial of orlistat plus diet versus diet and placebo, participants receiving orlistat lost more weight (8.76 kg vs 5.81 kg, $p < 0.001$) [67] and had a small but significant systolic BP reduction. However, orlistat's use is often limited by its side

effects (fatty stool, bloating and diarrhea). Other anorexic drugs such as phentermine and sibutramine have amphetamine-like properties which increase BP and were taken off the market. Recently, a large randomized placebo-controlled trial treated overweight and obese patients without diabetes with 3.0 mg of liraglutide (a glucagon-like peptide-1 analogue) as an adjunct to diet and exercise, which resulted in a mean weight loss of 8.4 kg as well as small reductions in systolic BP (4.2 mmHg) [68]. The effects of these agents as well as other novel therapies on body weight and BP warrant more investigation.

Other interventions such as bariatric surgery have been evaluated as a long-term strategy for weight reduction as well as prevention and treatment of obesity-related metabolic disorders. Table 42.2 lists several clinical studies evaluating the chronic effects of bariatric surgery on BP and renal function. The mechanisms by which bariatric surgery lowers BP and improves kidney function are not completely understood. Attenuated SNS activity and reduction in renal sodium reabsorption are two potential beneficial effects since bariatric surgery decreases markers of renal sympathetic activity. Overall, bariatric surgery has beneficial chronic effects to reduce BP, improve renal function, as well to improve hyperglycemia and diabetes which may have additional effects to prevent kidney injury and subsequent BP increases.

**Table 42.2** Clinical studies on the effects of bariatric surgery on blood pressure and renal function

| Type of bariatric surgery | Weight loss amount | Participants (*n*) | Follow-up (years) | Outcome | Source |
|---|---|---|---|---|---|
| Majority RYGB; some LAGB or SG | 61% EBW | 323 | 1 | GFR decreased from 133 to 122 mL/min in hyperfilterers and increased in those with renal dysfunction (GFR <90 mL/min) | Coupaye M et al. *Obese Surg*. (2016) |
| RYGB or SG | 68% EBW | 42 | 1 | 24-h SBP decreased by 13 mmHg | Careago M et al. *Surg Obese Relat Dis*. (2015) |
| LAGB | 2.2 kg | 87 | 13 | LAGB maintained weight without intensification of antihypertensive medications (31% in LAGB vs 60% of controls) | Zakaria AS et al. *Surg Obes Relat Dis*. (2016) |
| RYGB | > 9 unit drop in BMI | 19 | 1 | Reduced SBP by 12 mmHg | Halperin F et al. *JAMA Surg*. (2014) |

(continued)

**Table 42.2** (continued)

| Type of bariatric surgery | Weight loss amount | Participants (*n*) | Follow-up (years) | Outcome | Source |
|---|---|---|---|---|---|
| Majority RYGB or LAGB | 31% body weight | 2458 | 3 | Remission of HTN in 38% of patients with RYGB and 17% of LAGB | Courcoulas AP et al. *JAMA*. (2013) |
| RYGB | 26% body weight | 28 | 1 | ~12 mmHg drop in systolic blood pressure | Ikramuddin S et al. *JAMA*. (2013) |
| LAGB | 65% EBW | 149 | 2 | 8 mmHg reduction in SBP | Michaelson R et al. *Obesity*. (2013) |
| Biliopancreatic diversion | 50 kg | 25 | 4 | eGFR improved by 10.6 mL/min | Jose B et al. *Obes Surg*. (2013) |
| Variable banding, VPG or GB | 16.1% body weight | 1073 | 10 | 19% of surgical patients recovered from HTN (odds ratio 1.68, compared to conventional therapy) | Sjorstrom L et al. *N Engl J Med.* (2004) |
| GB | (a) 59% EBW<br>(b) 37% EBW | (a) 342<br>(b) 135 | (a) 5–7<br>(b) 10–12 | (a) HTN resolved in 66%<br>(b) HTN resolved in 51% | Sugerman H et al. *Ann Surg*. (2003) |

*RYGB* Roux-en-Y gastric bypass, *LAGB* laparoscopic gastric banding, *SG* sleeve gastrectomy, *EBW* excess body weight, *GFR* glomerular filtration rate, *SBP* systolic blood pressure, *BMI* body mass index, *HTN* hypertension, *VBG* vertical banded gastroplasty, *GB* gastric bypass

## 42.9 Summary and Perspectives

Accumulating evidence from experimental, clinical, and population research demonstrates that obesity is a major cause of primary hypertension and renal injury. The exact mechanisms of obesity hypertension are still under investigation; however, activation of the RAAS and SNS and physical compression of the kidneys may contribute to impaired renal-pressure natriuresis and increased renal sodium reabsorption leading to increased BP (Fig. 42.4.). This cascade of events driven by visceral adiposity, along with other metabolic complications of obesity (dyslipidemia, hyperglycemia, and inflammation), may synergistically initiate renal injury which causes further increases in BP and renal injury, making the hypertension more difficult to control. Maintenance of a healthy weight is important for primary prevention of hypertension while even modest weight loss can reduce BP in many overweight and obese individuals. Although most available drugs for long-term treatment of obesity have limited effectiveness and cause significant adverse effects, novel pharmacologic and surgical strategies for weight loss are currently being

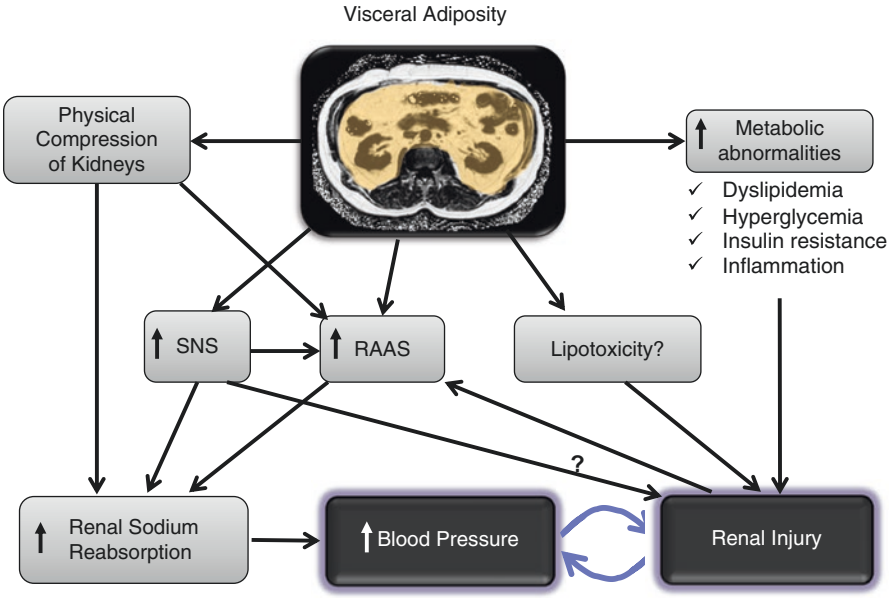



**Fig. 42.4** Integrated mechanisms by which visceral adiposity increases blood pressure and initiates renal injury which ultimately lead to a slowly developing vicious cycle, progressive renal injury and resistant hypertension. *SNS* sympathetic nervous system, *RAAS* renin-angiotensin-aldosterone system

evaluated as therapeutic options for obesity hypertension. Further investigation of the mechanisms of obesity hypertension and clinical trials of these novel treatment strategies are necessary for this prevalent and growing problem.

## References

1. Ogden CL, Carroll MD, Kit BK, Flegal KM (2014) Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA 311:806–814
2. Garrison RJ, Kannel WB, Stokes J 3rd, Castelli WP (1987) Incidence and precursors of hypertension in young adults: the Framingham Offspring Study. Prev Med 16:235–251
3. Stevens VJ, Obarzanek E, Cook NR et al (2001) Long-term weight loss and changes in blood pressure: results of the trials of hypertension prevention, phase II. Ann Intern Med 134:1–11
4. Jones DW, Miller ME, Wofford MR et al (1999) The effect of weight loss intervention on antihypertensive medication requirements in the Hypertension Optimal Treatment (HOT) study. Am J Hypertens 12:1175–1180
5. Neter JE, Stam BE, Kok FJ et al (2003) Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension 42:878–884
6. Schneider R, Golzman B, Turkot S et al (2005) Effect of weight loss on blood pressure, arterial compliance, and insulin resistance in normotensive obese subjects. Am J Med Sci 330:157–160
7. Cui Z, Truesdale KP, Bradshaw PT et al (2015) Three-year weight change and cardiometabolic risk factors in obese and normal weight adults who are metabolically healthy: the atherosclerosis risk in communities study. Int J Obes 39:1203–1208

8. Wing RR, Look AHEAD Research Group (2010) Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med 170:1566–1575
9. Sjostrom CD, Lystig T, Lindroos AK (2011) Impact of weight change, secular trends and ageing on cardiovascular risk factors: 10-year experiences from the SOS study. Int J Obes 35:1413–1420
10. Perng W, Rifas-Shiman SL, Kramer MS et al (2016) Early weight gain, linear growth, and mid-childhood blood pressure: a prospective study in project viva. Hypertension 67:301–308
11. Hall ME, do Carmo JM, da Silva AA et al (2014) Obesity, hypertension, and chronic kidney disease. Int J Nephrol Renovasc Dis 7:75–88
12. Jones DW, Kim JS, Andrew ME et al (1994) Body mass index and blood pressure in Korean men and women: the Korean National Blood Pressure Survey. J Hypertens 12:1433–1437
13. Pouliot MC, Despres JP, Lemieux S et al (1994) Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 73:460–468
14. Hall JE (2003) The kidney, hypertension, and obesity. Hypertension 41:625–633
15. Hall JE, Brands MW, Dixon WN, Smith MJ Jr (1993) Obesity-induced hypertension. Renal function and systemic hemodynamics. Hypertension 22:292–299
16. Carroll JF, Huang M, Hester RL et al (1995) Hemodynamic alterations in hypertensive obese rabbits. Hypertension 26:465–470
17. Hall JE, , do Carmo JM, da Silva AA et al (2015) Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. Circ Res 116:991–1006
18. Raitakari M, Ilvonen T, Ahotupa M et al (2004) Weight reduction with very-low-caloric diet and endothelial function in overweight adults: role of plasma glucose. Arterioscler Thromb Vasc Biol 24:124–128
19. Brunner EJ, Shipley MJ, Ahmadi-Abhari S et al (2015) Adiposity, obesity, and arterial aging: longitudinal study of aortic stiffness in the Whitehall II cohort. Hypertension 66:294–300
20. Shah AS, Dolan LM, Khoury PR et al (2015) Severe obesity in adolescents and young adults is associated with subclinical cardiac and vascular changes. J Clin Endocrinol Metab 100:2751–2757
21. Henegar JR, Bigler SA, Henegar LK et al (2001) Functional and structural changes in the kidney in the early stages of obesity. J Am Soc Nephrol 12:1211–1217
22. Palatini P (2012) Glomerular hyperfiltration: a marker of early renal damage in pre-diabetes and pre-hypertension. Nephrol Dial Transplant 27:1708–1714
23. Chandra A, Neeland IJ, Berry JD et al (2014) The relationship of body mass and fat distribution with incident hypertension: observations from the Dallas Heart Study. J Am Coll Cardiol 64:997–1002
24. Chughtai HL, Morgan TM, Rocco M et al (2010) Renal sinus fat and poor blood pressure control in middle-aged and elderly individuals at risk for cardiovascular events. Hypertension 56:901–906
25. Foster MC, Hwang SJ, Porter SA et al (2011) Fatty kidney, hypertension, and chronic kidney disease: the Framingham Heart tudy. Hypertension 58:784–790
26. Sugerman H, Windsor A, Bessos M, Wolfe L (1997) Intra-abdominal pressure, sagittal abdominal diameter and obesity comorbidity. J Intern Med 241:71–79
27. Hall JE, Louis K (1994) Dahl Memorial Lecture Renal and cardiovascular mechanisms of hypertension in obesity. Hypertension 23:381–394
28. Hall JE, Granger JP, do Carmo JM et al (2012) Hypertension: physiology and pathophysiology. Compr Physiol 2:2393–2442
29. Hall JE, Henegar J, Shek EW et al (1997) Role of renin-angiotensin system in obesity-induced hypertension. Circulation 96(8S):1–33
30. Robles RG, Villa E, Santirso R et al (1993) Effects of captopril on sympathetic activity, lipid and carbohydrate metabolism in a model of obesity-induced hypertension in dogs. Am J Hypertens 6:1009–1015

31. Alonso-Galicia M, Brands MW, Zappe DH, Hall JE (1996) Hypertension in obese Zucker rats. Role of angiotensin II and adrenergic activity. Hypertension 28:1047–1054
32. Reisin E, Weir MR, Falkner B et al (1997) Lisinopril versus hydrochlorothiazide in obese hypertensive patients: a multicenter placebo-controlled trial. Treatment in Obese Patients With Hypertension (TROPHY) Study Group. Hypertension 30:140–145
33. Dinh Cat AN, Friederich-Persson M, White A, Touyz RM (2016) Adipocytes, aldosterone and obesity-related hypertension. J Mol Endocrinol 57:F7–F21
34. Costa MB, Andrade Ezequiel DG, Morais Lovis JC et al (2010) Aldosterone antagonist decreases blood pressure and improves metabolic parameters in obese patients with the metabolic syndrome. J Clin Hypertens (Greenwich) 12:753–755
35. de Paula RB, da Silva AA, Hall JE (2004) Aldosterone antagonism attenuates obesity-induced hypertension and glomerular hyperfiltration. Hypertension 43:41–47
36. Sarzani R, Guerra F, Mancinelli L et al (2012) Plasma aldosterone is increased in class 2 and 3 obese essential hypertensive patients despite drug treatment. Am J Hypertens 25:818–826
37. Nishimoto M, Fujita T (2015) Renal mechanisms of salt-sensitive hypertension: contribution of two steroid receptor-associated pathways. Am J Physiol Renal Physiol 308:F377–F387
38. Grassi G, Mark A, Esler M (2015) The sympathetic nervous system alterations in human hypertension. Circ Res 116:976–990
39. Hall JE, da Silva AA, do Carmo JM et al (2010) Obesity-induced hypertension: role of sympathetic nervous system, leptin, and melanocortins. J Biol Chem 285:17271–17276
40. Wofford MR, Anderson DC Jr, Brown CA et al (2001) Antihypertensive effect of alpha- and beta-adrenergic blockade in obese and lean hypertensive subjects. Am J Hypertens 14: 694–698
41. Kassab S, Miller MT, Novak J et al (1998) Endothelin-a receptor antagonism attenuates the hypertension and renal injury in Dahl salt-sensitive rats. Hypertension 31:397–402
42. Henegar JR, Zhang Y, Rama RD et al (2014) Catheter-based radiorefrequency renal denervation lowers blood pressure in obese hypertensive dogs. Am J Hypertens 27:1285–1292
43. Hall JE, Crook ED, Jones DW et al (2002) Mechanisms of obesity-associated cardiovascular and renal disease. Am J Med Sci 324:127–137
44. Van Vliet BN, Hall JE, Mizelle HL et al (1995) Reduced parasympathetic control of heart rate in obese dogs. Am J Phys 269:H629–H637
45. Arone LJ, Mackintosh R, Rosenbaum M et al (1995) Autonomic nervous system activity in weight gain and weight loss. Am J Phys 269:R222–R225
46. Thrasher TN (2006) Arterial baroreceptor input contributes to long-term control of blood pressure. Curr Hypertens Rep 8:249–254
47. Lohmeier TE, Warren S, Cunningham JT (2003) Sustained activation of the central baroreceptor pathway in obesity hypertension. Hypertension 42:96–102
48. Iliescu R, Lohmeier TE, Tudorancea I et al (2015) Renal denervation for the treatment of resistant hypertension: review and clinical perspective. Am J Physiol Renal Physiol 309: F583–F594
49. Lohmeier TE, Liu B, Hildebrandt DA et al (2015) Global- and renal-specific sympathoinhibition in aldosterone hypertension. Hypertension 65:1223–1230
50. Wolk R, Shamsuzzaman AS, Somers VK (2003) Obesity, sleep apnea, and hypertension. Hypertension 42:1067–1074
51. Bassi M, Furuya WI, Zoccal DB et al (2015) Control of respiratory and cardiovascular functions by leptin. Life Sci 125:25–31
52. Moreau JM, Messenger SA, Ciriello J (2015) Effects of angiotensin II on leptin and downstream leptin signaling in the carotid body during acute intermittent hypoxia. Neuroscience 310:430–441
53. Lohmeier TE, Iliescu R, Tudorancea I et al (2016) Chronic interactions between carotid baroreceptors and chemoreceptors in obesity hypertension. Hypertension 68:227–235
54. Maki-Nunes C, Toschi-Dias E, Cepeda FX et al (2015) Diet and exercise improve chemoreflex sensitivity in patients with metabolic syndrome and obstructive sleep apnea. Obesity (Silver Spring) 23:1582–1590

55. Lim K, Burke SL, Head GA (2013) Obesity-related hypertension and the role of insulin and leptin in high-fat-fed rabbits. Hypertension 61:628–634
56. do Carmo JM, da Silva AA, Rushing JS, Hall JE (2012) Activation of the central melanocortin system contributes to the increased arterial pressure in obese Zucker rats. Am J Physiol Regul Integr Comp Physiol 302:R561–R567
57. Kuo JJ, da Silva AA, Tallam LS, Hall JE (2004) Role of adrenergic activity in pressor responses to chronic melanocortin receptor activation. Hypertension 43:370–375
58. da Silva AA, do Carmo JM, Kanyicska B et al (2008) Endogenous melanocortin system activity contributes to the elevated arterial pressure in spontaneously hypertensive rats. Hypertension 51:884–890
59. do Carmo JM, da Silva AA, Cai Z et al (2011) Control of blood pressure, appetite, and glucose by leptin in mice lacking leptin receptors in proopiomelanocortin neurons. Hypertension 57:918–926
60. Tallam LS, da Silva AA, Hall JE (2006) Melanocortin-4 receptor mediates chronic cardiovascular and metabolic actions of leptin. Hypertension 48:58–64
61. Greenfield JR (2011) Melanocortin signalling and the regulation of blood pressure in human obesity. J Neuroendocrinol 23:186–193
62. Tallam LS, Stec DE, Willis MA et al (2005) Melanocortin-4 receptor-deficient mice are not hypertensive or salt-sensitive despite obesity, hyperinsulinemia, and hyperleptinemia. Hypertension 46:326–332
63. Hering D, Marusic P, Walton AS et al (2014) Sustained sympathetic and blood pressure reduction 1 year after renal denervation in patients with resistant hypertension. Hypertension 64:118–124
64. Bhatt DL, Kandzari DE, O'Neill WW et al (2014) A controlled trial of renal denervation for resistant hypertension. N Engl J Med 370:1393–1401
65. Zappe DH, Capel WT, Keen HL et al (1996) Role of renal afferent nerves in obesity-induced hypertension. Am J Hypertens 9:20A
66. Wu T, Gao X, Chen M, van Dam RM (2009) Long-term effectiveness of diet-plus-exercise interventions vs. diet-only interventions for weight loss: a meta-analysis. Obes Rev 10:313–323
67. Davidson MH, Hauptman J, DiGirolamo M et al (1999) Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. JAMA 281:235–242
68. Pi-Sunyer X, Astrup A, Fujioka K et al (2015) A randomized, controlled trial of 3.0 mg of Liraglutide in Weight Management. N Engl J Med 373:11–22

# Secondary Hypertension: Infrequently Considered Aspects—Illicit/Recreational Substances, Herbal Remedies, and Drug-Associated Hypertension

43

Adel E. Berbari, Najla A. Daouk, and Abdo R. Jurjus

## 43.1 Introduction

Secondary hypertension, which includes renal, endocrine, and vascular syndromes, is reported to account for about 5–10% of blood pressure elevation in the general population [1]. However the changing dietary patterns, easy access to over the counter drugs, the development of large number of pharmacologic and medicinal agents for the management of various disorders, and increasing use by the public of herbal preparations have contributed to an ever increasing incidence of identifiable forms of hypertension [2].

The aim of this chapter is to describe other forms of identifiable hypertension which, often may be unsuspected or missed, or may even lead to further blood pressure elevation.

## 43.2 Dietary Patterns

Among many of the known modifiable risk factors, dietary manipulations play a critical role in the prevention and management of hypertension [3, 4]. Several observational and epidemiologic studies have shown that vegetarians have lower blood pressure (BP) than the general population, while omnivorous have higher BP and a higher incidence of hypertension [5].

A.E. Berbari, M.D. (✉) • N.A. Daouk
Department of Internal Medicine, American University of Beirut Medical Center, 11-0236, Riad El Solh, 1107 2020 Beirut, Lebanon
e-mail: ab01@aub.edu.lb

A.R. Jurjus Ph.D.
Department of Anatomy, Cell Biology and Physiological Sciences, American University of Beirut, 11-0236, Riad El Solh, 1107 2020 Beirut, Lebanon



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_43

Several short- and long-term studies have evaluated the role of diet items on BP and incident hypertension [6, 7].

Human diet consists of meat, plant food, and dairy products.

### 43.2.1 Meat and Meat Products

Numerous epidemiologic, observational, and clinical studies have indicated that consumption of meat is associated with an increase in BP.

There are three sources of meat [8, 9]:

- Red meat: beef, veal, sheep, lamb, and pork
- White meat: chicken, turkey, poultry, rabbit, and fish
- Processed meat: bacon, bologna, sausage (red meat and poultry), salami, ham, processed fish, and organ meats

Processed and unprocessed meats differ in their sodium and nitrate contents and other food compounds, commonly used as preservatives in the former food item, and may have deleterious effects on BP, cardiovascular system, and target organs [10].

The relation between consumption of meat and BP changes was first reported in 1926 by Donaldson [5, 11]. In that study, administration of meat diets to vegetarian college students was associated with an elevation of BP within 2 weeks [5, 11]. Similar observations were reported by Sacks [12]. In a controlled trial involving 21 strict vegetarians, addition of 250 grams of beef isocalorically for 4 weeks was associated with a significant 3% rise in systolic BP and 19% increase in serum cholesterol. There was no effect on diastolic BP [12].

Several long-term cross-sectional epidemiologic and observational studies revealed an association between protein intake and BP changes, incident hypertension, and cardiovascular outcome [13–16]. In the Western Chicago Electric cohort study involving 1710 male participants aged 45–57 years with no cardiovascular disease or hypertension at baseline, men who consumed 8–20 or more weekly servings of 120 portions of red meat had a 5.4–6.0 mmHg greater rise in systolic BP over 7 years compared to those whose meat intake was less than 8 weekly servings [6]. In the Coronary Artery Risk Development in Young Adults (CARDIA) study of 4304 white and black participants aged 18–30 years at baseline, after 15 years of follow-up, a 39% risk of elevated BP (BP $\geq$ 130/85 mmHg) was reported in participants whose red and processed meat was in the highest bracket [10]. A similar association of red meat with incident hypertension was described in a large cohort of 44,616 disease-free French women [13]. Women who consumed $\geq$5 servings per week (1 meat serving = 50 g) of processed red meat exhibited a 17% higher risk of hypertension compared to women whose intake was $\leq$1 serving/week [13]. In this study, however, no relationship was observed for unprocessed red meat [13]. In the Women's Health Study (WHS), a prospective trial of 28,766 female middle-aged and elderly (aged >45 years) US professionals, red meat intake was associated with

an increased risk of hypertension, while poultry intake was not [15]. However other studies which evaluated the relation of poultry intake to the development of hypertension were inconsistent [15–18]. In the INTERMAP study which included Western and East Asian population, the increase in BP was associated with intake of both processed and unprocessed red meat and poultry [16].

The mechanisms by which red meat consumption is associated with BP changes and risk of hypertension are poorly understood but appear to be multifactorial, resulting from the interaction of multiple dietary factors [15]. Red meat is a major source of saturated fat, cholesterol, and animal proteins and has iron [15]. Several large cohort studies have demonstrated a direct relation between saturated fat and cholesterol with an increased risk of hypertension [19]. Increases in body iron may promote insulin resistance and predisposition to the development of hypertension and vascular disease [15, 20, 21]. In addition, red meat, especially the processed categories, contains a significant amount of sodium [16]. Further, during preparation of processed meat (red meat/poultry), various additives, and preservatives and other chemicals are used [15]. These toxic compounds impair vascular structure and function, leading to atherosclerosis and hypertension [15].

Carnitine content in red meat has also been implicated in the pathogenesis of angiopathy and hypertension [22].

In human subjects, carnitine in red meat is processed by gut microorganisms into trimethylamine which is then converted into trimethylamine-N-oxide [22]. The latter metabolite has been reported to induce metabolic disturbances, inflammatory reactions, endothelial dysfunction, and vascular smooth muscle cell proliferation [22, 23]. These events may provoke an elevation in BP and development of hypertension [22, 23].

According to an NIH report, the redder the meat, the more is its carnitine content [22, 24]. Beef has the highest, while chicken has the lowest carnitine amount [24] (Table 43.1).

On the other hand, several other clinical trials and epidemiologic observational surveys have reported an inverse relation between protein, BP changes, and incident hypertension [25–27]. In most of these studies, however, it is unclear whether the protein evaluated is of plant or animal source [26]. Plant and animal proteins differ in several respects, namely, in macronutrients, amino acids, minerals, and fiber content [10, 28]. These elements, rich in plant proteins, have been shown to modulate BP and may account for lower BP levels and incidence of hypertension reported in vegetarians and in DASH and similar dietary programs [6].

**Table 43.1** Relation between carnitine content of meat items and blood pressure (BP) alterations modified from reference [24]

| Meat item | Carnitine content (mg/g meat) | Yearly systolic BP increase (mmHg) |
|---|---|---|
| Beef | 81 mg/85 g | 0.70–0.78 |
| Pork | 24 mg/85 g | 0.24 |
| Chicken | 3–5 mg/113 g | None |

## 43.3 Substance Abuse

### 43.3.1 Tobacco/Nicotine Smoking

#### 43.3.1.1 Cigarettes

Cigarette smoking is associated with acute and chronic cardiovascular effects. Studies in which intra-arterial and indirect blood pressure measurements were made revealed that smoking one cigarette causes an increase in both blood pressure and heart rate, effects which may persist up to 1 h [29–31]. The height in both parameters is roughly proportionate to the nicotine content of the cigarette [30]. Ambulatory blood pressure recording studies revealed that in smokers, the daytime blood pressure levels are significantly higher (presumably when they are smoking) than night blood pressure levels (when they abstain from smoking) [32]. Further, heart rates tend to be persistently higher in smokers [32].

The significant immediate and repetitive hemodynamic effects of acute smoking which usually persist for 45–60 min may be missed in the usually smoke-free medical environment of the clinic/office [31].

#### 43.3.1.2 Nargileh (Water Pipe/Shisha) Smoking

Nargileh (water pipe/shisha smoking) is increasing at an alarming popularity especially in youth [33]. Contrary to popular belief, nargileh smoking is not safe but is associated with significant acute cardiovascular hemodynamic alterations which may predispose in the long term to cardiovascular disease [33, 34]. Compared to cigarette smoking, the rise in systolic, diastolic, and mean arterial pressures, heart rate, and carbon monoxide (CO) levels are significantly greater with water pipe smoking [34]. The acute elevation in carbon monoxide levels may result in carbon monoxide (CO) intoxication which may be associated with syncope, dizziness, headache, and shortness of breath [34].

### 43.3.2 Caffeine

Caffeine is the most widely consumed stimulant beverage in the world [35, 36]. It is a component of coffee, tea, cola soft drinks, caffeinated bottled water, high-caffeine energy drinks, and chocolate (Table 43.2) [35, 36]. In addition, caffeine is used as an adjuvant in many prescription and over-the-counter medications [36]. However,

**Table 43.2** Caffeine content of some beverages [35, 36]

| Source | Caffeine content |
|---|---|
| Coffee | 60–120 mg/100 ml |
| Cola soft drink | 15–24 mg/150 ml |
| Decaffeinated coffee | 3–4 mg/150 ml |
| Tea | 20–40 mg/150 ml |
| Instant coffee | 80 mg/200 ml |
| Brewed tea | 40 mg/200 ml |

caffeine is consumed mostly in the form of coffee in most countries and tea in the Nordic and Middle Eastern States [37].

Caffeine is a xanthene derivative alkaloid which resembles closely uric acid and is found naturally in coffee beans, tea leaves, kola nuts, and cocoa beans [38, 39].

After ingestion, caffeine is almost completely absorbed in the gastrointestinal tract within 5 min and, being lipid soluble, penetrates all biologic membranes and is distributed in all body tissues [38, 40]. Peak levels are reached within 15–45 min [38, 41]. Absorption is reduced by food intake and is slower in colas than in coffee and tea [38, 41]. In practice, coffee typically contains twice as much caffeine as tea [42].

Caffeine is extensively metabolized by the liver with an average half-life of 4–6 h [38, 40]. Its metabolism is prolonged by chronic liver disease, pregnancy, and use of contraceptive pills [38, 40]. In contrast, smoking accelerates its metabolism and its clearance [38, 40]. Smoking cessation can double caffeine concentration in the blood, which may enhance smoking withdrawal symptoms [38, 40].

About 60–70% of caffeine is excreted unchanged in the urine [38]. Elimination half-life is about 5 h [38]. Since caffeine is consumed throughout the day, its plasma concentration is highest in the late afternoon and lowest on waking up in the morning due to overnight abstinence [38].

In the USA and Canada, the daily caffeine intake is 2–4 mg/kg in adults and 1.1 mg/kg in children and adolescents, aged 5–18 years [37, 38]. A dose of 15 mg/kg represents heavy caffeine ingestion [37, 38].

Caffeine is linked to several health outcomes. It exerts a wide range of biologic actions, namely, hemodynamic responses, activation of the autonomic nervous system and changes in cerebral cortical activity, and stimulation of several neuroendocrine hormones [42].

Several studies have evaluated the hemodynamic responses to caffeine. Acute caffeine intake is associated with transient elevation in both systolic and diastolic BP at rest and is enhanced by mental and physical stress [42–44]. A single dose of caffeine of 200–250 mg equivalent to 2–3 cups of coffee increases systolic BP by 3–14 mmHg and diastolic BP by 4–13 mmHg, respectively, in normotensive subjects [45]. The acute pressor response occurs within 30 min coinciding with an increase in plasma caffeine concentration [46, 47]. Moreover this pressor response appears to be greater in older subjects and in those who do not usually consume caffeine and is more prominent in hypertension and hypertension-prone individuals [35]. Acutely ingested caffeine elevates BP even in hypertensive patients receiving beta-blockers or diuretics [48, 49].

The pressor actions of acute caffeine consumption are characterized by vasoconstriction of the precapillary resistance vessels and increased systemic vascular resistance and increased arterial stiffness rather than enhanced cardiac contractility and cardiac output and are attributed to inhibition of adenosine receptors and reduced endogenous adenosine synthesis [50, 51].

Although it is well established that acute exposure to caffeine intake is associated with significant pressor actions, the data on the effects of chronic caffeine consumption are conflicting [42–45]. Development of tolerance to the pressor actions has been reported in only half of regular consumers [52]. However, habitual coffee

intake was not associated with an increased incidence of hypertension in both men and women [53, 54]. In the light of these conflicting observations, it would be advisable to have patients record their home BP before and within an hour after drinking coffee or tea [55]. Those who experience a significant pressor response should be advised to reduce or abstain from caffeine intake [55].

Addiction to caffeine appears to be infrequent [38]. However, caffeine withdrawal syndrome, characterized by headache, fatigue, anxiety, impaired psychomotor performance, nausea, and vomiting, may occur in some individuals, although intense desire for caffeine is infrequent [38, 56].

#### 43.3.2.1 Coffee/Tea

Coffee and tea, caffeine-containing drinks, are widely consumed on a daily basis. Both beverages have been reported to induce acute cardiovascular responses which appear to be linked to their caffeine content and to the presence bioactive subclasses [42].

##### Coffee

Acute intake of coffee is associated with an elevation in BP [57, 58]. Caffeine appears to be the active component responsible for this hemodynamic effect as regular coffee increases BP, whereas decaffeinated coffee has no effect [57, 58]. Further, a meta-analysis of 16 randomized controlled trials which included 1010 subjects assessed the cardiovascular actions of caffeine tablets and coffee consumption [57]. Although the caffeine doses were similar in both acute treatment groups (225–798 mg/d versus 295–750 mg/d in coffee and caffeine trials, respectively), BP elevations were larger for caffeine tablets (SBP/DBP = 4.16/2.41 mmHg) than for coffee intake (SBP/DBP = 1.22/0.49 mmHg) [57]. The lower pressor effect of coffee was attributed to the presence of increases of bioactive compounds [57–59].

Brewed coffee (filter, espresso, instant), when consumed in moderate amounts (5–6 cups/day), is a rich source of minerals and trace elements (potassium, magnesium, manganese, niacin), soluble fibers, and antioxidants polyphenols [60, 61]. It has been postulated that the presence of these minerals and bioactive compounds in coffee may outweigh the adverse cardiovascular actions and pressor effects in caffeine tablets. This hypothesis was confirmed by the prospective study in US Nurses in which caffeinated cola which is poor in polyphenols increases the risk of hypertension, while coffee had no effect [54].

Interaction of coffee with smoking and alcohol consumption may be affected. In hypertensive subjects, the combination of coffee intake and smoking induce a higher and more sustained pressor response than either agent alone [49]. In a cross-sectional study using ambulatory BP monitoring in patients with mild essential hypertension, moderate smoking and coffee intake was associated with a significant elevation in daytime systolic BP compared to non-smoking and non-coffee hypertensive consumers [62]. In contrast to the pressor coffee-smoking relationship, intake of coffee significantly lowers both systolic and diastolic blood pressures in prehypertensive and hypertensive subjects with a regular alcohol drinking pattern [63].

**Tea**

Tea, a drink brewed from the dried leaves of *Camellia sinensis*, is the most frequently consumed beverage in the world apart from water [64]. Tea contains caffeine at 3% of dry weight and polyphenolic compounds at about 40% of dry weight and providing more than half of the total flavonoid intake [65, 66].

A regular cup of brewed tea generally contains about 50% less caffeine than a similar cup of brewed coffee [36].

Consumption of a cup of brewed tea containing 180 mg caffeine is associated with a transient pressor response of equal or even higher magnitude than caffeine alone which peaks at 30 min and persists up to 60 min post ingestion [67]. This transient acute pressor effect of tea has been attributed to its caffeine content [67]. In contrast, long-term intake of tea has no pressor effect but may even cause a mild reduction in BP [67, 68].

In contrast, the attenuated pressor response and more prolonged depressor actions of tea have been attributed to its content of flavonoid-like polyphenols and flavonols substances [69]. The prominent health benefits of tea have been attributed to green tea which appears to be due to its high content of catechins, a class of compounds which belong to the family of flavonoid-like polyphenols [69].

### 43.3.3 Alcohol/Ethanol

Unlike many substances of abuse, alcohol is associated with both beneficial and adverse effects. Light to moderate alcohol intake is associated with a favorable cardiovascular outcome, while heavy to excessive consumption is linked to hemodynamic disturbances and increased risk of cardiovascular events [38].

Ethanol or ethyl alcohol represents the active component of consumable alcoholic beverages [70].

Regular heavy to excessive consumption of ethanol is associated with increased BP levels and prevalence of hypertension [70–72]. An association between heavier ethanol (alcohol) intakes was first reported in 1915 by Lian in French military personnel who consumed more than 2.5 l/day of wine [73].

The ethanol-BP relationship was confirmed subsequently by several epidemiologic observational and interventional studies [74–76]. In the pioneering Kaiser Permanente cross-sectional studies which include 8700 ambulatory adult subscribers, Klatsky [77, 78] reported that:

- Among drinkers in both genders, consumption of more than two daily alcoholic beverages was associated with progressive elevation in both systolic and diastolic blood pressures.
- Although occurring at all ages, the ethanol-BP elevation was stronger in elderly subjects.
- Ethanol-related hypertension appears to regress with abstinence as past drinkers had similar BP levels as lifelong abstainers.
- The usual beverage choice (wine, liquor, beer) was not a major factor.

Several studies have reported that at a threshold of 210 g of alcohol per week (30 g/day), there was a positive correlation between daily consumed amount and levels of both systolic and diastolic BP, predisposing to an increased incidence of hypertension, whereas an intake of lower quantities of alcohol (10 g/d of ethanol) was associated with lower BP [79]. The highest BP levels were recorded in individuals consuming six to eight daily drinks, whereas chronic intake of drinks more than nine per day was associated with lower BP values [80, 81]. This observation has been attributed to the increased occurrence of liver disease [80, 81].

A standard drink is defined as an alcoholic beverage which contains 10 g of ethanol and which is equivalent to one glass of wine (100 ml), one glass of beer (250 ml), or one glass of liquor or whisky (20 ml). The type of alcohol beverage does not play a major role as drinks containing higher percentages of alcohol are consumed in lower quantities [81].

In a meta-analysis evaluating ethanol problems in the general population, alcohol abuse and dependence were noted in 70% of current, 16–24% of lifelong alcoholics and 30% among the depressed [82].

Although the pressor effect of alcohol is well established, acute drinking is characterized by a biphasic BP response. The influence on BP is dependent on the dose of alcoholic beverage and timing of BP recording [83, 84]. BP is reported to decrease 3–5 h post ingestion and rise again 12–18 h post ingestion [70]. Several interventional studies have confirmed these observations. In a cross-sectional Brazilian study, BP was lower in men who had ingested alcohol less than 3 h before BP recording but higher in those who consumed the beverage 13–24 h before measurement [85]. In another interventional study using ambulatory BP monitoring in patients with type 2 diabetes, consumption of 250–300 ml of red wine with every evening meal was associated with a reduction in overnight and an increase in awaking BP the following day, with a trend toward an extreme dipping pattern, a parameter predisposing to cerebrovascular accidents [86]. Indeed, heavy alcohol intake (>46 g/d) has been linked to an increased risk of early morning BP surge which may be relevant to the reported increased risk of stroke in heavy alcohol imbibers [87].

Food intake appears to be more protective against the detrimental effects of ethanol. The incidence of hypertension is greater in individuals who consume alcohol without food consumption than in those who drink with food [88].

In contrast to its immediate vasodepressor actions, chronic ethanol consumption, even of only moderate amounts, may raise BP, whereas larger doses may be responsible for a significant increase in incidence of hypertension [89]. Compared to abstainers, the prevalence of hypertension (BP > 140/90 mmHg) is threefold to fourfold higher in those who ingest three to five drinks per day [90]. Similarly, the intake of six or more drinks per day may result in 100% increase in the incidence of more severe hypertension (BP > 160/95 mmHg) [77]. In fact, as much 10% of hypertension in men can be attributed directly to alcohol excess [91]. When heavy imbibers quit or reduce their intake, their BP usually falls [92].

The mechanism(s) of alcohol related to BP elevation and hypertension have not been completely elucidated. Several factors have been implicated [93]:

- Activation of the renin-angiotensin-aldosterone system
- Stimulation of the sympathetic nervous system
- Increased cortisol secretion
- Impaired glucose/insulin metabolism
- Impaired peripheral vascular tone caused by impaired calcium and sodium transport into vascular smooth muscle cells
- Heart rate variability
- Endothelial dysfunction
- Genetic predisposition
- Abnormal anthropometric and metabolic parameters such as obesity, dyslipidemia, hyperuricemia, smoking, and hypomagnesemia

Several approaches have been recommended for the management of the hypertensive alcoholic patients [38, 70, 81, 92, 93]:

- Alcohol consumption should be carefully assessed to determine whether it exceeds the safe threshold of 210 g per week.
- Reduction of excessive consumption to two portions (30 g/day) in men and one portion (15 g/day) in women will result in a fall of 3–4 mmHg in systolic BP, even reaching normotensive levels in prehypertensive/mild hypertensive subjects. If elevated BP levels persist, antihypertensive medications should be initiated, preferably with inhibitors of the renin-angiotensin system and/or beta-blockers as chronic alcoholics are at increased risk of alcoholic cardiomyopathy. Excessive alcohol consumption may be a cause of resistant hypertension.
- Binge drinking should be strongly avoided.
- Alcoholic beverages should preferably be consumed with meals.
- Alcohol consumption in moderate daily amounts does not require any change [75].

### 43.3.4 Illicit and Recreational Drugs

Illicit and recreational drug use poses a significant health problem worldwide [94]. Although the majority of illicit drug use is marijuana, especially with the recent increased legalization for recreational and medical purposes, other illicit drugs including cocaine, heroin, hallucinogens, and prescription drugs remain frequently used and associated with significant cardiorenal events [94, 95]. However, only cocaine and marijuana are discussed in this section. Heroin and hallucinogens appear to have minimal, if any, pressor actions [94, 95].

#### 43.3.4.1 Cocaine

Cocaine intoxication and abuse increase BP and produce a spectrum of cerebrocardiovascular events due to adrenergic overactivity [96]. Cocaine acts on vascular smooth muscles both indirectly by blocking norepinephrine uptake at the

sympathetic nerve terminals and directly by altering cellular calcium flux [97]. Cocaine use is associated with acute BP elevation and hypertensive crisis but not chronic hypertension. However from the data of the National Health and Nutrition Examination Survey 2005–2008, which represents a large sample of the US population, chronic cocaine use was independently associated with BP ≥ 135/80, especially when used frequently during a lifetime [94]. When ingested with beta-blockers, cocaine may cause transient severe hypertension [96].

In Afro-Americans, chronic cocaine use may exacerbate the chronic hypertensive state which becomes refractory to treatment, leading to renal vascular disease, nephrosclerosis, and renal failure requiring dialysis [98].

Cocaine ingestion, in pregnant women, increases the risk of hypertension and early placental abruption [96]. Furthermore, prenatal cocaine exposure may cause hypertension in the newborn by interfering with the development of sympathetic nervous system and increasing circulating catecholamines [99].

Although chronic cocaine abuse does not appear to cause hypertension, it may be associated with chronic kidney disease [100].

#### 43.3.4.2 Marijuana (Cannabis)

Marijuana (cannabis) which belongs to the carbaminoids remains the most commonly used illicit drug in the USA especially after legalization of its use for recreational and medicinal purposes [38]. There are three common preparations depending on their ingredient content, delta-9-tetrahydrocannabinol [38].

Marijuana (cannabis) has been reported to induce hemodynamic and electrophysiologic actions on the cardiovascular system characterized by enhanced sinus automaticity and facilitation of A-V nodal conduction and, in some cases, sinus tachycardia [38, 101, 102].

However, acute marijuana use has been associated with opposite effects on BP. While preclinical studies reported a dose-dependent increase in heart rate and BP in others, a fall in BP and postural hypotension occurred [103]. In contrast, in recent population studies, a positive association between recent cannabis use and heart rate, BP mainly systolic and pulse pressure [95, 104].

### 43.3.5 Drug-Related Hypertension

#### 43.3.5.1 Sympathomimetic Amines

Sympathomimetic agents represent a class of vasoactive amines that activate the sympathetic nervous system [105]. All sympathomimetics have pressor actions by stimulation of α-adrenergic receptors directly or indirectly causing vasoconstriction [106].

It is well established that sympathomimetic amines cause dose-related increases in BP [107]. Although sympathomimetic-induced hypertension does not appear to be clinically significant in healthy individuals, it could lead to marked BP elevation and therefore sympathomimetics should be avoided in hypertensive subjects [107, 108].

Sympathomimetic amines are used in a wide array of conditions such as nasal decongestants, anorexics, and central stimulants [105–107].

Sympathomimetic amines include amphetamines and similar compounds such as pseudoephedrine, phenylpropanolamine, and ephedrine [106].

Pseudoephedrine is a bronchodilator and nasal vasoconstrictor. It is commonly used to treat symptoms of rhinitis and rhinorrhea [107]. It may moderately increase BP and heart rate [107]. These effects are enhanced by immediate release formulations, higher doses, and short-term medication administration [107]. Patients with stable well-controlled hypertension do not seem to be at increased risk for BP elevation when pseudoephedrine is used in modest doses [109]. However patients with cardiovascular disease should be advised to monitor their BP carefully after starting pseudoephedrine-containing medications [107]. Sustained release preparations should be generally preferred to avoid elevations in BP [107].

When applied topically, as phenylephrine containing ophthalmic solution, cases of hypertension have been reported [2]. Dipivalyl adrenaline, an adrenaline prodrug, used topically in the treatment of chronic simple glaucoma, may also raise BP [2].

Most nonprescription anorexic agents contain combinations of an antihistamine and an adrenergic agonist (phenylpropanolamine, ephedrine, pseudoephedrine, or caffeine) [96]. They have been reported to cause a small but significant elevation in systolic BP [96]. Excessive doses may result in severe hypertension and, rarely, in cerebrovascular events and even death [2].

Central stimulants such as amphetamine and methylphenidate are increasingly used in several disorders including narcolepsy, depression-associated fatigue, stroke, and attention-deficit hyperactivity disorder (ADHD) [105]. They can cause a mild elevation in both systolic and diastolic BP in both normotensive and hypertensive individuals [105].

Addition of sympathomimetic agents to beta-blockers may increase BP, because of unopposed α adrenergic vasoconstriction [2]. This pressor action can be counteracted by the use of α blockers or a combined α β blockers [2].

#### 43.3.5.2 Analgesics

Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are widely prescribed therapeutic agents worldwide [110].

##### Nonsteroidal Anti-Inflammatory Drugs

Elderly subjects frequently have hypertension and arthritis. Both conditions require pharmacologic treatment both for BP reduction and pain relief. Most of the agents used for pain relief belong to the class of NSAIDs [111]. The use of these agents is associated with both beneficial effects and adverse reactions [111].

NSAIDs inhibit the two isoforms of cyclooxygenase (COX) enzymes, namely, COX1 and COX2 [112]. Both COX1 and COX2 are expressed within the normal adult kidney, with COX1 found in the glomerulus and afferent arterioles, while COX2 is present in the macula densa and renal medullary interstitium [107, 112]. Prostaglandins produced by COX1 promote vasodilatation of the renal vascular bed leading to reduction in renal vascular resistance and increasing renal perfusion, while prostaglandins produced by COX2 have diuretic and natriuretic actions [107, 112]. By blocking both isoenzymes, NSAIDs may alter renal function and BP homeostasis [107, 112, 113].

The impact of NSAIDs on BP has been assessed in several observational studies and clinical trials [107, 110–113].

In normotensive subjects, the use of traditional and nonselective NSAIDs was associated with an increased risk of BP elevation and hypertension [114]. The risk of hypertension was determined by the frequency of use and dose of NSAIDs [114–116]. In the Nurses' Health Study, women using NSAID at least 5 or more days per month were at a significantly higher risk of developing hypertension [114, 116, 117]. Similar results were observed in a cohort of apparently healthy male physicians in the Physicians' Health Study [114, 118]. In both studies, increasing daily doses of NSAIDs led to an increasing risk of developing high BP [114, 118].

In hypertensive subjects, traditional nonselective NSAIDs may destabilize BP control [112, 114, 119]. Two meta-analyses suggested that in subjects with well-controlled hypertension, there was a statistically significant elevation in MAP of 5.4 mmHg [114, 119]. However the destabilizing effect was dependent upon both NSAIDs and antihypertensive agents administered [114, 119]. Among the various traditional nonselective NSAIDs, indomethacin, naproxen, and piroxicam were associated with the greatest elevation in BP [96, 119]. Furthermore, the nullifying effect on well-controlled BP is more pronounced in hypertensive subjects receiving angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or beta-blockers [96, 112]. In contrast, NSAIDs have no significant effect on BP in patients well controlled with calcium channel blockers [96, 112].

Data on the impact of COX2 inhibitors on BP are limited. In a study on 40 normotensive subjects on low-salt diet, administration of naproxen, celecoxib, or placebo had no significant change on BP [112, 120]. However as in traditional nonselective NSAIDs, the pressor effect of COX2 inhibitors appears to be dose dependent. In studies comparing the efficacy and safety of celecoxib with placebo on reducing rate of colorectal carcinoma, celecoxib 400 mg twice daily was associated with 5.2 mmHg increase in systolic BP [112, 120]. However, no increase in BP was observed with celecoxib administered 400 mg once daily or in the usual doses of 100–200 mg daily [96].

The impact of COX2 inhibitors in hypertensive patients is controversial. While some studies reported that celecoxib, the most frequently clinically prescribed COX2 inhibitor, induced an elevation in BP in well-controlled hypertensive patients, in others, this agent appears to have no effects on BP [96, 111, 121–123]. However, the pressor action of celecoxib appears to be determined by dose and frequency of administration [96]. As is the case with traditional nonselective NSAIDs, the nullifying effect on controlled hypertension is observed in patients receiving angiotensin converting enzyme inhibitors and angiotensin receptor blockers, but not on those on calcium channel blockers [112].

Although it is well established that NSAIDs cause an elevation in BP, certain groups of patients appear to be more susceptible to their pressor actions including the elderly, diabetes, renal functional impairment, and salt sensitivity [124].

The mechanism of action of NSAIDs on BP has not been completely elucidated. However, sodium retention due to changes in renal blood flow and glomerular

filtration rate and increased systemic vascular resistance associated with prostaglandin inhibition have been implicated in their BP changes [111, 112].

It is important for the clinician to keep in mind that NSAIDs of all classes are not safe drugs and their use may be associated with serious adverse reactions [125]. In addition to their BP destabilization, NSAIDs may cause acute renal failure in hypertensive patients who often are receiving drugs which may alter body fluid volumes [125, 126].

#### Acetaminophen

Acetaminophen, also known as paracetamol, is the commonly used nonprescription analgesic worldwide [112]. The mechanism of its analgesic action remains elusive [112].

Data on the effects of acetaminophen on BP are scarce. Although considered a safe analgesic, several studies have indicated that acetaminophen intake is associated with an increased risk of incident hypertension [110, 112]. In the Nurse Study I and II, women who took acetaminophen >500 mg per day, the risk of incident hypertension was twice as high as women who did not use the analgesic [110, 116]. Similar observations were reported in the Health Professionals Follow-up study [110, 127]. Men who consumed acetaminophen 6–7 days per week had an increased risk of incident hypertension [127]. Further, in a randomized double-blind placebo-controlled crossover study in patients with coronary artery disease, acetaminophen 1 gram three times per day over 2 weeks induced a significant increase in BP [110, 112, 128].

#### Aspirin

Aspirin which inhibits prostaglandin synthesis is considered to be special nonselective NSAIDs [110].

Two meta-analyses which evaluated the effect of large doses of aspirin, 1.5–2 grams daily on BP, in hypertensive subjects, did not demonstrate any significant pressor action [110, 129]. However, at higher doses, aspirin has been shown to reduce the antihypertensive efficacy of angiotensin converting enzyme inhibitors which also interfere with prostaglandin synthesis [110, 130]. Therefore patients receiving larger doses of aspirin may not profit from angiotensin converting enzyme inhibitors [130].

Similarly, low-dose aspirin of 75 mg/day does not interfere with BP reduction efficacy of antihypertensive agents, including those containing angiotensin converting enzyme inhibitors [131]. Moreover, taken at bedtime, low-dose aspirin may even lower BP [132, 133].

### 43.3.6 Herbal Products/Remedies

Herbal remedies, alternative therapies and supplements widely used by large segment of the population, can cause significant elevation in BP and interactions with cardiovascular drugs [134]. Hence, the importance of obtaining a detailed medical

history to inquire about the use of herbal therapies and supplements to unmask identifiable medically related causes of hypertension [134].

A large number of herbal products have been reported to cause BP elevation and hypertension [105]. However this section is devoted to the discussion of better known or more frequently used herbal products and medicinal items which appear to be causally related to incident hypertension.

#### 43.3.6.1 Liquorice

Liquorice toxicity is a syndrome of pseudoaldosteronism characterized by hypertension, hypokalemia, hypernatremia, alkalosis, low renin activity, and hypoaldosteronism [135]. In addition to hypertension and hypokalemia, excessive liquorice intake is associated with rhabdomyolysis, muscle paralysis, respiratory impairment, hypertensive emergencies, hypertensive encephalopathy, hyperparathyroidism, and acute renal failure [136–138].

Liquorice has been well known by mankind for thousands of years and has been reportedly discovered in the stores of ancient tombs of Egyptian pharaohs [139]. Liquorice is an extract of the root of the plant *Glycyrrhiza glabra*, a common herb in chronic traditional medicine. Liquorice contains glycyrrhizin which is hydrolyzed by intestinal microflora to the pharmacologically active forms glycyrrhetinic acid and glycyrrhizic acid [134]. The liquorice-related active components have no direct effect on renal function but inhibit the enzyme 11β-hydroxysteroid dehydrogenase preventing the metabolism of cortisol to inactive cortisone [140, 141]. The increased concentrations of cortisol which are 100–1000 times higher than those of aldosterone activate the mineralocorticoid receptors leading to a syndrome of mineralocorticoid excess characterized by hypokalemia, metabolic alkalosis, and hypertension [138, 141]. Although urinary cortisol is elevated, the serum cortisol tends to be normal [141]. In addition, intake of glycyrrhetinic acid is associated with prolongation of the half-life of plasma cortisol levels, leading to an increase in the serum cortisol to cortisone ratio [142].

The rise in BP induced by liquorice consumption depends upon the dose, and the maximal effect is reached after the first 2 weeks [139]. Usually, the clinically manifest effects become evident when the intake of glycyrrhetinic acid exceeds 400 mg daily [138]. Although the World Health Organization suggested that consumption of 100 mg/day of glycyrrhetinic acid would be unlikely to cause adverse reactions, even doses as low as 75 mg/day have been reported to cause a significant BP elevation [138, 143].

There is no interindividual variance in BP response to liquorice, but women appear to experience more adverse reactions than men [139, 144].

Essential hypertension, diuretics, salt sensitivity, old age, and chronic inflammatory conditions appear to enhance the mineralocorticoid effects of liquorice [138, 144, 145].

Liquorice is increasingly used in several herbal products, teas, laxatives, tobacco products, food items, as a flavoring agent in candies, chewing gums, and breath fresheners [139]. However the amount of glycyrrhetinic acid, the metabolically

active agent, is different in these items [139]. Several of these liquorice products which contain glycyrrhetinic acid can cause BP elevation [105]. In these products, the liquorice is considered true unmodified liquorice extracted from the liquorice plant [105]. In contrast, many items labeled as liquorice either contain no true liquorice or glycyrrhetinic acid has been removed [105]. Hence these latter products have no hemodynamic actions.

The diagnosis of liquorice-induced hypertension should be suspected if renin concentration or plasma renin activity is suppressed [139]. The diagnosis is confirmed by the measurement of metabolites of cortisol and cortisone in the urine as the ratio of the metabolites of cortisol and cortisone in urine is increased with liquorice consumption [139]. However in clinical practice, in cases the patient admits the consumption of liquorice product, the most appropriate diagnostic approach would be to discontinue liquorice and follow the patient for several weeks up to 4 months when renin suppression would have subsided [139].

Management of liquorice-induced pseudoaldosteronism requires withdrawal of the offending agent and potassium supplementation for the hypokalemia [141]. Normalization of the clinical and laboratory findings occurs within 2–4 months [146]. If hypertension persists, antihypertensive therapy is indicated.

#### 43.3.6.2 Ginseng

Ginseng, which is of two types, Asian (*Panax ginseng*) and North American (*Panax quinquefolius* ginseng), has been widely used for a large number of conditions and illnesses, including vitality, immune function, improvement of cognitive and physical performance and sexual function, cancer, and cardiovascular disorders [134]. Although small doses can cause small reduction in BP, large doses and prolonged use of ginseng have been reported to cause hypertension and behavioral changes [134, 147]. A ginseng abuse syndrome, characterized by diarrhea, hypertension, nervousness, dermatologic eruptions, and insomnia, has been described after the intake of single large doses or prolonged periods of use [148].

Ginseng may reduce the effectiveness of warfarin and lead to subtherapeutic anticoagulation [134, 149].

#### 43.3.6.3 Yohimbine

Yohimbine is a prescription drug found in the bark of the tree *Pausinystalia yohimbe* [134]. Although it is not available as an over-the-counter product, it may be found in some herbal preparations [150].

Yohimbine, a presynaptic alpha-2 adrenergic antagonist and possible monoamine oxidase inhibitor, has been used for the treatment of erectile dysfunction, reportedly with effects better than placebo [134, 151]. However, especially at higher doses, yohimbine can increase BP [134, 150]. Other adverse reactions include mania, agranulocytosis, bronchospasm, Raynaud's phenomenon, and a systemic lupus-like syndrome [134].

Yohimbine should not be used in patients taking tricyclic antidepressants [134].

## 43.4 Therapeutic Drugs

### 43.4.1 Recombinant Human Erythropoietin

Recombinant human erythropoietin (r-HuEPO) is widely used for the treatment of anemia of patients with chronic renal failure and in patients with malignancy [96, 152]. Although it improves the quality of life, administration of r-HuEPO is associated with the development of hypertension in 20–30% of patients occurring within 2 weeks to 4 months [96, 153, 154]. However, no change in BP or a low incidence of hypertension has been reported in patients not yet on dialysis and in non-uremic patients [155–157]. Likewise, r-HuEPO administration does not cause an acute elevation in BP [96].

Several risk factors appear to predispose to the development or worsening of hypertension in dialysis patients:

1. Presence of preexisting hypertension [96].
2. Rapid increase in hematocrit or a low baseline hematocrit prior to r-HuEPO administration [96].
3. High doses or intravenous administration of the drug [96].
4. Presence of the native kidney [96].
5. Genetic predisposition to hypertension [96, 158].
6. Age: younger individuals appear to be more predisposed to BP elevation [96].

Several factors have been postulated to account for erythropoietin-induced hypertension [96, 155–162]:

1. Increase in hematocrit and blood viscosity [96, 155].
2. Hemodynamic alterations characterized by mild decrease in cardiac index and an increase in systemic vascular resistance [96, 159]. These hemodynamic changes have been attributed to the reversal of hypoxic vasodilatation with the correction of the anemia [96].
3. Activation of neurohumoral system: in some hemodialysis patients, r-HuEPO stimulates the synthesis of catecholamines which contribute to BP elevation [96].
4. Direct vasopressor action on vascular smooth muscles related to an increase in intracellular calcium concentration [160–162]. This observation favors the possibility of genetic predisposition.

The erythropoietin-related hypertension is generally not a serious problem and is easily amenable to therapy, although a hypertensive crisis and encephalopathy may occur [96, 163]. Recommended therapeutic measures include:

1. A combination of fluid removal by dialysis and conventional antihypertensive medications (angiotensin converting enzyme inhibitors and/or calcium channel blockers) [96]
2. Reduction of the dose or even cessation of r-HuEPO therapy for several weeks [96]
3. Phlebotomy in cases of refractory hypertension [2, 96]

### 43.4.2 Immunosuppressive Agents

Calcineurin inhibitors, which include cyclosporine and tacrolimus, are potent immunosuppressive drugs [164]. They are considered as the cornerstone of immunotherapy to prevent rejection after organ transplantation and occasionally to treat autoimmune diseases [164]. In spite of their proven effectiveness in preventing rejection after organ transplantation, they are associated with prominent adverse reactions [164]. Of these effects, hypertension is the most common and prominent [164].

The incidence of hypertension varies with the patient population evaluated [96]. Although both cyclosporine and tacrolimus cause hypertension, tacrolimus, which was introduced later and is less well studied, appears to cause less increase in BP [123, 164].

The prevalence rates of hypertension in patients receiving cyclosporine for nontransplant disorders, such as uveitis, rheumatoid arthritis, and psoriasis, vary between 25 and 54% and in transplant recipients (heart, kidney, liver, or bone marrow) range between 65 and 100% [165].

In cyclosporine-induced hypertension, BP starts to increase within few days after initiation of immunotherapy before any changes in renal function or sodium balance occur [165]. Hypertension is generally mild to moderate, but in few patients it may become severe, associated with encephalopathy [96]. The hypertension is dose dependent and may be reversed with early withdrawal of the drug. However, prolonged cyclosporine administration will result in persistent BP elevation despite drug withdrawal [165, 166].

Cyclosporine-induced hypertension is characterized by loss of nocturnal fall in BP, nocturnal headache, salt sensitivity, and renal dysfunction [165, 166]. Serum uric acid is often elevated, while serum magnesium is reduced [165, 166].

Hypokalemic metabolic acidosis may occur, resulting from inhibition of renal potassium and hydrogen excretion [165].

Mechanisms of cyclosporine-induced hypertension remain elusive. Several systems appear to participate in the BP elevation [164–166]. Characteristically, the systemic and renal resistances are increased, renal blood flow is reduced, and the sympathetic nervous system is enhanced, while the renin-angiotensin system is inhibited [164–166].

In the management of cyclosporine-related hypertension, the following approaches have been recommended. In case of persistent hypertension, it is advisable to withdraw and substitute cyclosporine immunosuppression by other agents [96, 165, 166]. This approach may lead to partial fall in BP [96]. Diuretics and angiotensin II antagonists should be preferably avoided [165, 166]. Potassium-sparing diuretics, if required, can be used but with caution [165, 166]. Dihydropyridine calcium channel blockers, the antihypertensive agent of choice, are very effective in lowering BP [96, 123, 165, 166]. Beta-blockers and labetalol are also effective in reducing BP [165, 166].

### 43.4.3 Steroids

There are four major types of steroids that may cause an increase in BP [167]: corticosteroids, mineralocorticoids, estrogenic steroids, and anabolic steroids [167].

#### 43.4.3.1 Corticosteroids

Hypertension occurs in about 20% of patients receiving synthetic corticosteroids [96]. The BP elevation is however dependent upon the dose and type of corticosteroids [96, 168]. Cortisol, at a dose of 80–120 mg/day, increases BP by about 15 mmHg within 24 h [96]. In contrast, at a lower dosage, cortisol has no significant effect on BP [123].

The hypertension-induced corticosteroid is characterized by loss of nocturnal fall in BP and, hemodynamically by increased total blood volume, cardiac output and systemic vascular resistance [169]. It occurs mostly in elderly and in patients with a positive family history of primary hypertension [169].

The mechanism of corticosteroid-related hypertension remains unclear but appears to be multifactorial [169].

Hypertension is relatively rare in patients who receive exogenous glucocorticoids because those steroid derivatives have less mineralocorticoid activity [168].

Although there are no effective preventive approaches, diuretics, angiotensin converting enzyme inhibitors, and angiotensin II receptor blockers have been recommended for the management of corticosteroid-related hypertension [123].

#### 43.4.3.2 Mineralocorticoids

Certain exogenous compounds such as 9α fluoroprednisolone and 9α fluorocortisol increase BP by activating mineralocorticoid receptors (MR) [96]. Skin ointments, antihemorrhoidal preparations, ophthalmic drops, and nasal sprays which contain 9α fluoroprednisolone and sympathomimetic amines may cause significant BP elevation when used in excessive amount [96, 169].

Prolonged use of high-dose ketoconazole, an antimycotic agent, may alter enzymatic degradation of steroids leading to severe hypertension [2, 96].

Management of the hypertension requires the withdrawal of these substances [2].

#### 43.4.3.3 Sex Hormones

##### Oral Contraceptive Hormones

Oral contraceptive hormones are of two types, the combined or estrogen-containing compounds and progesterone-only pills, also known as “minipill” [170].

The oral combined contraceptive pills, which contain estrogen and progesterone, are widely used as a method of contraception [96, 171]. Although they are generally safe, the oral combined contraceptive pills cause a minimal elevation in BP and, in 5% of patients, hypertension [96, 172]. In women taking the higher formulation, the risk of hypertension is 50% higher than in nonusers and 10% in past users [173].

Hypertension is generally mild but episodes of severe and malignant hypertension may occur [96, 169, 172].

History of hypertension in pregnancy, family history of history, cigarette smoking, diabetes, obesity, renal disease, and black race increase the risk of development of hypertension [54, 172].

The mechanism of hypertension induced by estrogen-containing contraceptive compounds is unclear. Disturbances in endothelial function, the renin-angiotensin-aldosterone system, and insulin sensitivity have been postulated to play a role in hypertension development [174–176].

Cessation of estrogen-containing contraceptive is associated with reversal of hypertension [172]. However, if elevated BP persists, appropriate hypertension workup should be performed [177].

If oral estrogens containing contraceptive pills are administered, caution is recommended with regular BP recordings especially during the first 3 months [167].

There is no association between hypertension and use of progesterone-only pills [96, 170]. The progesterone-only pill (minipill) is indicated in women who have high BP caused by combined oral contraceptive compounds or other etiologies [170]. Similarly, postmenopausal hormone replacement therapy has minimal effect on BP in normotensive women. It may even reduce BP in postmenopausal hypertensive women [96, 178].

Administration of estrogen to men for the treatment of prostate cancer has been associated with BP elevation and hypertension [96].

#### 43.4.3.4 Anabolic Androgenic Steroids

Administration of anabolic androgenic steroids has been reported to cause hypertension which may persist for some time after cessation of the drug [105].

Danazol, a semisynthetic androgen used for the treatment of endometriosis and hereditary angioedema, may cause hypertension [96, 172].

### 43.4.4 Antidepressants, Anxiolytics, and Antipsychotics

Psychopathologic or mood disorders frequently coexist with chronic somatic diseases such as diabetes, hypertension, chronic kidney disease, and cardio-cerebrovascular disease and tend to increase the morbidity of these physical conditions [179, 180]. Identification and medical management of mood disorders improve the quality of life and health-related comorbidities of those chronic physical ailments [181].

Pharmacotherapy of mood disorders comprises a wide array of agents which include antidepressants, anxiolytics, tranquilizers, and neuroleptics (antipsychotics) [2, 96]. However, only drug classes that may cause BP elevation and hypertension will be discussed in this section.

#### 43.4.4.1 Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors are used to treat patients with depression [2, 96]. They exert their action by delaying the metabolism of sympathomimetic amines and 5-hydroxytryptophan and by enhancing the norepinephrine stores in postganglionic sympathetic neurons [2, 96].

Monoamine oxidase inhibitors can induce severe hypertension and even a hypertensive crisis, particularly with concomitant administration of exogenous

sympathomimetic amines or tyramine-containing food items such as Parmigiano cheese, chianti wine, snails, beer, chicken liver, yeast, coffee, citrus fruits, canned figs, broad beans, avocados, chocolate, and bananas [2, 96, 182]. Among the monoamine oxidase inhibitors, tranylcypromine is the most dangerous compound, while moclobemide and brofaromine are least likely to cause an elevation in BP [2, 96]. Selegiline, a type B monoamine oxidase inhibitor which is used in Parkinson's disease, may also increase BP [171].

Because of their significant adverse reaction profile, it has been recommended to restrict the use of monoamine oxidase inhibitors to patients with depressive disorders resistant to other antidepressants [183].

#### 43.4.4.2 Tricyclic Antidepressants

Tricyclic antidepressants, which block the uptake of the neurotransmitter in the synapse in the central nervous system, have been reported to cause an elevation in BP and hypertension, mainly in patients with panic disorders [2, 96, 171, 184]. These agents may also trigger a hypertensive crisis in unrecognized pheochromocytoma [185].

#### 43.4.4.3 Anxiolytics

Unlike the older benzodiazepines, buspirone, a nonbenzodiazepine anxiolytic agent, is a serotonin receptor type 1α agonist [186]. Compared to benzodiazepines, it is as effective in the treatment of anxiety disorders and has a milder adverse reaction profile [186]. However buspirone has been reported to increase BP by its metabolite 1-2 pyrimidinyl piperazine which is an $\alpha_2$ adrenoceptor antagonist and therefore should not be administered concomitantly with monoamine oxidase inhibitors [2, 96].

Other serotonin agonists produce a sustained and dose-dependent BP elevation [2, 96]. Venlafaxine, a nontricyclic serotonin/norepinephrine reuptake inhibitor, is used in the treatment of depression and anxiety [123]. It causes an increase in BP by an increase in norepinephrine levels and subsequent potentiation of noradrenergic neurotransmitter [107]. The extended release formulation of venlafaxine causes hypertension in 3% of patients on regular doses of 75–150 mg and in 13% of those receiving larger doses of ≥300 mg [107]. However dosing of ≥300 mg is not common, and therefore the risk of venlafaxine-induced hypertension does not require discontinuation of the drug in most patients [107, 187]. The hypertensive effect of venlafaxine is more pronounced in older subjects and in men [107].

Attacks of severe hypertension have been also reported with other serotonin agonists such as fluoxetine, combination of fluoxetine and selegiline, and thioridazine [2, 96].

Lithium intoxication may occasionally be associated with an elevation in BP [2, 96]. The mechanism of this adverse reaction remains elusive [2, 96].

Carbamazepine is widely used in several medical conditions, including adult and pediatric epilepsy, trigeminal neuralgia, neuropathic pain, and bipolar affective disorders [107, 187, 188]. Cardiovascular toxicity from carbamazepine occurs most frequently in overdosing and is characterized by sinoatrial and atrioventricular block, arrhythmias, congestive heart failure, hypertension, hypotension, syncope,

edema, aggravation of coronary artery disease, sick sinus syndrome, and occasionally death [96, 107, 188].

Carbamazepine-associated hypertension, an infrequent complication, results from aggravation of well-controlled treated hypertension, or rarely, de novo BP elevation in previously normotensive subjects [107, 189, 190]. Although the mechanism of hypertension remains unclear, it has been attributed to increased clearance of various antihypertensive agents with subsequent loss of BP control [107, 189, 190].

#### 43.4.4.4 Antipsychotics

Clozapine, a newer atypical antipsychotic agent, is used in the management of schizophrenic symptoms in patients' refractory to classical antipsychotics [2, 96, 191]. This drug has been reported to increase BP and hypertension in about 12% of patients and to cause pseudo-pheochromocytoma syndrome [2, 96]. The clozapine-induced hypertension appears to be related to sympathetic overactivity as the BP elevation appears to be blocked by co-administration of propranolol, a nonselective beta-blocker [192].

Other newer atypical antipsychotics are associated with hypertension such as olanzapine and ziprasidone [192].

In addition to hypertension, hypotension, including orthostatic hypotension, is a frequent side effect of newer atypical antipsychotics [193], contributing to risk of injury and falls in the elderly [193]. Combination of cardiovascular and antihypertensive medications may aggravate the hypotensive effects of newer atypical antipsychotics [193].

### 43.4.5 Antineoplastic Therapy

Hypertension is a well-known risk of cancer chemotherapy [194]. Further poorly controlled hypertension can markedly impact the management of cancer and even lead to the withdrawal of certain therapies [194].

Hypertension is the most frequent associated cardiovascular comorbidity in patients with malignancy [194]. Its prevalence increased from 29% prior to chemotherapy to 39–40% after the introduction of newer antineoplastic modalities [96, 194].

BP elevation and hypertension are frequent complications of several classes of antineoplastic agents, including angiogenesis inhibitors, alkylating agents, calcineurin, corticosteroids, immunosuppressants after stem cell transplantation, and head and neck radiation therapy [96, 195, 196].

#### 43.4.5.1 Antiangiogenesis Therapies

Recently, several antiangiogenesis drugs (also known as antivascular endothelial growth factor (VEGF) agents) have been introduced for the management of various malignancies [123]. This class of medications includes monoclonal antibodies such as bevacizumab or orally available small molecules that inhibit VEGF-stimulated tyrosine kinases such as lapatinib, sunitinib, axitinib, and pazopanib [123].

Although this group of agents has resulted in significant remissions in several cancers and prolongation of disease-free periods, they are associated with significant cardiovascular toxicity [123, 196].

Hypertension occurs frequently with VEGF therapy, and the risk of BP elevation is similar with all this class of compounds [123, 197]. Hypertension is usually mild and resolves with withdrawal of the drug [123, 197]. However hypertension may be severe and associated with posterior leukoencephalopathy syndrome and even may be life threatening in 1% [123, 198]. It has been suggested that the development of hypertension is a predictor of a beneficial response to antiangiogenesis therapy [123, 199].

The mechanism of VEGF-induced hypertension has not been fully elucidated but appears to be multifactorial [123]. Reduction in nitric oxide synthesis, microvascular rarefaction, loss of antioxidative function, and activation of the endothelin system play a role in the BP elevation [123, 200–203].

Cancer chemotherapy, in particular novel therapeutic agents, is associated with vascular complications and metabolic disturbances [204, 205]. Aggressive BP control is advised in order to minimize the risk of target-organ damage.

Inhibitors of the renin-angiotensin system, diuretics, beta-blockers, and calcium channel blockers can be used to lower BP [206, 207]. However the non-dihydropyridine calcium antagonists which are CYP3A4 inhibitors and nifedipine, a dihydropyridine calcium channel antagonist which induce VEGF secretion, should be avoided in the treatment of antiangiogenesis-associated hypertension [123, 206, 207].

#### 43.4.5.2 Head and Neck Radiation Therapy and Surgery

Head and neck radiation therapy and surgery can damage systemic baroreceptors and their connections [196].

Radiation therapy for head and neck cancer may cause injury to cranial nerves, and this injury tends to occur after an interval of months, or, in some cases, years after irradiation [208, 209]. Similarly, damage of systemic baroreceptors can result from unilateral or bilateral endarterectomy or surgical excision of tumor masses in relevant regions [210–212].

These procedures may lead to failure of systemic baroreceptor function which is characterized by a wide range of clinical manifestations [196]. Hypertensive syndromes are the most frequent clinical presentations [196].

Hypertension can occur in two forms either as a chronic labile state of BP elevation also known as volatile hypertension or as an acute hypertensive crisis [196]. Labile chronic or volatile hypertension is the most frequently encountered presentation of baroreflex failure. It frequently develops insidiously with progressive gradual decline in baroreceptor function [196]. It is precipitated by mental or physical stress and is characterized by bouts of BP elevation, lasting for minutes to hours, associated with palpitation/tachycardia, light-headedness or dizziness, and severe headache [196, 213, 214]. With time, the pressor peaks become attenuated and are replaced by depressor episodes [196].

The hypertensive crisis, which occurs following a surgical intervention in the neck, causes injury to glossopharyngeal or vagus nerves [196]. The clinical presentation is characterized by severe unremitting hypertension, with SBP exceeding 250 mmHg, tachycardia, headache, and diaphoresis [196, 212].

The differential diagnosis of baroreceptor failure includes an extensive list of clinical entities [196]. Although exclusion of the various clinical conditions requires use of a large number of laboratory tests, the key feature suggestive of baroreceptor failure is a history of injury to the systemic baroreceptor region by prior radiation therapy or surgery [196].

The primary goal of therapy of patients with baroreflex failure is the reduction in frequency and magnitude of life-threatening bouts of severe BP elevation and heart rate [154]. Clonidine, an $\alpha_2$ adrenoceptor agonist, is the pharmacologic agent of choice for the control of BP bouts [196, 215]. Large doses of clonidine are frequently required [215]. The use of transdermal patches may reduce the inconvenience of frequent oral dosing [196, 215]. In patients with well-controlled BP over months or years, treatment can be shifted from clonidine to benzodiazepines [196]. High doses may be required [196].

Guanidine and guanethidine which inhibit the release of norepinephrine from peripheral sympathetic nerve endings are very effective in controlling the pressor surges in baroreceptor failure [216].

Agents that enhance sympathetic nervous system stimulation and exacerbate baroreceptor failure are contraindicated [196]. These drugs include tricyclic antidepressants, amphetamines, monoamine oxidase inhibitors, and tyramine-containing food items [196].

### 43.4.6 Human Immunodeficiency Virus Status and Antiretroviral Therapy

The introduction of highly active antiretroviral therapy (HAART) in the mid-1990s has resulted in significant reduction in human immunodeficiency virus (HIV)-related morbidity and mortality [217, 218]. However, it also leads to the appearance of short- and long-term events [219]. Cardiovascular disease and metabolic alterations have been increasingly reported [220]. The data on hypertension, a major risk factor, in the HIV population are still controversial [220–222].

HIV infection does not appear to confer an increased risk of hypertension [220, 223]. No correlation has been reported between HIV infection, HIV RNA level, or CD4-cell count [220]. In contrast, HAART therapy in HIV-positive patients has been associated with an increase in BP and increased prevalence of hypertension [217, 220]. In a cohort study that included 5578 patients who were receiving HAART therapy, the risk of developing systolic hypertension was related to the duration of treatment [217]. In other studies, the increase in systolic BP levels was attributed to increased arterial stiffness, and the pressor action was more marked in elderly subjects and in those with higher systolic BP [217].

The pressor actions of HAART therapy appear to be dependent on the drug classes. Standard HAART consists of a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) to which either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a boosted protease inhibitor (PI) is added: NNTI- and non-NNRTI [224]. In a cross-sectional study involving 612 adults attending the Sexual Health Outpatient Department, HAART regimen which includes NNRTI was associated with an increase in BP [224].

It has been recommended to measure BP on all HIV patients and to initiate antihypertensive treatment when appropriate [224].

### 43.4.7 Amphotericin B

Amphotericin B remains the mainstay for the management of invasive fungal infections [2, 225]. Although it is an extremely effective medication, amphotericin B is associated with serious and severe adverse reactions [226]. Hypertension has been described in some patients during amphotericin B infusions, both in normotensives and well-controlled hypertensives [227, 228]. BP may increase soon after initiation of amphotericin B infusion and may reach markedly elevated levels, leading even to a hypertensive crisis [228, 229].

Hypertension usually subsides following the interruption of antifungal therapy but may require administration of antihypertensive drugs [228].

The mechanism of amphotericin-induced hypertension remains unclear, although a direct vasoconstrictive effect has been reported in animals [230].

### 43.4.8 Bromocriptine

Bromocriptine mesylate is commonly used for the suppression of lactation in postpartum women and prolactin inhibition in patients with prolactinoma [96]. Hypertension has been reported in postpartum women receiving bromocriptine [2, 96, 231]. The hypertensive syndrome may be severe, often associated with cerebrovascular complications [232]. Likewise, prepartum administration of bromocriptine increases the risk of postpartum hypertension [231].

Paradoxically, bromocriptine induces hypotension in healthy subjects [2].

The mechanism of bromocriptine induced-rise in BP has been attributed to alterations in intravascular blood viscosity [233].

### 43.4.9 Antiemetic Agents

Metoclopramide, a dopaminergic antagonist structurally related to procainamide, is effective in treating and preventing vomiting [234]. It has been reported to cause transient BP elevation when administered intravenously in high doses in the course of cisplatin therapy [96].

Although it is useful in the management of several gastrointestinal disorders, metoclopramide is associated with serious cardiovascular effects when administered

intravenously in large doses over long periods of time [234]. Due to the cardiovascular risk associated with metoclopramide, patient monitoring is indicated [234].

Other antiemetics, such as alizapride and prochlorperazine, have been also reported to cause transient BP elevation when administered intravenously during the course of cisplatin therapy [96, 235].

### 43.4.10 Dipeptidyl Peptidase-IV Inhibitors

Selective dipeptidyl peptidase-IV (DPP-4) inhibitors, a novel class of antidiabetic drugs, improve glycemic control in patients with type 2 diabetes mellitus by reducing degradation of incretin hormones [236]. By altering the breakdown of several vasoactive hormones, DPP-4 inhibitors may affect BP control [237]. In two clinical trials, vildagliptin, a DPP-4 inhibitor, caused a BP reduction [238, 239]. In spontaneously hypertensive rats, sitagliptin, a DPP-4 inhibitor, administered with placebo or a low-dose angiotensin converting enzyme inhibitor (ACE) lowered BP, while this effect was counteracted with high-dose ACE inhibitors [240]. This effect was blocked by a ganglionic blocker [240]. Similar observations were reported with sitagliptin in patients with the metabolic syndrome [237]. Sitagliptin with placebo or low-dose enalapril, an ACE inhibitor, lowered BP, while high-dose enalapril reversed the sitagliptin-induced BP reduction [237]. During high-dose ACE inhibition, sitagliptin administration was associated with increased norepinephrine concentrations [237]. These findings suggest that activation of the sympathetic nervous may oppose the antihypertensive actions of high-dose ACE inhibition during sitagliptin [237].

## 43.5 Antihypertensive Therapy and Drug-Drug Interactions

Most hypertensive patients require a combination of antihypertensive agents for the control of their elevated BP [241]. In addition, due to the presence of an abnormal metabolic profile and or comorbid conditions, these patients receive other therapeutic medications, which predisposes them to the risk of drug-drug reactions [242].

Drug-drug interactions occur more frequently in elderly subjects due to age-related reduction in renal function and administration of a large number of therapeutic agents [243].

Some of the drug-drug interactions involve BP control [244]. BP levels may increase or antihypertensive efficacy may be reduced [244, 245].

### 43.5.1 Pressor-Associated Actions/Antidepressor Actions

Several classes of therapeutic agents or procedures may cause an increase in BP and or reduce the efficacy of antihypertensive medications (Table 43.3). All these agents/procedures have been discussed in other sections of the present chapter.

**Table 43.3** Pressor/antidepressor-associated actions

| Name of agent | Refer to section number |
|---|---|
| Nicotine/smoking | 3.1 |
| Caffeine | 3.2 |
| Alcohol/ethanol | 3.3 |
| Cocaine | 3.4.1 |
| Marijuana | 3.4.2 |
| Sympathomimetic amines | 3.5.1 |
| Nonsteroidal anti-inflammatory drugs | 3.5.2 |
| Acetaminophen | 3.5.2 |
| Aspirin | 3.5.2 |
| Liquorice | 3.6.1 |
| Ginseng | 3.6.2 |
| Yohimbine | 3.6.3 |
| Erythropoietin | 4.1 |
| Immunosuppressive agents | 4.2 |
| Corticosteroids | 4.3.1 |
| Mineralocorticoids | 4.3.2 |
| Oral contraceptive pills | 4.3.3 |
| Anabolic steroids | 4.3.4 |
| Monoamine oxidase inhibitors | 4.4.1 |
| Tricyclic antidepressants | 4.4.2 |
| Anxiolytics | 4.4.3 |
| Antipsychotics | 4.4.4 |
| Antineoplastic agents/procedures | 4.5 |
| Human immunodeficiency virus status and retroviral therapy | 4.6 |
| Amphotericin B | 4.7 |
| Bromocriptine | 4.8 |
| Antiemetic agents | 4.9 |
| Dipeptidyl peptidase-4 inhibitor (sitagliptin) | 4.10 |

### 43.5.2 Rebound and Withdrawal Syndromes

Sudden discontinuation of any hypertensive therapy may be associated with a withdrawal syndrome characterized by [246, 247]: (i) rapid return of BP to pretreatment levels, (ii) overshoot of BP above pretreatment levels, and (iii) rebound of the BP associated with evidence of sympathetic overactivity.

A withdrawal syndrome has been reported more frequently with clonidine or any centrally acting antihypertensive drug (alpha-methyldopa, guanabenz, guanfacine) [2, 246, 247]. Patients receiving a combination of central adrenergic blocker, especially clonidine and a beta-blocker are more susceptible when the centrally acting drug is withdrawn while the beta-blocker is continued [246]. This has been attributed to the unopposed stimulation of peripheral $\alpha_1$ receptors by a surge of catecholamine secretion [246, 248].

**Conclusion**

Changing dietary patterns, increasing use of herbal remedies, illicit/recreational products, nicotine, coffee/tea, and alcohol are contributing to an increased risk of hypertension. Further, the introduction of novel therapeutic regimens, although

promising for the underlying primary pathology, can be associated with an increased risk of BP elevation and cardiovascular disease. These factors and conditions which may interfere with BP control are frequently unrecognized as causes of secondary hypertension.

## References


1. Rossi GP, Seccia TM, Pessina AC (2010) Secondary hypertension: the ways of management. Curr Vasc Pharmacol 8:753–768
2. Grossman E, Messerli FH (1995) High blood pressure. A side effect of drugs, poisons, and food. Arch Intern Med 155:450–460
3. Appel LJ, Moore TJ, Obarzanek E et al (1997) A clinical trial of the effects of dietary patterns on blood pressure. New Engl J Med 336:1117–1124
4. The Trials of Hypertension prevention Collaborative Research Group (1997) Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. Arch Intern Med 157:657–667
5. Beilin LJ, Rouse IL, Armstrong BK et al (1988) Vegetarian diet and blood pressure levels: incidental or causal association. J Clin Nutr 48:806–810
6. Miura K, Greenland P, Stamler J et al (2004) Relation of vegetable, fruit and meat intake to 7-year blood pressure change in middle-aged men—The Chicago Electric Study. Am J Epidemiol 159:572–580
7. Rebholz CM, Friedman EE, Powers LJ et al (2012) Dietary protein intake and blood pressure: a meta-analysis of randomized controlled trials. Am J Epidemiol 176:527–543
8. Sinha R, Cross AJ, Graubard BI et al (2009) Meat intake and mortality a prospective study of over half a million people. Arch Intern Med 169:562–571
9. Binnie MA, Barlow K, Johnson V, Harrison C (2014) Red meats: time for a paradigm shift in dietary advice. Meat Sci 98:445–451
10. Steffen LM, Kroenke CH, Yu X et al (2005) Associations of plant food, dairy product, and meat intakes with 15-y incidence of elevated blood pressure in young black and white adults: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Am J Clin Nutr 82:1169–1177
11. Donaldson AN (1926) The relation of protein foods to hypertension. Cal West Med 24:328–331
12. Sacks FM, Donner A, Castelli WP et al (1981) Effect of ingestion of meat on plasma cholesterol of vegetarians. JAMA 246:640–644
13. Lajous M, Bijon A, Fagherazzi G et al (2014) Processed and unprocessed red meat consumption and hypertension in women. Am J Clin Nutr 100:948–952
14. Elliott P, Stamler J, Dyer AR et al (2006) Association between protein intake and blood pressure: the INTERMAP study. Arch Intern Med 166:79–87
15. Wang L, Manson JE, Buking JE, Sesso HD (2008) Meat intake and the risk of hypertension in middle-aged and older women. J Hypertens 26:215–222
16. Oude Griep LM, Seferidi P, Stamler J et al (2016) Relation of unprocessed, processed red meat and poultry consumption to blood pressure in East Asian and Western adults. J Hypertens 34:1721–1729
17. Ascherio A, Hennekens C, Willet WC et al (1996) Prospective study of nutritional factors, blood pressure, and hypertension among US women. Hypertension 27:1065–1072
18. Masala G, Bendinelli B, Versari D et al (2008) Anthropometric and dietary determinants of blood pressure in over 7000 Mediterranean women: the European Prospective Investigation into Cancer and Nutrition-Florence Cohort. J Hypertens 26:2112–2120
19. Stamler J, Liu K, Ruth KJ et al (2002) Eight-year blood pressure change in middle-aged men: relationship to multiple nutrients. Hypertension 39:1000–1006
20. Tuomainen TP, Nyyssönen K, Salonen R et al (1997) Body iron stores are associated with serum insulin and blood glucose concentrations. Population study in 1013 Eastern Finnish men. Diabetes Care 20:426–428

21. Fernandez-Real JM, Ricart-Engel W, Arroyo E et al (1998) Serum ferritin as a component of the insulin resistance syndrome. Diabetes Care 21:62–68
22. Gonzalez F, Liu B, Machado RF, Chen J (2015) Does red meat metabolism induce hypertension? Austin J Pulm Respir Med 2:1019
23. Wilsontang WH, Wang Z, Bruce S et al (2013) Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med 368:1575–1584
24. National Institutes of Health. Carnitine—Fact sheet for health professionals
25. Altorf-van der Kull W, Engberink MF, Brink EJ et al (2010) Dietary protein and blood pressure: a systematic review. PLoS One 5(8):e12102
26. Teunissen-Beekman KFM, Baak V (2013) The role of dietary protein in blood pressure regulation. Curr Opin Lipidol 24:65–70
27. Stamler J, Elliott P, Keeteloot H et al (1996) Prevention of cardiovascular disease: inverse relation of dietary protein markers with blood pressure: findings for 10020 men and women in the INTERSALT study. Circulation 94:1629–1634
28. Rouse IL, Armstrong BK, Beilin LJ, Vandongen R (1983) Blood pressure lowering effect of a vegetarian diet: controlled trial in normotensive subjects. Lancet 1:5–10
29. Omvik P (1996) How smoking affects blood pressure. Blood Press 5:71–77
30. Pickering TG (2001) The effects of smoking and nicotine replacement therapy on blood pressure. J Clin Hypertens 3:319–321
31. Groppelli A, Giorgi DM, Omboni S et al (1992) Persistent blood pressure increase induced by heavy smoking. J Hypertens 10:495–499
32. Mikkelsen KL, Wiinberg N, Høegholm A et al (1997) Smoking related to 24-h ambulatory blood pressure and heart rate: a study in 352 normotensive Danish subjects. Am J Hypertens 10:483–491
33. El-Zaatari ZM, Chami HA, Zaatari GS (2015) Health effects associated with waterpipe smoking. Tob Control :i31–i43
34. Kadhum M, Jaffery A, Haq A et al (2014) Measuring the acute cardiovascular effects of Shisha smoking: a cross-sectional study. JRSM Open 5(6):1–7
35. Hartley TR, Sung BH, Pincomb GA et al (2000) Hypertension risk status and effect of caffeine on blood pressure. Hypertension 36:137–141
36. Bunker ML, McWilliams M (1979) Caffeine content of common beverages. J Am Diet Assoc 74:28–32
37. Chou T (1992) Wake up and smell the coffee. Caffeine, coffee and medical consequences. West J Med 197:544–553
38. Frishman WH, Del Vecchio A, Sanal S, Ismail A (2003) Cardiovascular manifestations of substance abuse-Part 2: alcohol, amphetamines, heroin, cannabis and caffeine. Heart Dis 5:253–271
39. Graham DM (1978) Caffeine: its identity, dietary sources, intake and biological effects. Nutr Rev 36:97–102
40. Curatolo PW, Robertson D (1983) The health consequences of caffeine. Ann Intern Med 98:641–653
41. Schneider JR (1987) Effects of caffeine ingestion on heart rate, blood pressure, myocardial oxygen consumption, and cardiac rhythm in acute myocardial infarction patients. Heart Lung 16:167–174
42. Quinlan P, Lane J, Aspinall L (1997) Effect of hot tea, coffee, and water ingestion on physiological responses and mood: the role of caffeine, water and beverage type. Psychopharmacology 134:164–173
43. Smits P, Thien T, Vanit Laar A (1985) The cardiovascular effects of regular and decaffeinated coffee. Br J Clin Pharmacol 19:852–854
44. Greenberg W, Shapiro D (1987) The effects of caffeine and stress on blood pressure in individuals with and without a family history of hypertension. Psychophysiology 24:151–156
45. Nurminen ML, Niittynen L, Korpela R, Vapaatalo H (1999) Coffee, caffeine and blood pressure: a critical review. Eur J Clin Nutr 53:831–839
46. Smith A, Maben A, Brockman PIP (1994) Effects of evening meals and caffeine on cognitive performance, mood and cardiovascular function. Appetite 22:57–65

47. Passmore AP, Kondowe GB, Johnston GD (1987) Renal and cardiovascular effects of caffeine: a dose response study. Clin Sci 72:749–756
48. Freestone S, Ramsay LE (1982) Effect of coffee and cigarette smoking on the blood pressure of untreated and diuretic treated hypertensive patients. Am J Med 73:348–353
49. Smits P, Hoffmann H, Thien T et al (1983) Hemodynamic and humoral effects of coffee after $B_1$-selective and nonselective B-Blockade. Clin Pharmacol Ther 34:153–158
50. Pincomb GA, Lovallo WR, Passey RB et al (1985) Effects of caffeine on vascular resistance, cardiac output and myocardial contractility in young men. Am J Cardiol 56:119–122
51. Mahmud Z, Feely J (2001) Acute effect of caffeine on arterial stiffness and aortic pressure waveform. Hypertension 38:227–231
52. Lovallo WR, Wilson MF, Vincent AS et al (2004) Blood pressure response to caffeine shows incomplete tolerance after short-term regular consumption. Hypertension 43:760–765
53. Klag MJ, Wang NY, Meoni LA et al (2002) Coffee intake and risk of hypertension: the Johns Hopkins precursors study. Arch Intern Med 162:657–662
54. Winkelmayer WC, Stampfer MJ, Willet WC, Curhan GC (2005) Habitual caffeine and the risk of hypertension in women. JAMA 294:2330–2335
55. Kaplan NM (2010) Other forms of identifiable hypertension. In: Kaplan NM, Victor RG (eds) Kaplan's clinical hypertension, 10th edn. Wolters Kluwer Health/Lippincott Williams and Wilkins, Philadelphia, pp 392–409
56. Griffiths RR, Woodson PP (1988) Reinforcing properties of caffeine studies in humans and laboratory animals. Pharmacol Biochem Behav 29:419–427
57. Noordzij M, Uiterwaal CSPM, Arends LR et al (2005) Blood pressure response to chronic intake of coffee and caffeine: a meta-analysis of randomized controlled trials. J Hypertens 23:921–928
58. Mesas AE, Leon-Munoz LM, Rodriguez-Artalejo F, Lopez-Garcia E (2011) The effect of coffees on blood pressure and cardiovascular disease in hypertensive individuals: a systematic review and meta-analysis. Am J Clin Nutr 94:1113–1126
59. Viani R (1993) The composition of coffee. In: Garatini S (ed) Caffeine, coffee and health. Raven Press, New York, pp 17–41
60. Diaz-Rubio ME, Saura-Calixto F (2007) Dietary fiber in brewed coffee. J Agric Food Chem 55:1999–2003
61. Geleijnse JM (2008) Habitual coffee consumption and blood pressure: an epidemiological perspective. Vasc Health Risk Manag 4:963–970
62. Narkiewicz K, Maraglino G, Biasion T et al (1995) Interactive effect of cigarettes and coffee on daytime systolic blood pressure in patients with mild essential hypertension. J Hypertens 13:965–970
63. Funatsu K, Yamashita T, Nakamura H (2005) Effect of coffee intake on blood pressure in male habitual alcohol drinkers. Hypertens Res 28:521–527
64. Graham HN (1992) Green tea consumption and polyphenol chemistry. Prev Med 21:334–350
65. Harbowy ME, Ballantinc DA (1997) Tea chemistry. Crit Rev Plant Sci 16:415–480
66. Song WO, Chonk OK (2008) Tea is the major source of flavan-3-ol and flavanol in the US diet. J Nutr 138:S1543–S1547
67. Hodgson JH, Puddey IB, Burke V et al (1999) Effects on blood pressure of drinking green and black tea. J Hypertens 17:457–463
68. Peng X, Zhou R, Wang B et al (2014) Effect of green tea consumption in blood pressure: a meta-analysis of 13 randomized controlled trials. Sci Rep 4:6251
69. Khan N, Mukhtar H (2007) Tea polyphenols for health promotion. Life Sci 81:519–533
70. Kodavali L, Townsend RR (2006) Alcohol and its relationship to blood pressure. Curr Hypertens Rep 8:338–344
71. Beilin LJ, Puddy IB (1993) Alcohol, hypertension and cardiovascular disease implications for management. Clin Exp Hypertens 15:1157–1170
72. Klatsky AL (2002) Alcohol and cardiovascular diseases. Ann N Y Acad Sci 957:7–15
73. Lian C (1915) L'alcolisme cause d'hypertension arterielle. Bull Acad Natl Med 74:525–528
74. Marmot MG, Elliott P, Shipley MJ et al (1994) Alcohol and blood pressure: the INTERSALT Study. BMJ 308:1263–1267

75. Witteman JCM, Willett WC, Stampfer MJ et al (1990) Relation of moderate alcohol consumption and risk of systemic hypertension in women. Am J Cardiol 65:633–637
76. Estruch R, Coca A, Rodicio JL (2005) High blood pressure, alcohol and cardiovascular risk. J Hypertens 23:226–229
77. Klatsky AL, Friedman GD, Siegelaub AB, Gérard MJ (1977) Alcohol consumption and blood pressure-Kaiser-Permanente Multiphasic Heath Examination data. New Engl J Med 296:1194–1200
78. Klatsky AL (2000) Alcohol and hypertension. In: Oparil S, Weber MA (eds) Hypertension: a companion to Brenner and Rector's the Kidney. WB Saunders Company, Philadelphia, pp 211–219
79. Fuchs FD, Chambless LE, Whelton PK et al (2001) Alcohol consumption and the incidence of hypertension. The Atherosclerosis Risk in Communities (ARIC) study. Hypertension 37:1242–1250
80. Klatsky AL, Friedman GD, Armstrong MA (1986) The relationships of alcohol beverage use and other traits to blood pressure: a new Kaiser Permanente study. Circulation 73:628–636
81. Huntgeburth M, Freyhaus H, Rosenkranz S et al (2005) Alcohol consumption and hypertension. Curr Hypertens Rep 7:180–185
82. Sullivan LE, Fiellin DA, O'Connor PG et al (2005) The prevalence and impact of alcohol problems in major depression: a systematic review. Am J Med 11:330–341
83. Abe H, Kawano Y, Kojima S et al (1994) Biphasic effects of repeated alcohol intake on 24 hour blood pressure in hypertensive patients. Circulation 89:2626–2633
84. Rosito GA, Fuchs FD, Duncan BB (1999) Dose dependent biphasic effect of ethanol on 24hour blood pressure in normotensive subjects. Am J Hypertens 12:236–240
85. Moreira LB, Fuchs FD, Moraes RS et al (1998) Alcohol intake and blood pressure: the importance of time elapsed since last drink. J Hypertens 16:175–180
86. Mori TA, Burke V, Zilkens RR et al (2016) The effects of alcohol on ambulatory blood pressure and other cardiovascular risk factors in type 2 diabetes: a randomized intervention. J Hypertens 34:421–428
87. Ohira T, Tanigawa T, Tabata M et al (2009) Effects of habitual alcohol intake on ambulatory blood pressure, heart rate and its variability among Japanese men. Hypertension 53:13–19
88. Stranges S, Wu T, Dorn JM et al (2004) Relationship of alcohol drinking patterns to risk of hypertension: a population-based study. Hypertension 44:813–819
89. Thadani R, Camargo CA Jr, Stampfer MJ et al (2002) Prospective study of moderate alcohol consumption and risk of hypertension in young women. Arch Intern Med 162:569–574
90. Arkwright PD, Beilin LJ, Rouse I et al (1982) Effects of alcohol use and other aspects of life-style on blood pressure levels and prevalence of hypertension in a working population. Circulation 66:60–66
91. MacMahon S (1987) Alcohol consumption and hypertension. Hypertension 9:111–121
92. Xin X, He J, Frontini MG et al (2001) Effects of alcohol reduction on blood pressure. Hypertension 38:1112–1117
93. Estruch R, Coca A, Rodicio JL (2011) High blood pressure, alcohol, and cardiovascular risk. J Hypertens 12:43–44
94. Akkina SK et al (2012) Illicit drug use, hypertension and chronic kidney disease in the US adult population. Transgenic Res 160:391–398
95. Alshaarawy O, Elbaz HA (2016) Cannabis use and blood pressure levels. United States National Health and Nutrition Examination Survey 2005–2012. J Hypertens 34:1507–1512
96. Grossman E, Messerli FH (2008) Secondary hypertension interfering substances. J Clin Hypertens 10:556–566
97. Saruta T (2002) Hypertension from exogenous substances. In: Mancia G, Chalmers J, Julius S, Saruta T, Weber M, Ferrari A, Wilkinson I (eds) Manual of hypertension, Chapter 45. Churchill Livingston, Churchill, pp 248–256
98. Bakir AA, Dunea G (1996) Drugs of abuse and renal disease. Curr Opin Nephrol Hypertens 5:122–126

99. Horn PT (1992) Persistent hypertension after prenatal cocaine exposure. J Pediatr 121:288–291
100. Norris KC, Thornhill-Joynes M, Robinson C et al (2001) Cocaine use, hypertension and end-stage renal disease. Am J Kidney Dis 38:523–528
101. Miller RH, Dhingra RC, Kanakis C et al (1977) The electrophysiological effects of Delta 9- Tetrahydrocannabinol (cannabis) on cardiac conduction in man. Am Heart J 94:740–747
102. Johnson S, Domino EF (1971) Some cardiovascular effects of Marijuana smoking in normal volunteers. Cin Pharmacol Ther 12:762–768
103. Sidney S (2002) Cardiovascular consequences of Marijuana use. J Clin Pharmacol 42(11 Suppl):648–708
104. Rodondi N, Pletcher MJ, Liu K et al (2006) Marijuana use, diet, body mass index and cardiovascular risk factors (from the CARDIA study). Am J Cardiol 98:478–484
105. Sander GE (2014) Secondary hypertension. Drugs and herbal preparations that increase pressure. J Am Soc Hypertens 8:946–948
106. Wing LMH, Tonkin AL (1994) Drug-induced hypertension. In: Swales JD (ed) Textbook of hypertension. Blackwell Scientific Publications, Oxford, pp 923–940
107. Hulisz D, Lagzdins M (2008) Drug-induced hypertension. US Pharm 33:HS11–HS20
108. Cantu C, Arauz A, Murillo-Bonilla LM et al (2003) Stroke associated with sympathomimetics contained in over-the-counter cough and cold drugs. Stroke 34:1667–1672
109. Coates ML, Rembold CM, Far BM (1995) Does pseudoephedrine increase blood pressure in patients with controlled hypertension. J Fam Pract 40:22–26
110. Sudano I, Flammer AJ, Roas S et al (2012) Nonsteroidal anti-inflammatory drugs, acetaminophen and hypertension. Curr Hypertens Rep 14:304–309
111. Morgan T, Anderson A (2003) The effect of nonsteroidal drugs on blood pressure in patients treated with different antihypertensive drugs. J Clin Hypertens 5:53–57
112. White NB, Marfatia R, Baker WL (2012) Treating pain and inflammation in hypertension. In: Berbari AE, Mancia G (eds) Special issues in hypertension. Springer-Verlag Italia, Milan
113. Hao CM, Breyer MD (2004) Hypertension and cyclooxygenase inhibitors: target the renal medulla. Hypertension 44:396–397
114. Wilson SL, Poultier NR (2006) The effects of non-steroidal anti-inflammatory drugs and other commonly used non-narcotic analgesics on blood pressure level in adults. J Hypertens 24:1457–1469
115. Curham GC, Willet WC, Rosner B, Stampfer MJ (2002) Frequency of analgesic use and risk of hypertension in younger women. Arch Intern Med 162:2204–2208
116. Forman JP, Stampfer MJ, Curham GC (2005) Non-narcotic analgesic dose and risk of incident hypertension in US women. Hypertension 46:500–507
117. Dedier J, Stampfer MJ, Hankinson SE et al (2002) Non-narcotic analgesic use and the risk of hypertension in US women. Hypertension 40:604–608
118. Kurth J, Hennenkens CH, Sturmer T et al (2005) Analgesic use and the risk of subsequent hypertension in apparently healthy men. Arch Intern Med 165:1903–1909
119. Armstrong EP, Malone DC (2003) The impact of nonsteroidal anti-inflammatory drugs on blood pressure, with an emphasis on newer agents. Clin Ther 25:1–18
120. Rossat J, Maillard M, Nussberger J et al (1999) Renal effects of selective cyclooxygenase-2 inhibition in normotensive salt depleted subjects. Clin Pharmacol Ther 66:76–84
121. Solomon SD, Pfeffer MA, Mc Murray JJ et al (2006) Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. Circulation 114:1028–1035
122. Johnson AG, Nguyen TV, Day RO (1994) Do nonsteroidal anti-inflammatory drugs affect blood pressure? A metaanalysis. Ann Intern Med 121:289–300
123. Grossman E, Messerli FH (2012) Drug-induced hypertension: an unappreciated cause of secondary hypertension. Am J Med 125:14–22
124. De Leeuw PW (1996) Non-steroidal anti-inflammatory drugs and hypertension. The risks in perspective. Drugs 51:179–187

125. Beilin LJ (2002) Non-steroidal anti-inflammatory drugs and antihypertensive drug therapy. J Hypertens 20:849–850
126. Whelton A (2000) Renal and related cardiovascular effects of conventional and COX2 specific NSAIDs and non-NSAIDs analgesics. Am J Ther 7:63–74
127. Forman JP, Rimm EB, Curhan GC (2007) Frequency of analgesic use and risk of hypertension among men. Arch Intern Med 167:394–399
128. Sudano I, Flammer AJ, Périat D et al (2010) Acetaminophen increases blood pressure in patients with coronary artery disease. Circulation 122:1789–1796
129. Pope JE, Anderson JJ, Felson DT et al (1993) A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. Arch Intern Med 153:477–484
130. Guazzi MD, Campodonico J, Celeste F et al (1998) Antihypertensive efficacy of angiotensin converting enzyme inhibition and aspirin concentration. Clin Pharmacol Ther 63:79–86
131. Zanchetti A, Hanson L, Leonetti G et al (2002) Low-dose aspirin does not interfere with the blood pressure lowering effects of antihypertensive therapy. J Hypertens 20:1015–1022
132. Hermida RC, Ayala DE, Calvo C et al (2003) Administration time-dependent effects of aspirin on blood pressure in untreated hypertensive patients. Hypertension 41:1259–1267
133. Messerli FH (2005) Aspirin: a novel antihypertensive drug? Or two birds with one stone. J Am Coll Cardiol 46:984–985
134. Vora CK, Mansoor GA (2005) Herbs and alternative therapies: relevance to hypertension and cardiovascular diseases. Curr Hypertens Rep 7:275–280
135. Farese RV Jr, Biglieri EG, Shackleton CH et al (1991) Licorice-induced hypermineralocorticoidism. N Engl J Med 325:1223–1227
136. Yasue H, Iroh T, Mizuno Y et al (2007) Severe hypokalemia, rhabdomyolysis, and respiratory impairment in a hypertensive patient taking herbal medicines containing licorice. Intern Med 46:575–578
137. Russo S, Mastropasqua M, Mosetti MA et al (2000) Low doses of liquorice can induce hypertension encephalopathy. Am J Nephrol 20:145–148
138. Sontia B, Mooney J, Gaudet L, Touyz RM (2008) Pseudohyperaldosteronism, liquorice, and hypertension. J Clin Hypertens (Greenwich) 10:153–157
139. Sigurjóndóttir HA, Franzson L, Manhem K et al (2001) Liquorice-induced rise in blood pressure: a linear dose-response relationship. J Hum Hypertens 15:549–552
140. Stewart PM, Wallace AM, Valentino R et al (1987) Mineralocorticoid activity of liquorice: 11-beta-hydroxysteroid dehydrogenase activity comes of age. Lancet 2:821–824
141. Dai DW, Singh I, Hershman JM (2016) Lozenge-induced hypermineralocorticoid state: a unique case of licorice lozenges resulting in hypertension and hypokalemia. J Clin Hypertens 18:159–160
142. MacKenzie MA, Hoefnagels W, Jansen RW et al (1990) The influence of glycyrrhetinic acid on plasma cortisol and cortisone in healthy young volunteers. J Clin Endocrinol Metab 70:1637–1643
143. World Health Organization (2005) Evaluation of certain food additives. World Health Organ Tech Rep Ser 928:1–156
144. Sigurjóndóttir HA, Manhem K, Axelson M, Wallerstedt S (2003) Subjects with essential hypertension are more sensitive to the inhibition of 11 beta-HSD by liquorice. J Hum Hypertens 17:125–131
145. Ferrari P, Sansonnens A, Dick B, Frey FJ (2001) In vivo 11 beta-HSD-2 activity: variability, salt-sensitivity, and effect of licorice. Hypertension 38:1330–1336
146. Epstein MT, Espiner EA, Donald RA, Hughes H (1977) Liquorice toxicity and the renin-angiotensin-aldosterone axis in man. Br Med J 1:209–210
147. Siegel RK (1979) Ginseng abuse syndrome. Problems with the Panacea. JAMA 241:1614–1615
148. Chen KJ (1981) The effect and abuse syndrome of guinseng. J Tradit Chin Med 1:69–72
149. Yuan CS, Wei G, Dey L et al (2004) American guinseng reduces warfarin's effect in healthy patients: a randomized, controlled trial. Ann Intern Med 141:23–27
150. Jalili J, Askeroglu U, Alleyne B, Guyuron B (2013) Herbal products that may contribute to hypertension. Plast Reconstr Surg 131:168–173

151. Ruck B, Shih RD, Marcus SM (1999) Hypertensive crisis from herbal treatment of impotence. Am J Emerg Med 17:317–318
152. Bokemeyer C, Aapro MS, Courdi A et al (2004) EORTC guidelines for the use of erythropoietic proteins in anemic patients with cancer. Eur J Cancer 40:2201–2216
153. Luft FC (2000) Erythropoietin and arterial hypertension. Clin Nephrol 53(Suppl 1):561–564
154. Mashio G (1995) Erythropoietin and systemic hypertension. Nephrol Dial Transplant 10(Suppl 2):74–79
155. Brown CD, Friedman EA (1990) Clinical and blood rheologic stability in erythropoietin-treated predialysis patients. Am J Nephrol 10(Suppl 2):29–33
156. Kulzer P, Schaefer RM, Krahn R et al (1994) Effectiveness and safety of recombinant human erythropoietin (r-HuEPO) in the treatment of anemia of chronic renal failure in non dialysis patients. European Multicentre Study Group. Int J Artif Organs 17:195–202
157. Ludwig H, Fritz E, Kotzmann H et al (1990) Erythropoietin treatment of anemia associated with multiple myeloma. N Engl J Med 322:1693–1699
158. Ishimitsu T, Tsukada H, Ogawa Y et al (1993) Genetic predisposition to hypertension facilitates blood pressure elevation in hemodialysis patients treated with erythropoietin. Am J Med 94:401–406
159. Verbeelen D, Bossuyt A, Smitz A et al (1989) Hemodynamics of patients with renal failure treated with recombinant human erythropoietin. Clin Nephrol 31:6–11
160. Vogel V, Kramer HJ, Backer A et al (1997) Effects of erythropoietin on Endothelin-1 synthesis and the cellular calcium messenger system in vascular endothelial cells. Am J Med 10:289–296
161. Miller BA, Scaduto RC, Tillotson DL et al (1988) Erythropoietin stimulates a rise in intracellular free calcium concentration in single early human erythroid precursor. J Clin Invest 82:309–315
162. Morikawa K, Kuroda M, Hasegawa T (1993) Is the intracellular calcium-mediated pathway involved in erythropoietin-induced hypertension? Nephron 65:503–504
163. Novak BL, Force RW, Mumford BT et al (2003) Erythropoietin-induced hypertensive urgency in a patient with chronic renal insufficiency: case report and review of the literature. Pharmacotherapy 23:265–269
164. Hoorn EJ, Walsh SB, McCormick JA et al (2012) Pathogenesis of calcineurin-induced hypertension. J Nephrol 25:269–275
165. Cifkova R, Haller H (2011) Cyclosporine-induced hypertension. Eur Soc Hypertens Scientific Newsletter 12:15–16
166. Cifkova R, Haller H (2001) Cyclosporine-induced hypertension. J Clin Hypertens 19:2283–2285
167. Elliott WJ (2006) Drug interactions and drugs that affect blood pressure. J Clin Hypertens 8:731–737
168. Kaplan N (2010) Hypertension induced by cortisol or deoxycorticosterone. In: Kaplan NM, Victor RG (eds) Kaplan's clinical hypertension, 10th edn. Wolters Kluwer/Lippincott William and Wilkins, Philadelphia, pp 378–391
169. Grossman E, Messerli FH (2004) Iatrogenic and drug-induced hypertension. In: Mansoor GA (ed) Secondary hypertension: clinical presentation diagnosis and treatment. Humana Press Inc, Totowa NJ, pp 21–35
170. Hussain SF (2004) Progestogen-only pills and high blood pressure: is there an association? A literature review. Contraception 69:89–97
171. Shufelt CL, Merz NB (2009) Contraceptive hormone use and cardiovascular disease. Am Coll Cardiol 53:221–231
172. Grossman E, Messerli FH (2003) Management of drug-induced and iatrogenic hypertension. In: Izzo JL Jr, Black HR (eds) Hypertension primer, 3rd edn. Lippincott Williams and Wilkins, Dallas TX, pp 516–519
173. Chasan-Taber L, Willett WC, Manson JE et al (1996) Prospective study of oral contraceptives and hypertension among women in the United States. Circulation 94:483–489
174. Virdis A, Pinto S, Versari D et al (2003) Effect of contraceptives on endothelial function in the peripheral microcirculation of healthy women. J Hypertens 21:2275–2280

175. Ribstein J, Halimi JM, du Cailar G, Mimran A (1999) Renal characteristics and effect of angiotensin suppression in oral contraceptive use. Hypertension 33:90–95
176. Godsland IF, Walton C, Felton C et al (1992) Insulin resistance, secretion and metabolism in users of oral contraceptives. J Clin Endocrinol Metab 74:64–70
177. Committee Practice Bulletins-Gynecology ACOG (2001) ACOG practice bulletin. The use of hormonal contraception in women with coexisting medical conditions. Number 18, July 2000. Int J Gynaecol Obstet 75:93–106
178. Affinito P, Palomba S, Bonifacio M et al (2001) Effects of hormonal replacement therapy in postmenopausal hypertensive patients. Maturitas 40:75–83
179. Wang L, Zhong Z, Huj J et al (2015) Sertraline plus deanxit to treat patients with depression and anxiety in chronic somatic disease: a randomized controlled trial. BMC Psychiatry 15:84
180. Bhattacharya R, Shen C, Sambamoothi U (2014) Excess risk of chronic physical conditions associated with depression and anxiety. BMC Psychiatry 14:10
181. Ganasegeran K, Renganathan P, Manaf RA, Al-Dubai SA (2014) Factors associated with anxiety and depression among type 2 diabetes outpatients in Malaysia: a descriptive cross-sectional single center study. BMJ Open 4:e004794
182. Fallon B, Foote B, Walsh BT, Roose SP (1988) Spontaneous hypertensive episodes with monoamine oxidase inhibitors. J Clin Psychiatry 49:163–165
183. Rossi GP, Seccia TM, Maniero C, Pessina AC (2011) Drug-related hypertension and resistance to antihypertensive treatment: a call for action. J Hypertens 29:2295–2309
184. Louie AK, Louie EK, Lannon RA (1992) Systemic hypertension associated with tricyclic antidepressant treatment in patients with panic disorder. Am J Cardiol 70:1306–1309
185. Korzets A, Floro S, Ori Y et al (1997) Clomipramine-induced pheochromocytoma crisis a near fatal complication of a tricyclic antidepressant. J Clin Psychopharmacol 17:428–430
186. Peroutka SJ (1985) Selective interaction of novel anxiolytics with 5-hydroxytryptamine 1A receptors. Biol Psychiatry 20:971–979
187. [No authors listed] (1993) Venlafaxine: a new dimension in antidepressant pharmacotherapy. J Clin Psychiatr 54:119–126
188. Jette N, Veregin T, Guberman A (2002) Carbamazepine-induced hypertension. Neurology 59:275–276
189. Elenbass JK, Evans B (2001) Carbamazepine-induced cardiovascular toxicity (drug consult). In: Hutchison TA, Shahan DR, Anderson ML (eds) Drugdex system. Micromedex, Greenwood Village, CO. expires 12/2001
190. Iaria P, Blacher J, Asplanato M et al (1999) A new cause of resistant arterial hypertension: coprescription with anticonvulsant treatments (in French). Arch Mal Coeur Vaiss 92:1005–1009
191. Henderson DC, Daley TB, Kunkel L et al (2004) Clozapine and hypertension: a chart review of 82 patients. J Clin Psychiatry 65:686–689
192. Woo YS, Kim W, Chae JH et al (2009) Blood pressure changes during clozapine or olanzapine treatment in Korean schizophrenic patients. World J Biol Psychiatry 10:420–425
193. Khasawneh FT, Shankar GS (2014) Minimizing cardiovascular adverse effects of atypical antipsychotic drugs in patients with schizophrenia. Cardiol Res Pract 2014:273060
194. Mouhayar E, Salahudeen A (2011) Hypertension in cancer patients. Tex Heart Inst J 38:263–265
195. Moslehi JJ (2016) Cardiovascular toxic effects of targeted cancer therapies. N Engl J Med 375:1457–1467
196. Ketch T, Biaggioni I, Robertson RM, Robertson D (2002) Four faces of baroreflex failure: hypertensive crisis, volatile hypertension, orthostatic tachycardia and malignant vagotonia. Circulation 105:2518–2523
197. Wu S, Chen JJ, Kudelka A et al (2008) Incidence and risk of hypertension with Sorafenib in patients with cancer: a systematic review and meta-analysis. Lancet Oncol 9:117–123
198. Levy CF, Oo KZ, Fireman F et al (2009) Reversible posterior leukoencephalopathy syndrome in a child treated with bevacizumab. Pediatr Blood Cancer 52:669–671

199. Bono P, Elfuing H, Utrianen T et al (2009) Hypertension and clinical benefit of bevacizumab in the treatment of advanced renal cell carcinoma. Ann Oncol 20:393–394
200. Kappers MH, Van Esch JH, Sluiter W et al (2010) Hypertension induced by the tyrosine kinase inhibitor sunitinib is associated with increased circulating endothelin-1 levels. Hypertension 56:675–681
201. Hood JD, Meininger CJ, Ziche M, Granger HJ (1998) VEGF upregulates ec NOS message, protein and NO production in human endothelial cells. Am J Phys 274(Part II):H1054–H1058
202. Aparicio-Gallego G, Afonso-Afonso FJ, Leon-Mateos L et al (2011) Molecular basis of hypertension side effects induced by sunitinib. Anti-Cancer Drugs 22:1–8
203. Lankhorst S, Saleh L, Danser AA, van den Meiracker AH (2015) Etiology of angiogenesis inhibition-related hypertension. Curr Opin Pharmacol 21:7–13
204. Bair SM, Choueri TK, Moslehi J (2013) Cardiovascular complications associated with novel angiogenesis inhibitors: emerging evidence and evolving perspectives. Trends Cardiovasc Med 23:104–113
205. Li W, Croce K, Steensma DP et al (2015) Vascular and metabolic implications of novel targeted cancer therapies- Focus on kinase inhibitors. J Am Coll Cardiol 66:1160–1178
206. Dirix LY, Maes H, Sweldens C (2007) Treatment of arterial hypertension (AHT) associated with angiogenesis inhibitors. Ann Oncol 18:1121–1122
207. Mir O, Coriat R, Ropert S et al (2012) Treatment of bevacizumab induced- hypertension by amlodipine. Investig New Drugs 30:702–707
208. Robertson RM (1996) Baroreflex failure. In: Robertson D, Polinski RJ (eds) Primer on the autonomic nervous system. Academic Press, New York, pp 197–201
209. Shapiro I, Ruiz-Ramon P, Fainman C et al (1996) Light-headedness and defective cardiovascular reflexes after neck radiotherapy. Blood Press Monit 1:81–85
210. Towne JB, Bernhard VM (1980) The relationship of postoperative hypertension to complications following carotid endarterectomy. Surgery 88:575–580
211. Sigaudo-Roussel D, Evans DH, Naylor AR et al (2002) Determination in carotid baroreflex during carotid endarterectomy. J Vasc Surg 36:793–798
212. De Toma G, Nikolanti V, Plocco M et al (2000) Baroreflex failure syndrome after bilateral excision of carotid body tumors: an underestimated problem. J Vasc Surg 81:806–810
213. Kuchel O, Cusson JR, Larochelle P et al (1987) Posture- and emotion—induced severe hypertensive paroxysms with baroreceptor dysfunction. J Hypertens 5:277–283
214. Aksamit TR, Floras JS, Victor RG et al (1987) Paroxysmal hypertension due to sinoaortic baroreceptor denervation in humans. Hypertension 9:309–314
215. Robertson D, Hollister AS, Biaggioni I et al (1993) The diagnosis and treatment of baroreflex failure. N Engl J Med 329:1449–1455
216. Hoffman BB, Carruthers SG (2002) Cardiovascular disorders: hypertension. In: Carruthers SG, Hoffman BB, Melmon KL et al (eds) Clinical pharmacology. McGraw-Hill, New York, pp 65–234
217. Seaberg EC, Munoz A, Lu M et al (2005) Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003. AIDS 19:953–960
218. Palella FJ Jr, Delaney KM, Moorman AC et al (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 338:853–860
219. Bonnet F, Morlat P, Chene G et al (2002) Causes of death among HIV-infected patient in the era of highly active antiretroviral therapy Bordeaux, France 1998–1999. HIV Med 3:195–199
220. Palacios R, Santos J, Garcia A et al (2006) Impact of highly active antiretroviral therapy on blood pressure in HIV-infected patients. A prospective study in a cohort of naïve patients. HIV Med 7:10–15
221. Galindo Puerto MJ (2002) AHT and HIV- a new problem? Nutr Metab Disord HIV Infect 1:33–37
222. Gazzaruso C, Bruno R, Garzaniti A et al (2003) Hypertension among HIV patients: prevalence and relationships to insulin resistance and metabolic syndrome. J Hypertens 21:1377–1382

223. Mattana J, Siegal FP, Sankaran RK, Singhal PC (1999) Absence of age-related increase in systolic blood pressure in ambulatory patients with HIV infection. Am J Med Sci 317:232–237
224. Wilson SL, Scullard G, Fidler SJ et al (2009) Effects of HIV status and antiretroviral therapy on blood pressure. HIV Med 10:388–394
225. Gallis HA, Drew RH, Pickard WW (1990) Amphotericin B: 30 years of clinical experience. Rev Infect Dis 12:308–329
226. Walsh TJ, Hiermenz JW, Seibel NL et al (1998) Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. Clin Infect Dis 26:1383–1396
227. Rodrigues CA, Yamamoto M, Arantes Ade M et al (2006) Amphotericin B-induced hypertension, severe hypertension in a young patient: case report and review of the literature. Ren Fail 28:185–187
228. Le Y, Rana KZ, Dudley MN (1996) Amphotericin B-associated hypertension. Ann Pharmacother 30:765–767
229. Omizo MK, Bryant RE, Loveless MO (1993) Amphotericin B-induced malignant hypertension. Clin Infect Dis 17:817–818
230. Sawaya BP, Weihprecht H, Campbell WR et al (1991) Direct vasoconstriction as possible cause for amphotericin B-induced nephrotoxicity in rats. J Clin Invest 87:2097–2107
231. Watson DL, Bhatia RK, Norman GS et al (1989) Bromocriptine mesylate for lactation suppression: a risk for postpartum hypertension? Obstet Gynecol 74:573–576
232. Comabella M, Alvarez-Sabin J, Rovira A, Codina A (1996) Bromocriptine and postpartum cerebral angiopathy: a causal relationship? Neurology 46:1754–1756
233. Katz M, Kroll D, Pak I et al (1985) Puerperal hypertension, stroke, and seizures after suppression of lactation with bromocriptine. Obstet Gynecol 66:822–824
234. Rumore MM (2012) Cardiovascular adverse effects of metoclopramide: review of literature. Int J Case Reports Images 3:1–10
235. Roche H, Hyman G, Nahas H (1985) Hypertension and intravenous antidopaminergic drugs. N Engl J Med 312:1125–1126
236. Aschner P, Kipnes MS, Lunceford JK et al (2006) Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care 29:2632–2637
237. Marney A, Kunchakarra S, Byrne L, Brown NJ (2010) Interactive hemodynamic effects of dipeptidyl peptidase-IV inhibition and Angiotensin converting enzyme inhibition in humans. Hypertension 56:728–733
238. Bosi E, Camisasca RP, Collober C et al (2007) Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Care 30:890–895
239. Nathwani A, Lebeaut A, Byier SS et al (2006) Reduction in blood pressure treated with vildagliptin as monotherapy or in combination with metformin for type 2 diabetes. Diabetes 55:A113
240. Jackson EK, Dubinion JH, Mi Z (2008) Effects of dipeptidyl peptidase iv inhibition on arterial blood pressure. Clin Exp Pharmacol Physiol 35:29–34
241. Mancia G, De Backer G, Dominiczak A et al (2007) 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 25:1105–1187
242. Kelly WN (2001) Potential risks and prevention, part 4: reports of significant adverse drug events. Am J Health Syst Pharm 58:1406–1412
243. Williamson J, Chopin JM (1980) Adverse reactions to prescribed drugs in the elderly: a multicenter investigation. Age Ageing 9:73–80
244. Opie LH (1996) Cardiovascular drug interactions. In: Messerli FH (ed) Cardiovascular drug therapy, 2nd edn. WB Saunders Company, Philadelphia, pp 347–353

245. van Zwieten PA, Alfoldi S, Farsang C (2011) Interactions between antihypertensive agents and other drugs. ESH Clinical Practice Newsletters 12:31–32
246. Neusy AJ, Lowenstein J (1989) Blood pressure and blood pressure variability following withdrawal of propranolol and clonidine. J Clin Pharmacol 29:18–24
247. Kaplan NM (2010) Treatment of hypertension: drug therapy. In: Kaplan NM, Victor RG (eds) Kaplan's clinical hypertension, 10th edn. Wolters Kluwer/Lippincott William and Wilkins, Philadelphia, pp 192–273
248. Lilja M, Jounela AJ, Juustila HJ, Paalzow L (1982) Abrupt and gradual change from clonidine to beta blockers in hypertension. Acta Med Scand 211:375–380

# Part IX

# Hypertensive Phenotypes: Blood Pressure Disorders of Pregnancy and Pediatric Hypertension

# Hypertensive Disorders of Pregnancy

# 44

Gianni Bellomo

## 44.1 Blood Pressure and Cardiovascular Adaptations in Normal Pregnancy

Normal pregnancy is associated with significant vascular and hemodynamic changes that are not limited to the fetoplacental system (Table 44.1). We will provide in this chapter a brief overview of such changes: a more detailed discussion can be found in other excellent reviews [1–5].

Heart rate, due to a rise in vasomotor sympathetic activity which occurs in the first weeks of gestation [6–8], tends to increase progressively during normal pregnancy, reaching its peak near term, overall about 20–25% over preconception.

Both systolic and diastolic (the latter more so) blood pressures tend to decrease early in pregnancy, to reach a nadir by the middle of second trimester (on average 5–10 mmHg lower than prepregnancy values). Blood pressure progressively increases thereafter, returning to preconception values near term or a few weeks after delivery. It is important to note that, as these changes occur very early in pregnancy, blood pressure measured even during the first weeks of gestation may not be representative of preconception pressure. Vasodilation, a reduction of peripheral vascular resistance, accompanied by an increased arterial compliance, is probably at the origin of the blood pressure reduction [6].

Plasma volume tends to rise within the first few weeks of gestation, and volume expansions rises progressively throughout pregnancy, by an average 50% (20–100%) [7–11] over preconception values. Plasma volume changes are mediated by activation of the renin-angiotensin-aldosterone system (RAAS) which persists through the 30th week of gestation, leading to sodium retention with a net gain of approximately 950–1000 mg [5, 9–11] even though, due to hemodilution, plasma osmolality and serum sodium levels are reduced. In addition, relaxin may induce an

G. Bellomo
Department of Nephrology, MVT Hospital, Str.Buda 1, 06059 Todi(Pg), Italy
e-mail: gianni.bellomo@uslumbria1.it



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_44

**Table 44.1** Cardiovascular adaptation in normal pregnancy

| Hemodynamic parameter | Pregnancy-induced change | Return to preconception levels |
|---|---|---|
| Heart rate | Increases progressively throughout pregnancy | 1–2 weeks postpartum |
| Blood pressure | Decreases, starting 6–8 weeks of gestation through the end of 2nd trimester, then begins to rise again | End of 3rd trimester, few weeks postpartum |
| Plasma volume | Increases starting 6–8 weeks of gestation and progressively throughout pregnancy | Few weeks postpartum |
| Peripheral vascular resistance | Decreases, starting 5 weeks of gestation, reaching nadir by middle of 2nd trimester, then remains stable throughout pregnancy | Within 2 weeks postpartum |
| Cardiac output | Increases starting 5–6 weeks of gestation, through middle of 2nd trimester, then plateaus | Within 2 weeks postpartum |
| Cardiac contractility | No change | |
| Renal plasma flow | Increases starting 5–6 weeks of gestation, reaching a peak at middle 2nd trimester, then decreases progressively toward term | Within 2–3 weeks postpartum |

increase in vasopressin secretion [13], which in turn leads to increased thirst and drinking; during pregnancy, total body water increases by 6–8 L, with both blood and interstitial volume expansion. Although an increase in red blood cell mass [14] occurs in pregnancy, the out of proportion volume expansion is responsible for a mild, physiologic anemia. Volume expansion causes an increased secretion of atrial natriuretic peptide [15] which is detectable by the 12th week of gestation and persists 1–2 weeks after delivery and is responsible for postpartum polyuria.

Systemic vasodilation and decreased peripheral vascular resistance occur early in pregnancy [2, 7], well before the low-resistance uterine circulation is fully established, reaching a nadir (approximately 35–40% over baseline) by the middle second trimester and then plateaus and declines progressively to reach preconception levels within the first 2 weeks postpartum. The mechanisms at the basis of such a decrease in peripheral vascular resistance are not fully clarified yet but likely reflect the effects of several hormones and signaling pathways, including estrogens, progesterone, prostaglandins, and relaxin [12–19]; furthermore, reduced vascular responsiveness to pressor substances such as norepinephrine, angiotensin II, and vasopressin is well documented in pregnancy [3, 4, 20, 21].

Renal vascular resistance is also decreased, leading to an approximately 80% increase in renal plasma flow and 50% in glomerular filtration rate, with consequent reduced serum levels of urea, creatinine, and uric acid, peaking in the middle second trimester and returning to preconception levels near term or soon postpartum [5, 22].

Cardiac output increases early in pregnancy and rises quickly into the second trimester; it is estimated [23–25] that at 24 weeks of gestation, cardiac output reaches levels equal to 40–50% over baseline [23–25] in a singleton pregnancy, whereas it may rise up to 60% in twin pregnancies.

Finally, myocardial contractility, as well as right and left ventricular ejection fraction, do not seem to be affected by pregnancy [1].

## 44.2 Classification of Hypertension in Pregnancy and Diagnostic Criteria

Although the hypertensive disorders of pregnancy (HDP) remain a leading cause of maternal and perinatal morbidity and mortality worldwide [26, 27], a definite, widespread, universal consensus on the classification and diagnostic criteria for HDP has never been achieved [28]. This lack of consensus may have led to between-center differences in rates of adverse maternal and fetal outcomes for the various HDP, particularly preeclampsia, as well as to the difficulty in designing and conducting clinical trials. So far, the classification [29] proposed by the ACOG (American College of Obstetricians and Gynecologists) Task Force on Hypertension in Pregnancy (Table 44.2) has been widely used; more recently [28], a revised classification (Table 44.3) was proposed by the International Society for the Study of Hypertension in Pregnancy (ISSHP). Other classifications have been developed by the World Health Organization (WHO) and other institutions/scientific societies [28].

Although not specifically mentioned in the above-cited classification, a general tendency is arising to distinguish between early-placental (<34 weeks of gestation) and late-maternal (>34 weeks of gestation) preeclampsia [30, 31]. Early- and late-onset preeclampsias share some etiological features, differ with regard to several risk factors, and may lead to different outcomes. The two types of preeclampsia should probably be treated as distinct entities from an etiological and prognostic [30, 31] standpoint.

**Table 44.2** Classification of HDP according to ACOG Task Force on Hypertension in Pregnancy 2013 [29]

| |
|---|
| *Preeclampsia-eclampsia* (blood pressure elevation [≥140 mmHg systolic or ≥90 mmHg diastolic], after 20 weeks of gestation with proteinuria ≥300 mg/24 h or any of the severe features of preeclampsia) |
| *Chronic hypertension* (of any cause that predates pregnancy) |
| *Chronic hypertension with superimposed preeclampsia* (chronic hypertension in association with preeclampsia) |
| *Gestational hypertension* (blood pressure elevation [≥140 mmHg systolic or ≥90 mmHg diastolic], after 20 weeks of gestation in the absence of proteinuria or any of the severe features of preeclampsia) |

**Table 44.3** Classification of HDP according to ISSHP 2014 [28]

| |
|---|
| Chronic hypertension |
| Gestational hypertension |
| Preeclampsia – De novo or superimposed on chronic hypertension [≥140 mmHg systolic or ≥90 mmHg diastolic] proteinuria (spot urine protein/creatinine >30 mg/mmol [0.3 mg/mg] or >300 mg/day or at least |
| White coat hypertension |

According to ACOG classification, features of severe preeclampsia include any of the following:

> Severe hypertension: systolic >160 or diastolic >110 mmHg on two occasions at least 4 h apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time); thrombocytopenia (platelet count <100,000/mm$^3$); impaired liver function (elevated blood levels of liver transaminases to at least twice the normal concentration); severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both; new development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dL, or doubling of serum creatinine in the absence of other renal disease); pulmonary edema; new-onset cerebral or visual disturbances.

According to ISSHP, definition of severe preeclampsia includes any of the following: proteinuria (spot urine protein/creatinine >30 mg/mmol [0.3 mg/mg] or >300 mg/day or at least 1 g/L. ['2 +'] on dipstick testing) and other maternal organ dysfunction: renal insufficiency (creatinine >90 μmol/L [1.02 mg/dL]), liver involvement (elevated transaminases – at least twice upper limit of normal ± right upper quadrant or epigastric abdominal pain), neurological complications (examples include eclampsia [seizures], altered mental status, blindness-visual disturbances, stroke, or more commonly hyperreflexia when accompanied by clonus, severe headaches when accompanied by hyperreflexia, persistent visual scotomata), hematological complications (thrombocytopenia – platelet count below 150,000/dL, DIC [disseminated intravascular coagulation], hemolysis), and uteroplacental dysfunction(fetal growth restriction).

The ACOG and ISSHP differ mainly for the diagnostic role attributed to proteinuria, which the former considers a *condition* sine qua non for establishing a diagnosis of preeclampsia, whereas ISSHP, in the presence of any of the abovementioned clinical features, does not deem proteinuria as a strict diagnostic criterion, although ACOG acknowledges that a diagnosis of severe preeclampsia is not necessarily dependent on the presence of proteinuria. Finally, fetal growth restriction is no longer considered a feature of severe preeclampsia by ACOG.

## 44.3 Proteinuria and Blood Pressure Measurement

From the above consideration, it appears evident that correct diagnosis and classification of HDP depend heavily on the quality and accuracy of proteinuria and blood pressure measurement, which are important as the levels of blood pressure and the presence of proteinuria may influence clinical management [32–34]. A 24 h urine collection is still considered by many [34] as the optimal method for the detection of proteinuria in pregnancy. Alternatively, either a timed excretion that is extrapolated to 24 h urine value or a *protein/creatinine ratio* of at least 0.3 (each measured as mg/dL) is acceptable. The *dipstick method* is not considered appropriate by ACOG for diagnostic use unless other approaches are not readily available. 1+ is considered as the

cutoff for the diagnosis of proteinuria; however, a 24 hour collection may be unpractical at times, particularly when quick clinical decisions are to be made: in such instances a spot urine protein/creatinine ratio may be adequate, allowing to speed up decision-making, although the evidence supporting such a practice is insufficient [29].

Regarding blood pressure (BP) measurement in pregnancy, the following recommendations, with varying strength of evidence, have been issued [35]: BP should be recorded with the woman seated comfortably and her arm resting at the level of her heart and her legs resting on a flat surface. Supine posture is not recommended because of the possible occurrence of the supine hypotension syndrome. The inter-arm variation is usually less than 10 mmHg, with 8% and 2% of pregnant women having an inter-arm difference of at least 10 mmHg for systolic and diastolic BP, respectively [36]. Anyway, the arm with higher values should be used for subsequent measurements.

The systolic BP is identified at Korotkoff phase 1 (K1) and the diastolic BP at Korotkoff phase 5 (complete disappearance of sounds, K5) [37]. In the (not so rare) instances when Korotkoff sounds are audible down to zero mmHg, phase 4 (K4, muffling) should be accepted.

The use of correct cuff size is fundamental for accurate BP measurement. Cuff should be adapted to the woman's arm circumference, with an inflatable bladder covering 80% used if the upper arm circumference is greater than 33 cm but lower than 44 cm and a thigh cuff used if the upper arm circumference is over 44 cm [33]. The rate of cuff deflation should be $\leq$2 mm per second to avoid underestimating systolic BP [38].

### 44.3.1 Measurement Devices

Mercury sphygmomanometers remain the gold standard for BP measurement in pregnancy, although their availability is becoming more and more limited, because of concerns about occupational health. Suitable alternatives may be calibrated aneroid sphygmomanometers or automated devices validated for use in preeclampsia; automated devices may provide mean BP values similar to those obtained with mercury sphygmomanometers; however, they tend to show wide intraindividual variation, and their accuracy may be further compromised in preeclampsia [39, 40]. Automated BP devices not validated for use in preeclampsia may under- or overestimate BP, and comparison of recordings using mercury sphygmomanometry or a calibrated aneroid device is recommended [39].

In the office setting, when BP elevation is mild and preeclampsia is not suspected, either ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) may be of use to confirm or exclude persistently elevated BP. When HBPM is used, maternity care providers should ensure that patients have adequate training in measuring their BP and interpreting the readings.

Non-mercury auscultatory sphygmomanometers present an option with appropriately trained observers [41]. Information regarding device validation is provided by the British Hypertension Society.

It is advisable that each unit should maintain a mercury sphygmomanometer for calibration and validation of automated and aneroid devices [42]. Healthcare providers must ensure that devices for measuring blood pressure are properly validated, maintained, and regularly recalibrated according to manufacturers' instructions as recommended by the British Hypertension Society (BHS) [42]. A comprehensive list of approved devices for HBPM can be found at http://www.dableducational.org, http://www.bhsoc.org/default.stm and http://www.hypertension.ca/devices-endorsed-by-hypertension-canada-dp1.

Twenty-four hour ambulatory blood pressure monitoring (ABPM) is generally reserved to identify women with white coat hypertension (WCH) [43, 44] and to avoid unnecessary treatment. It may also be useful in assessing pregnant women with raised BP before 20 weeks of gestation, 30–40% of which will be shown to have WCH [45], with approximately half of them requiring no treatment throughout pregnancy and the other half developing true hypertension [46].

The prognostic value of ABPM is limited in later pregnancy and for predicting adverse outcomes in women with HDP [47], with ambulatory diastolic BP displaying greater sensitivity and specificity than systolic BP [44].

## 44.4 Gestational (Transient) Hypertension

Gestational hypertension can be defined as the de novo development of hypertension after 20 weeks of gestation, without any of the abnormalities that define preeclampsia; blood pressure generally returns to normal within 3 months postpartum; otherwise, the woman is considered as having chronic hypertension. This condition is usually believed to be benign; however, it can progress to preeclampsia in approximately 25% of cases, particularly when the hypertension presents before 32–34 weeks [35].

It is estimated that approximately 35% of women with gestational hypertension at <34 weeks develop preeclampsia over an average of 5 weeks [29]. Women with prior gestational hypertension are likely to have recurrent gestational hypertension (median 21%) rather than preeclampsia (median 4%) [48]. Conversely, women with prior preeclampsia may develop gestational hypertension (median 22%) in subsequent pregnancies.

### 44.4.1 White Coat Hypertension and Masked Hypertension

WCH is defined as a persistently elevated office BP with normal BP outside the medical setting [49]; it is estimated that in the general population, up to one in four patients with elevated clinic or office BP does actually have WCH [50]. WCH in early pregnancy (approximately 30%) is common [51]. Forty percent of women with WCH will progress to persistent hypertension and 8% to preeclampsia. WCH carries a risk of adverse maternal-fetal outcomes, such as severe hypertension, preterm delivery, and NICU admission intermediate between normotension and either

pre-existing or gestational hypertension [52, 53]. WCH can be diagnosed by having clinic or office BP recorded by a nurse, rather than a doctor, preferably using repeated BP readings [43].

Ideally, the diagnosis is confirmed by demonstrating normal BP using 24 h ABPM in the first half of pregnancy, but the ISSHP guidelines acknowledge that this may be, at times, unpractical [44, 54, 55].

According to the ISSHP guidelines, the following take-home messages regarding WCH must be considered: it is reasonable to withhold antihypertensive therapy in this group; BP should continue to be monitored regularly at home; increased surveillance is required throughout pregnancy to identify the onset of preeclampsia; and in areas where home BP measurements are not available, maternal BP should be checked regularly, preferably weekly, by a healthcare worker.

Masked hypertension (MH) is defined as a clinical condition in which a patient's office BP level is <140/90 mmHg, but ambulatory or home BP readings are in the hypertensive range [56]. MH in early pregnancy is as common as WCH [56], but associated perinatal risks are unknown. Outcomes with masked hypertension equate to those of gestational hypertension [57].

MH could be considered (and ABPM/HBPM performed) when unexplained maternal or perinatal complications arise, which are generally associated with hypertensive disorders of pregnancy.

### 44.4.2 Chronic Hypertension

Chronic hypertension in pregnancy is defined as documented BP of at least 140 mmHg systolic or 90 mmHg diastolic pressure before pregnancy or, for women who first present for care during pregnancy, before 20 weeks of gestation [29, 39, 58]. Its prevalence ranges between 0.2 and 5% worldwide [29, 59, 60] and is estimated around 3% in the USA, consistently increasing in the industrialized countries [61–63]; such an increase is most likely related to older age of the prospective mothers in Western countries and to increased prevalence of obesity, a known risk factor for hypertension. The diagnosis of chronic hypertension may not be easy in pregnant women whose preconception or early first trimester BP is not known, as the physiological second trimester fall in BP can obscure pre-existing hypertension and although very rarely, preeclampsia can present before 20 weeks' gestation [29, 35].

Although most women with chronic hypertension have favorable maternal and fetal outcomes, these women are at increased risk for pregnancy complications, as compared with the general population. The risk of an adverse outcome increases with the severity of hypertension and end-organ damage. In particular, the overall risk of developing preeclampsia has been estimated around 17% and 25% compared to 3–5% in normotensive women and of early preeclampsia (before gestation week 34) around 10% [64–66]. Pregnant women with chronic hypertension are more likely to undergo cesarean section (50%) and to give birth to a small for gestational age (SGA) baby (27%–50%) [64, 67].The risk of placental abruption is increased more than twice in women with chronic hypertension, the more so in those who

develop preeclampsia [68]. Furthermore, a recent study [69] has shown an increased frequency of congenital malformations (in particular cardiac malformations) in the offspring of women with chronic hypertension, compared to offspring of normotensive women, independent of pharmacologic treatment. Finally (Table 44.4), some antihypertensive agents carry risks in pregnancy and should be discontinued before

**Table 44.4** Pharmacologic treatments of chronic hypertension in pregnancy

| Drugs by class | Dose range | Effect of pregnancy on disposition | Common side effects | Comments |
|---|---|---|---|---|
| Central α-agonists | | | | |
| Methyldopa | 250–1500 mg, given in 2 daily doses | Unknown | Sedation, weakness, orthostatic hypotension | Long-term data on safety. Probably first choice drug |
| Clonidine | 0.15–0.3 mg, given in 2–3 daily doses | Unknown | Somnolence, bradycardia, xerostomia | First trimester exposure associated with birth defects, concerns about safety |
| Combined α- and β-blocker | | | | |
| Labetalol | 100–1200 mg orally twice daily | +++(β isomer), +(α isomer | Asthma exacerbation, weakness, orthostatic hypotension(iv use) | Safe, can be used as first choice, iv formulation available for use in emergencies |
| B-blockers | | | | |
| Metoprolol | 25–200 mg orally twice daily | +++ | Asthma exacerbation, weakness, depression, bradycardia | Possible association with IUGR |
| Atenolol | 25–200 mg, orally, once daily | + | Asthma exacerbation, weakness, depression, bradycardia | Possible association with IUGR. Other β-blockers such as propranolol and pindolol have been used safely, but data are insufficient |
| Non-dihydropyridine calcium channel blockers | | | | |
| Verapamil | 40–120 mg, orally, three times daily | + | Constipation, hypotension, weakness, bradycardia | May be used to prevent preterm labor; caution when uteroplacental perfusion is compromised |

**Table 44.4** (continued)

| Drugs by class | Dose range | Effect of pregnancy on disposition | Common side effects | Comments |
|---|---|---|---|---|
| Dihydropyridine calcium channel blockers | | | | |
| Nifedipine (long-acting preparation) | 20–120 mg, once daily(twice daily may be necessary in some instances | ++ | Edema, hypotension, headache, weakness, flushing | Probably safe, widely used. Use of short-acting nifedipine is typically not recommended, given the risk of hypotension. Possible interaction with magnesium sulfate, avoid concomitant use |
| Amlodipine | 2.5–10 mg, orally, once daily | ++ | Edema, hypotension, headache, weakness, flushing | Few data available, probably safe |
| Other vasodilators | | | | |
| Hydralazine | 50–300 mg daily in 2–4 divided doses | Unknown | Headache, tachycardia, nausea | Intravenous formulation is available to treat hypertensive emergencies |
| Diuretics | | | | |
| Hydrochlorothiazide | 12.5–50 mg orally, once daily | Unknown | Hypokalemia, hypotension, dizziness, muscle cramps | Previous concerns about increased risk of an adverse outcome are not supported by recent data |
| Angiotensin converting enzyme inhibitors or angiotensin receptor blockers are contraindicated in pregnancy due to the risk of birth defects and fetal or neonatal renal failure | | | | |

[a]*IUGR* intrauterine growth restriction

conception [70–72]. As approximately 50% of pregnancies in the USA are unplanned, it is of the uttermost importance to provide counseling to hypertensive women of reproductive age regarding such risks as part of routine care [73].

The great majority of women with chronic hypertension experience a decrease in BP during pregnancy, equivalent to that observed in normotensive women, with BP falling toward the end of the first trimester and rising again to preconception values during the third trimester. Consequently, antihypertensive medications can often be tapered during pregnancy. However, besides the subset of women with chronic hypertension who develop preeclampsia, an additional 7–20% will experience worsening of hypertension with the progression of pregnancy without the development of preeclampsia [64].

Notably, a lack of consensus exists about the benefits of treating mild to moderate hypertension in pregnancy, as well as the BP goals to be pursued: a recent study [74] comparing tight BP control (diastolic BP ≤ 85 mmHg) to less tight control (diastolic BP ≤ 100 mmHg) on a composite primary outcome of pregnancy loss or high-level neonatal care for more than 48 h during the first 28 postnatal days and a secondary outcome of serious maternal complications occurring up to 6 weeks postpartum or until hospital discharge, whichever was later, showed no significant differences in the primary or secondary outcomes among the two groups; however, women assigned to the less tight control group had a higher frequency of severe hypertension (40.6% vs. 27.5%, $p < 0.001$). A recent statement from the Society of Maternal-Fetal Medicine (SMFM) endorsed the strategy of not treating with antihypertensive agents pregnant women with mild to moderate hypertension without evidence of end-organ damage [75]. Table 44.4 shows the available pharmacologic treatments for chronic hypertension in pregnancy [29, 35, 39, 64, 70–82]. Table 44.5 summarizes the most recent guidelines for the management of chronic hypertension in pregnancy [29, 35, 39].

## 44.5 Preeclampsia

Preeclampsia, formerly known as toxemia of pregnancy, can be defined as new-onset hypertension, after the 20th week of gestation, associated with proteinuria and/or other signs of end-organ damage (see classification of HDP). The term *eclampsia* refers to the occurrence of seizures that cannot be attributed to other causes in a woman with preeclampsia.

### 44.5.1 Epidemiology and Risk Factors

The incidence of preeclampsia is estimated to range between 2.5 and 5%. An accurate estimate, as well as its global burden, is difficult to obtain, due to lack of data from several countries and standardization of diagnostic criteria [83–85]. Preeclampsia complicates about 3% of pregnancies in the USA, and similar incidence data are reported in Scandinavian countries, where specific registries are available (3.0%, 4.5%, and 3.0% in Sweden, Denmark, and Norway, respectively). A study performed in New Zealand found an incidence of 3.3% [83–85, 87]. Higher incidence rates have been observed, such as 8.7% in a study from Canada [83–85] and 8.4% in one from Washington State [83, 84]. Such wide variations are probably related to intrinsic characteristics of the populations studied and to the diagnostic criteria adopted.

Researchers from the WHO have conducted a systematic review [86] of studies on hypertensive disorders of pregnancy, representing approximately 39 million women from 40 countries; from this data set, they have derived a logistic regression model to estimate the global incidence of preeclampsia (4.6%, 95% uncertainty range 2.7–8.2%) and eclampsia (1.4%, 95% uncertainty range 1.0–2.0%).

**Table 44.5** Recently published guidelines for the management of chronic hypertension in pregnancy

| | ACOG (American College of Obstetricians and Gynecologists),2013 [29] | ISSHP (International Society for the Study of Hypertension in Pregnancy), 2014 [27] | CANADA, 2015 [35] | SOMANZ (Society of Obstetric Medicine of Australia and New Zealand), 2014 [39] |
|---|---|---|---|---|
| Prepregnancy evaluation or first assessment at pregnancy | Consider testing of creatinine, blood urea nitrogen, 24 h urine protein and creatinine clearance, uric acid, along with electrocardiography, echocardiography, ophthalmologic examination, and renal ultrasonography<br>Evaluate for secondary causes in presence of suggestive symptoms or signs | Not stated, refers to previous guidelines | Most women with pre-existing hypertension have essential hypertension, but the following tests should be performed (if not previously documented): urinalysis, serum creatinine and potassium, fasting blood glucose, electrocardiogram, routine measurement of plasma<br>Lipid levels are not advised until postpartum, as they rise in pregnancy. Additional baseline testing may be prudent with chronic conditions (e.g., nonalcoholic steatohepatitis) that may make it difficult to investigate whether future end-organ dysfunction is due to preeclampsia | Although most women will have essential hypertension, screening for secondary hypertension indicated urinalysis for protein. If proteinuria is evident on dipstick analysis, a "spot" urine protein/creatinine ratio should be obtained<br>Microscopy of centrifuged urinary sediment for white and red blood cells (including red cell morphology) and for casts; midstream urine culture<br>Blood:<br>Serum electrolytes and creatinine, uric acid and full blood examination, fasting blood glucose<br>ECG, renal ultrasound<br>Screening for pheochromocytoma if indicated: fasting free plasma metanephrines and normetanephrines<br>End-organ effects of hypertension (retinal, albuminuria, renal function, and echocardiogram) should be considered particularly when hypertension is severe, long-standing, or when it has not previously been detected |

(continued)

**Table 44.5** (continued)

| | ACOG (American College of Obstetricians and Gynecologists),2013 [29] | ISSHP (International Society for the Study of Hypertension in Pregnancy), 2014 [27] | CANADA, 2015 [35] | SOMANZ (Society of Obstetric Medicine of Australia and New Zealand), 2014 [39] |
|---|---|---|---|---|
| BP goals and threshold for treatment | BP goal 120–160 mmHg systolic and 80–105 mmHg diastolic, treatment is advised above these values | Maintain systolic and diastolic BP above 110 and 80 mmHg, respectively | Target BP lower than 140/90 mmHg, no additional benefit of diastolic BP <85 mmHg | Target BP 130–140 mmHg systolic and 80–90 mmHg diastolic but depends on factors to be weighed individually |
| Pharmacological treatment | Labetalol, long-acting nifedipine, methyldopa, thiazides (second line). Avoid ACE-inhibitors and angiotensin receptor blockers | Not stated, refers to previous guidelines | Non-severe hypertension: oral labetalol, methyldopa, long-acting nifedipine<br>Severe hypertension (BP ≥ 160/110 mmHg): IV labetalol or hydralazine, oral nifedipine<br>Avoid ACE-inhibitors and angiotensin receptor blockers | Non-severe hypertension: oral labetalol, methyldopa, long-acting nifedipine, oxprenolol<br>Severe hypertension (BP ≥ 160/110 mmHg): IV labetalol or hydralazine, or diazoxide; oral nifedipine<br>Avoid ACE-inhibitors and angiotensin receptor blockers |

Regarding temporal trends, preeclampsia incidence rates appear to be increasing along the years, according to data from Norway (from 3.7% between 1988 and 1992 to 4.4% between 1998 and 2002). A similar pattern has been reported in the USA [83–85] with age-adjusted rates rising from 2.4% between 1987 and 1988 to 2.9% of deliveries between 2003 and 2004. This temporal trend is not easily explained; however, the increased prevalence of risk factors such as obesity and older maternal age may play a role.

Conversely, the incidence of eclampsia appears to be decreasing; a recent study [85] conducted in California showed a decreased incidence of eclampsia from 8.0 cases per 10,000 deliveries in 2001 to 5.6 cases per 10,000 deliveries in 2007 ($p < 0.001$). A bimodal distribution in age-related risk, with the highest risks at the extremes of age, was observed. A possible explanation for this pattern may be found in improved maternal care.

Preeclampsia seems to follow a seasonal pattern: Hlimi [88] has recently reviewed studies on this subject, showing that seasonal trends may influence maternal health globally, the more so in developing countries: a statistically significant link between preeclampsia and seasonality has been shown in

sub-Saharan Africa, as well as in South and Central Asia, with a lower incidence recorded in the hot and dry season, increasing in the rainy and cooler season. A similar pattern has been reported in a study from Recife, in Brazil [89].

Finally, the risk of recurrence of preeclampsia in a second pregnancy is estimated around 7–15% [83, 87, 90], rising to 30% if the first two pregnancies were complicated by preeclampsia. A recent individual participant meta-analysis [87] showed a recurrence rate of 13.8% for preeclampsia, with a milder course for recurrent disease.

Several risk factors have been identified for preeclampsia (Table 44.6). A family history of preeclampsia increases the risk substantially, and preeclampsia tends to

**Table 44.6** Risk factors for preeclampsia

| Familial factors | Obesity |
|---|---|
| Family history of preeclampsia in first-degree relatives | **Primipaternity and sperm exposure** |
| Strong family history of cardiovascular disease (heart disease or stroke in two or more first-degree relatives) | Nulliparity, use of barrier contraception |
| **Obstetric factors** | Change of partner |
| Nulliparity | ICSI (intracytoplasmic sperm injection) |
| Multiple pregnancy | **Miscellaneous** |
| Previous pregnancy complicated by preeclampsia | Residence at high altitudes |
| Advanced maternal age | Seasonality |
| **Pre-existing medical conditions** | Exposure to air pollutant(ozone) |
| Antiphospholipid antibody syndrome and other thrombophilic states | Non-Hispanic black race |
| Renal disease | Gestational weight gain >16 kg |
| Diabetes mellitus | |
| Systemic lupus erythematosus | |
| Chronic hypertension | |

occur in daughters of mothers who, in turn, had preeclampsia [83, 91]. A paternal effect has also been documented [26], as men who fathered a pregnancy complicated by preeclampsia are more likely to father another pregnancy complicated by preeclampsia [92, 93]. A significant family history of cardiovascular disease leads to a threefold increased risk of preeclampsia [91]. Nulliparity, a previous pregnancy complicated by preeclampsia, multiple gestations, and maternal age 40 years or older increase the risk of preeclampsia by a factor of approximately 5.7, 3.5, and 1.7 [94], respectively. A number of comorbid conditions, such as the antiphospholipid syndrome and chronic kidney disease, are associated with a greater than sevenfold risk of developing preeclampsia [83, 94, 95], whereas such risk is increased 3.6–3.8 times in women with diabetes mellitus (99) or chronic hypertension [83]. Finally obesity and excess gestational weight gain are also risk factors for preeclampsia (100). Regarding primipaternity and sperm exposure, the observation that nulliparous women have a three-fold higher risk of preeclampsia compared with multiparous women and that women who use barrier contraception or who change partner, or conceive following intracytoplasmic sperm injection (ICSI) [93, 96], also carry an increased risk of developing preeclampsia may also have pathogenetic implications, indicating that exposure to partner's sperm may be protective, thus implicating some form of immune tolerance [92, 93, 96]. Table 44.6 summarizes risk factors for preeclampsia [88–110].

### 44.5.2 Pathogenesis

Preeclampsia is an endothelial disorder unique to human pregnancy, with multiple organ involvement; its hallmark the renal histological lesion, defined as "glomerular endotheliosis," represents a specific variant of thrombotic microangiopathy characterized by glomerular endothelial swelling with loss of endothelial fenestrae and occlusion of the capillary lumens; the lesion, however, is not specific of preeclampsia, as it was found in women with normal pregnancy as well as in both non-proteinuric and proteinuric hypertension [111] and is consequently not, as earlier believed, pathognomonic of preeclampsia [111]. Its cause remains elusive, and several theories have been proposed, hence the definition "disease of theories." Given the fact that important aspects of physiologic pregnancy, such as immune tolerance of the hemiallogeneic fetus and mechanisms of labor initiation, remain largely unexplained [29, 112], it comes as a consequence that the pathogenesis of preeclampsia is also difficult to elucidate. A wide consensus exists on the cardinal importance of the placenta for its development, as delivery of the placenta leads to resolution of the syndrome, and molar pregnancy is often complicated by preeclampsia. A common feature of preeclampsia (in particular in its early form, occurring before the 34th week of gestation) involves poor placentation, with defective and shallow cytotrophoblast invasion of the interstitial uterine compartment, although not in all cases. In many locations, spiral artery invasion is incomplete. Fewer endovascular cytotrophoblasts are visible, and some vessels retain portions of their endothelial lining with relatively intact muscular coats, although others

remain unchanged [113]. In physiologic pregnancy, cytotrophoblast invasion is accompanied by changes in gene expression profiles, with downregulation of epithelial-like molecules (such as cadherin) and upregulation of endothelial-like molecules, with a switch from an epithelial to an endothelial phenotype [113, 114]; abnormalities of such a finely tuned process might be at the basis of the abnormal placentation of preeclampsia [113, 114].

Currently, the most accredited pathogenetic theory of preeclampsia is based on unbalanced angiogenic and anti-angiogenic factors [115, 116]: in preeclampsia, there is increased expression of soluble fms-like tyrosine kinase-1 (sFlt1), also called VEGFR1, the soluble form of the receptor for vascular endothelial growth factor (VEGF), which is a pro-angiogenic cytokine produced by macrophages, T cells, tumor cells, and cytotrophoblast, and it is involved in angiogenesis and vasculogenesis; concurrently a decreased production of placental growth factor (PlGF) occurs; PlGF is also an angiogenic factor belonging to the VEGF family and which exists in four isoforms PlGF-1, PlGF-2, PlGF-3, and PlGF-4 [115–118]. These isoforms are central for the whole period of embryo development, taking part in vasculogenesis [115–118]. PlGF expression occurs in trophoblast, and during the first 30 weeks of a physiologic pregnancy, there is an increase of PlGF levels followed by a decrease. The expression of soluble Flt1 by the placenta is greatly increased in preeclampsia, and sFlt1 levels are markedly increased in the maternal circulation [119], where it antagonizes both VEGF and PlGF by binding them in the bloodstream, thus preventing interaction with their endogenous receptors [118, 119]. Several studies have shown these changes to occur early in the course of preeclamptic pregnancies [120], long before the onset of clinical disease, being also correlated with disease severity [121]. These early changes in angiogenic and anti-angiogenic levels may render them potentially useful as predictors/biomarkers of preeclampsia (see next section).

Preeclampsia is a heterogeneous disease, and other factors have been implicated or associated with the development of preeclampsia; for instance, endothelium-dependent relaxation is impaired in women with preeclampsia [122, 123] with reduced bioavailability of nitric oxide and prostacyclin ($PGI_2$). Furthermore, endothelin (ET-1) signaling has been shown to contribute to the enhanced vasopressor response typical of preeclampsia [116]. In preeclampsia an enhanced pressor response to angiotensin II (ANG II) is observed, antedating the onset of the clinical syndrome [124]; in addition, agonist angiotensin receptor autoantibodies have been detected in the circulation of women with preeclampsia, and these autoantibodies may be responsible for enhanced Ang II signaling [124, 125].

Oxidative stress, reflecting unbalanced prooxidant/antioxidant mechanisms, is probably the convergence point of several pathways leading to the development of preeclampsia; in fact, signs of increased production of oxidants, lipid peroxides, and isoprostanes with concurrently reduced levels of antioxidants are found in the preeclamptic placenta. Recent studies have suggested a relation between abnormal maternal inflammation, altered uteroplacental perfusion, and adverse pregnancy outcomes [126], mediated by altered maternal hemostasis and increased oxidative/nitrosative stress and vasoconstriction [126, 127].

The role of complement and its relation to hypertensive disorders of pregnancy have recently been reviewed [128]. An intact complement system is required for a successful pregnancy. Complement regulation in the placenta is finely tuned to prevent the maternal innate immune system from harming the fetus. Recent studies have shown that too little or too much complement at the wrong time in gestation can adversely affect the mother and the fetus. Excess activation leading to placental damage or fetal demise may be the result of inherited or acquired complement anomalies [128].

An additional intriguing hypothesis has been proposed, which exposes the role of fetal DNA, placental DNA, and trophoblast microparticles released into the maternal circulation as key factors in the development of the systemic inflammatory response of preeclampsia [129].

Finally, as already mentioned, the role of paternal factors has recently received attention: paternal age and thrombophilia, as well as single nucleotide polymorphisms in the genes encoding for PlGF and VEGF, have been associated with an increased risk of preeclampsia [92, 93].

### 44.5.3 Predictors/Biomarkers

A variety of biochemical, clinical, and demographic, or combinations thereof, markers have been proposed along the years (Table 44.7). A detailed coverage of the topic is beyond the scope of this chapter, and the interested reader may refer to several detailed reviews [116, 121, 135, 145]. Notably, few, if any, of the identified markers have withstood the test of time. Currently, PlGF levels and/or sFlt-1/PlGF ratio have been the object of clinical studies and seem to meet expectations. In a recent prospective, multicenter, observational study performed to derive and validate a ratio of serum sFlt-1 to PlGF that would be predictive of the absence or presence of preeclampsia in the short term in women with singleton pregnancies [131], it was shown that an sFlt-1:PlGF ratio of 38 or lower had a negative predictive value in the short term (i.e., no preeclampsia in the subsequent week) of 99.3% (95% confidence interval [CI], 97.9–99.9), with 80.0% sensitivity (95% CI, 51.9–95.7) and 78.3% specificity (95% CI, 74.6–81.7). The positive predictive value of a sFlt-1:PlGF ratio above 38 for a diagnosis of preeclampsia within 4 weeks was 36.7% (95% CI, 28.4–45.7), with 66.2% sensitivity (95% CI, 54.0–77.0) and 83.1% specificity (95% CI, 79.4–86.3). Another recent study of women with chronic kidney disease (CKD) or with established hypertension [132] has demonstrated that lower maternal levels of PlGF have greater accuracy (area under ROC curve 0.85) in the prediction of superimposed preeclampsia, compared to other biomarkers such as B-type natriuretic peptide (BNP), neutrophil gelatinase-associated lipocalin (NGAL), and serum relaxin concentrations.

Uric acid stands as a lone survivor among old markers for preeclampsia; it is inexpensive and easily measured, but its predictive power, when measured in the first trimester of pregnancy is low, with unsatisfactory sensitivity and specificity [133]; however, it has been shown in a prospective study of pregnant women referred

**Table 44.7** Predictors/biomarkers for preeclampsia

| Predictor/biomarker | Comment |
|---|---|
| PlGF, sFlt-1/PlGF ratio | Marker of angiogenic imbalance, acceptable sensitivity/specificity [130–132] potentially useful in women with chronic hypertension |
| Uric acid | Marker of purine metabolism and renal injury: Inexpensive, easy to measure, poor sensitivity/specificity early in pregnancy may be useful in prediction of preeclampsia in women who develop gestational hypertension [133, 134] |
| Podocyturia | Marker of renal involvement [135, 136] |
| Von Willebrand factor/ADAMTS13 ratio | Marker of coagulation imbalance [135] |
| Factor VII | Marker of hypercoagulability [135] |
| Pregnancy-associated plasma protein A (PAPP-A), PP13, ADAM-12, and matrix-metalloproteinases (MMPs) | Markers of compromised trophoblastic invasion/uterine artery remodeling [137] |
| Thrombomodulin | Marker of endothelial injury [135] |
| Asymmetric dimethylarginine (ADMA) | Endogenous inhibitor of the arginine–NO(nitric oxide) pathway [138] |
| Homocysteine and TIMP3 | Markers of epigenetic dysregulations [139] |
| Placental microRNAs expression | Markers of placental DNA methylation and histone modification [140, 141] |
| Angiotensin receptor1 autoantibodies | Induce vasoconstriction via stimulation of AT1 receptors on vascular smooth muscle cells [124, 125] |
| Marinobufagin (MBG) | Steroid compound that inhibits sodium transport and causes vasoconstriction, which can lead to hypertension [142] |
| Activin A | Member of the transforming growth factor (TGF)-β superfamily, pro-inflammatory. Increased concentration associated with preeclampsia [143] |
| Corin | Corin is a 1042-amino acid transmembrane protein which activates pro-ANP to active ANP (atrial natriuretic peptide); reduced levels predict preeclampsia [135] |
| Microparticles | Heterogeneous population of fragments (0.1–1.0 μm), released from the cell membranes of a variety of cells such as platelets, granulocytes, erythrocytes, endothelial cells during apoptosis or activation, which exert a variety of biological functions, may help predict early preeclampsia [129] |
| Uterine artery pulsatility index | It evaluates uteroplacental circulation [137, 144] |
| Multivariable model including lab, clinical, and demographic parameters | Potentially useful to predict early preeclampsia [145] |
| FMF (Fetal Medicine Foundation) algorithm | Potentially useful to predict early preeclampsia [145] |

for recent onset of hypertension that uric acid levels can predict development of preeclampsia, with receiver operating characteristic (ROC) analysis indicating that a 309 μmol/L cutoff predicted the development of preeclampsia (area under the curve, 0.955), with 87.7% sensitivity and 93.3% specificity [134].

A great number of prognostic models, with differing combinations of clinical, biochemical, and demographic parameters, have been developed over time. A recent review [145] identified 177 papers that reported the development of 263 prognostic models for 40 different outcomes. The most frequently predicted were preeclampsia ($n = 69$), preterm delivery ($n = 63$), mode of delivery ($n = 22$), gestational hypertension ($n = 11$), and small for gestational age infants ($n = 10$). The authors concluded that there is relatively little evidence about the models' performance, impact, and usefulness in clinical practice so that, at this point, clinical implementation cannot be recommended.

## 44.6 Clinical Features

Preeclampsia is a heterogeneous disease, at times difficult to diagnose, due to the wide range of clinical presentation and the lack of diagnostic tests with adequate sensitivity and specificity. As previously mentioned, cardinal features of this syndrome are new-onset hypertension (beyond the 20th gestation week) and proteinuria greater than 300 mg/24 h. Recent classifications (see specific subsection) may consider a diagnosis of preeclampsia in the absence of proteinuria, when signs of maternal organ or fetoplacental dysfunction are present [35, 39]. With the classical presentation, women typically develop preeclampsia after 20 weeks gestation and prior to 48 h postpartum [146]. However, in a significant proportion of women, the presentation may be atypical, lacking one of these cardinal signs, thus rendering the diagnosis difficult to confirm or exclude. It is estimated that approximately 20% of women with atypical preeclampsia present with minimal or no proteinuria [146]. On the other side, establishing a diagnosis of preeclampsia may be challenging in women with proteinuria antedating the pregnancy. The degree of proteinuria in preeclampsia may range from minimal to nephrotic; however, the amount of proteinuria does not seem to affect maternal or fetal outcomes [35, 147]. From a historical point of view, edema was considered as a component of the diagnostic triad of the syndrome; however, it is a too non-specific finding for diagnostic purposes, as a large proportion of pregnant women without preeclampsia present with edema by the end of their pregnancies.

## 44.7 Complications-Emergencies

### 44.7.1 Severe Preeclampsia

Preeclampsia encompasses a wide spectrum regarding clinical presentation, time of onset (ranging from the 20th week of gestation to 4–6 weeks postpartum), and severity. Current clinical guidelines support the differentiation between mild and severe forms, as the implication for medical and obstetrical management differs,

particularly at preterm gestations [29, 35, 39]. According to ACOG guidelines (with similar recommendations from other guidelines), features of severe preeclampsia include any of the following:

1. Hypertension: systolic >160 mmHg or diastolic >110 mmHg on two occasions at least 4 h apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time)
2. Thrombocytopenia (platelet count <100,000)
3. Impaired liver function (elevated blood levels of liver transaminases to twice the normal concentration), severe persistent right upper quadrant (RUQ), or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses or both
4. New development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dL or doubling of serum creatinine in the absence of other renal disease)
5. Pulmonary edema
6. New-onset cerebral or visual disturbances

The degree of proteinuria, conversely, is no longer considered among the diagnostic criteria for severe preeclampsia.

### 44.7.2 Eclampsia

In eclampsia, patients have the same findings as in preeclampsia, with the addition of generalized tonic-clonic seizures, not otherwise explained. It is a rare complication in developed countries. It is estimated to complicate approximately 0.1% of all pregnancies [148, 149], but in developing countries these figures may be higher (see epidemiology section).

Classically, headache, visual disturbance, or an altered level of consciousness are considered the symptoms of imminent eclampsia. However, there are no reliable clinical markers that predict eclampsia, and the presence of neurological symptoms and/or signs are seldom associated with seizures [148]. Seizures may occur antenatally, intrapartum, or postnatally, usually within 24 h of delivery but occasionally later. Hypertension and proteinuria may be absent prior to the seizure and not all women will have warning symptoms such as headache, visual disturbances, or epigastric pain [129].

The further from delivery that the seizure occurs, the more carefully should other diagnoses be pursued. In fact, cerebral venous thrombosis, in particular, may occur in the first few days of the puerperium. It must be borne in mind that eclampsia is not the commonest cause of seizures in pregnancy and that other conditions such as epilepsy and other medical problems must be considered carefully, particularly in the absence of typical features of severe preeclampsia.

### 44.7.3 HELLP Syndrome

The acronym HELLP stands for "Hemolysis Elevated Liver Enzymes Low Platelets" and summarizes the cardinal features of the syndrome [29, 35, 39]. It is a multiorgan disease characterized by thrombocytopenia, hemolytic anemia, and liver dysfunction believed to result from microvascular endothelial activation and cell injury; at times, one of the three may be lacking and elevation of blood pressure may not be universal. It is estimated to occur in 0.1–0.6% of all pregnancies and in 4–12% of patients with preeclampsia. HELLP syndrome, typically, presents between week 27 of gestation and delivery and immediately postpartum in 15–30% of cases. HELLP is a life-threatening complication of preeclampsia with maternal mortality rate ranging from 1 to 3% and a perinatal mortality rate approaching 35%, with most deaths occurring in class 1 HELLP (Table 44.8).

### 44.7.4 Cerebrovascular Emergencies

These will be treated briefly; the interested reader may find a detailed description in some excellent reviews [151].

Reversible Cerebral Vasoconstriction Syndrome (RCVS)

RCVS, sometimes referred to as postpartum angiopathy when presenting postpartum, carries significant morbidity and mortality [152–154]. It is an uncommon complication, and thus its exact incidence is unknown; however, the syndrome occurs more frequently in patients with preeclampsia associated with autoimmune disorders [153].

Characteristic features of RCVS are sudden onset of a severe thunderclap headache (often multiple thunderclap headaches) and segmental vasoconstriction of cerebral arteries documented on brain imaging. Approximately two-thirds of peripartum cases occur after delivery. RCVS can mimic eclampsia, as seizures are found in up to 28% of patients [153, 155–157].

Although the exact pathophysiological process resulting in RCVS is unknown, vasoactive agents, postpartum state, and physical and sexual activity have been implicated as inciting factors [156, 158]. The mainstay in diagnosis is MRI or CT angiography, which can appear normal in the first days of the process [159]. Transcranial Doppler can be used to follow the course of the disease [158]. RCVS is a rare disorder, with many symptoms overlapping with other disease processes. At present, there is no clear consensus on the treatment. The goal of therapy is to

**Table 44.8** Mississippi classification of HELLP syndrome [150]

| | Class 1 (severe) | Class 2 (moderate) | Class 3 (mild) |
|---|---|---|---|
| Platelets | ≤50,000/μL | 50,000–100,000/μL | 100,000–150,000/μL |
| AST or ALT | ≥70 IU/L | ≥70 IU/L | ≥40 IU/L |
| LDH | ≥600 IU/L | ≥600 IU/L | ≥600 IU/L |
| Incidence of bleeding | 13% | 8% | No increased risk |

relieve cerebral vasoconstriction in order to prevent potential neurological sequelae, and this should be accomplished in a tertiary, multidisciplinary care setting.

Posterior Reversible Encephalopathy Syndrome (PRES)

Preeclampsia, eclampsia, severe hypertension, and RCVS can all be complicated by PRES. Clinical features of PRES include the occurrence of headache, seizures, encephalopathy, and visual disturbances; neuroimaging may show signs of focal reversible vasogenic edema most commonly involving the parietal and occipital lobes, followed by the frontal and temporal lobes, which is best seen on MRI of the brain [160]. Symptoms develop suddenly and progress over 12–48 h [161]. Recommendations regarding the treatment of PRES are limited.

Potential inciting factors such as electrolyte disturbances, fluid overload, uremia, and sepsis may contribute to the development of PRES and should be recognized and treated. If medications, such as cytotoxic or immunosuppressive agents are thought to be causative, they should be decreased or stopped. As hypertension does occur in most patients with PRES, BP should be lowered (Table 44.9), often resulting in clinical improvement. Seizures are usually treated with phenytoin and other antiepileptic medications, unless the patient has eclampsia in which case, magnesium sulfate is recommended.

**Stroke** Stroke is uncommon in pregnancy, with reported incidence ranging from 4 to 34 per 100,000 deliveries, but accounts for more than 12% of all maternal deaths. The majority of strokes occur within 3 days of delivery in the postpartum period [162]. Risk factors include preeclampsia, eclampsia, chronic hypertension, migraines, cesarean delivery, sickle cell disease, systemic lupus erythematosus, thrombocytopenia, drug use (especially cocaine), African-American race, older age, greater parity, and multiple gestations [163]. It is of the utmost importance when a stroke occurs to establish as quickly as possible whether it is ischemic or hemorrhagic. Brain imaging with MRI or CT should be performed quickly. MRI is the preferred imaging modality in pregnancy, with potentially better sensitivity at identifying small infarcts, but CT is generally more readily available and performed first. Gadolinium-enhanced MRI contrast should be avoided unless absolutely necessary due to the lack of data regarding safety to the fetus.

### 44.7.5 Acute Kidney Injury (AKI)

AKI in pregnancy remains a cause of significant maternal-fetal mortality and morbidity. Its definition, and, hence, its incidence, varies widely in the literature, ranging from mild increase in serum creatinine (0.8 mg/dl) to dialysis requirement [164]. The incidence of AKI remains unacceptably high in developing countries. In a recent study from India [165], AKI occurred in approximately 1 in 50 pregnancies accounting for up to 20% of all cases of AKI, and it was associated with a high incidence of fetal/neonatal (39%) and maternal (20%) mortality. The specific factors responsible for the persistent high incidence of AKI in pregnancy in developing countries include septic abortions, usually performed in the absence of adequate

**Table 44.9** Pharmacologic treatment of hypertensive emergencies in pregnancy

| Drug | Dose range | Onset/peak/duration | Side effects | Comments |
|---|---|---|---|---|
| Labetalol | 20–80 mg, start with 20 mg IV bolus(2–3 min), then infusion 1–2 mg/min, max 300 mg | 5 min/30 min/2–6 h | Bradycardia, hypotension, fetal bradycardia | Caution in women with asthma and/or heart failure |
| Esmolol | IV bolus 500 μg/kg, then infusion 50 μg/kg/min, max 300 μg/kg/min | <1 min/5 min/15–30 min | 1st-degree heart block, maternal bradycardia, congestive heart failure, and bronchospasm; fetal bradycardia, persistent fetal β-blockade | First choice in case of aortic dissection or myocardial infarction |
| Hydralazine | Start with 5 mg IV; repeat 5–10 mg IV every 30 min, or 0.5–10 mg/h IV, to a maximum of 20 mg IV (or 30 mg IM) | 10–20 min/30 min /12 h | Headache, aggravation of angina, tachycardia, nausea, flushing, hypotension, lupus-like syndrome | First line drug for preeclampsia/eclampsia |
| Nifedipine | 5–10 mg capsule to be swallowed every 30 min | 5–10 min/30 min/4–6 h | Uncontrolled hypotension, stroke, myocardial infarction, flushing, headache, and reflex tachycardia | Caution: possible confusion with slow-release preparations. Possible interaction with MgSO4 |
| Diazoxide | 15–45 mg IV rapid bolus, to repeat every 5–10 min, max 300 mg | 3–5 min/5–10 min | Flushing, warmth along injection site, hypotension | Possibility of hypoglycemia |
| Urapidil | IV bolus 12.5–25 mg, then infusion 1–8 mg/h | 10 min/20–30 min/2–6 h | Nausea, hypotension, rash | Does not affect heart rate, cardiac output |

medical assistance, generally poor follow-up of pregnancy with limited or no screening of hypertensive complications of pregnancy, and relatively late referral of patients with these disorders [164, 165]. Conversely, the incidence of AKI in pregnancy has been steadily declining in developed countries, estimated to approximately 1:20,000 pregnancies [166], mainly explained by the near disappearance of postabortum sepsis after the legalization of abortion in most developed countries and the improved management of hypertensive complication.

AKI occurs more frequently in the late third trimester of pregnancy, and hypertensive complications (including HELLP) are currently its leading cause [164, 167]. Other causes include postabortum (first trimester) or puerperal sepsis, ante- or postpartum hemorrhage, intrauterine death, acute fatty liver of pregnancy, and thrombotic microangiopathy [164, 168, 169].

One of the most dreaded complications of AKI in pregnancy is represented by renal cortical necrosis (RCN), which consists of a patchy or diffuse ischemic destruction of the renal cortex. It occurs in 1.5–2% of all cases of AKI in developed countries and more frequently (3–7%) in developing countries [169, 170]. Obstetric complications such as septic abortions, placental abruption, and intravascular disseminated coagulation are the principal cause of RCN (50–70%) in developing countries [164, 170, 171]. The peculiar association of RCN and pregnancy remains to be explained.

## 44.8 Management of Preeclampsia/Eclampsia

Management of hypertension: a widespread consensus exists on the necessity of treating severe hypertension (≥160 mmHg systolic or 100–110 mmHg diastolic) [29, 35, 39, 64]. Treatment is directed at achieving a BP around 140 mmHg systolic and 85–90 mmHg. Overcorrection of BP is discouraged as it may lead to maternal-fetal hypoperfusion. Caution is advised when using short-acting nifedipine, as it may cause profound hypotension and may potentiate side effects of MgSO4 given for the prophylaxis or treatment of preeclampsia [29, 35, 39, 64]. Table 44.9 summarizes available drugs for the management of severe hypertension in pregnancy [29, 35, 39, 64, 97, 172–174].

**Timing of Delivery** Timing of delivery depends upon the severity of the maternal disease and the time of onset of the preeclampsia or gestational hypertension (Table 44.10). Immediate management refers to delivery planned within 48 h, usually after blood pressure stabilization and corticosteroid administration to accelerate fetal pulmonary maturity [29, 35, 39]. Expectant management refers to prolongation of the pregnancy beyond these 48 h with maternal and fetal monitoring; it is estimated that only 40% of women are eligible for expectant care [175]. There is general agreement that expectant care should be offered only in experienced centers equipped with neonatal intensive care units where neonates can be cared for at the woman's current gestational age [29, 35, 39]. Indications for urgent delivery are summarized

**Table 44.10** Timing of delivery and onset of preeclampsia [39]

| Gestation at onset | Previable < 23 weeks | 24–31 weeks | 32–36 weeks | 37 + 0 onward |
|---|---|---|---|---|
| Delivery plan | Consult with tertiary institution, likely to need termination of pregnancy or extreme preterm delivery. High-risk patient | Consult and transfer to tertiary institution, likely to need preterm delivery. Aim to prolong pregnancy where possible | Aim to prolong pregnancy where possible, deliver in institution with appropriate neonatal care | Plan delivery on best day in best way |

**Table 44.11** Indications for delivery in women with preeclampsia or gestational hypertension

| Maternal | Fetal |
|---|---|
| Gestational age ≥37 weeks | Severe fetal growth restriction |
| Deteriorating liver function | Non-reassuring fetal status |
| Persistent epigastric pain, nausea or vomiting with abnormal liver function tests | Placental abruption |
| Deteriorating renal function | Persistent oligohydramnios |
| Inability to control hypertension | Reversed end-diastolic flow on umbilical artery Doppler studies |
| Decreasing platelet count | Recurrent variable or late deceleration during stress test |
| Intravascular hemolysis | Fetal death |
| Persistent neurologic symptoms | |
| Pulmonary edema | |
| Eclampsia | |
| Progressive labor or rupture of membranes | |

in Table 44.11 [29, 35, 39]. Labor induction is indicated at 37 weeks of gestation or beyond, in order to reduce poor maternal outcome [175–177]. Regarding route of delivery, vaginal delivery can often be accomplished; however, the rate of cesarean sections increases inversely with gestational age [175–177].

Eclampsia: Eclampsia is defined as the occurrence of new-onset grand mal seizures in a woman with preeclampsia. Clinical symptoms predictive of eclampsia include persistent frontal or occipital headache, altered mental status, photophobia, blurred vision, and epigastric or right upper quadrant abdominal pain. The mainstay of treatment of eclampsia is magnesium sulfate, which has proved superior to other anticonvulsant agents such as diazepam or phenytoin [29, 35, 39]. For the treatment or prophylaxis of preeclamptic seizures it is given as a 4–6 g loading dose (15–20 min), followed by a 1–2 g/h maintenance dose for at least 24–48 h. Monitoring of blood magnesium levels is advised, as well as caution in concurrent use of calcium channel blockers. Magnesium sulfate may be administered in women with preeclampsia for prophylaxis; however, its widespread use for this indication remains controversial.

Finally, a recent small study of women with early preeclampsia has shown a beneficial effect of dextran-sulfate based apheresis, which can selectively remove sFlt-1 from the circulation [178].

## 44.9 Prevention of Preeclampsia

Strategies aimed at preventing preeclampsia have been studied extensively in the last two decades; however, no single intervention has proved unequivocally effective.

Antiplatelet agents, such as low-dose aspirin (100 mg or less, daily), have been studied extensively [29, 179–181] and a benefit for the prevention of preeclampsia clearly established, especially when aspirin is started before 16 weeks of gestation [29, 35, 39], although dependent on the baseline population risk: in fact, according to estimates of the PARIS group [182], the number needed to treat (NNT) to prevent a single event ranges from an average of 56 for a baseline event rate of 18% to 500 for a baseline event rate of 2%. Hence, treatment is best reserved for high-risk women such as diabetics, women with chronic hypertension, pre-existing renal disease, or with a previous history of preeclampsia. Calcium supplementation is recommended in women with low dietary intake (less than 600 mg/day), which is generally not the case in developed countries; a study from the NIH [35, 183], the Calcium for Preeclampsia Prevention (CPEP), concluded that calcium supplementation did not provide any benefit in terms of incidence of preeclampsia, blood pressure, or perinatal outcome.

A recent systematic review [184] has shown vitamin D supplementation to be safe during pregnancy and to be associated with increased 25 (OH) vitamin D levels and increased birth weight and length.

Statins (3-hydroxy-3 methylglutaryl coenzyme-A reductase inhibitors) are the most commonly prescribed cholesterol-lowering medications. Owing to pathophysiologic similarities between cardiovascular disease and preeclampsia, an increasing interest has arisen in studying this class of medications during pregnancy to prevent and/or treat preeclampsia. Animal studies have shown this class of agents to be able to inhibit cytokine-induced release of sFlt-1 [185, 186]. However most statins are lipophilic and cross the fetal membranes with potential adverse effects to the fetus [186]. Pravastatin is the only agent of this class that does not enter the embryonic compartment. In humans a small, pilot, randomized controlled trial investigating pravastatin use for the prevention of preeclampsia has been conducted [187]. According to the authors, the study provides preliminary safety and pharmacokinetic data regarding the use of pravastatin for preventing preeclampsia in high-risk pregnant women thus establishing the basis for a possible, larger clinical trial.

Finally, based on current evidence the following interventions are not recommended for the prevention of preeclampsia: dietary salt restriction during pregnancy, calorie restriction for overweight women, vitamins C and E, zinc, or thiazides [35]. Periconceptional and ongoing use of folate may be useful, but evidence is insufficient for recommendation [35].

## 44.10 Long-Term Sequelae of Preeclampsia

In most women affected by preeclampsia, even those with severe early-onset disease, clinical features are resolved within a few days after delivery of the baby and placenta. Despite the short-term clinical recovery, recent evidence consistently

shows that long-term cardiovascular health in women with a history of preeclampsia may be compromised [188–190]. Preeclampsia is a disease of the endothelium, and one is tempted to speculate that endothelial dysfunction may persist after resolution of clinical manifestations. A recent study [191], however, with a 10-year follow-up, has shown that flow-mediated vasodilatation (FMD) of the brachial artery and carotid intima-media thickness (IMT) was not altered in women with a previous pregnancy complicated by preeclampsia compared to a control group with normotensive pregnancies. Nonetheless, a subclinical endothelial dysfunction was hypothesized, as circulating levels of markers of early endothelial dysfunction, such as homoarginine and sFlt1, were slightly altered in the preeclampsia group.

Limited studies have shown that the hazard rate of developing a metabolic disorder such as type 2 diabetes mellitus was 3.12, 3.53, and 3.68 after gestational hypertension, preeclampsia, and eclampsia, respectively. Five years after a pregnancy complicated by the (HELLP) syndrome, a 4% increase in new-onset diabetes [192] was observed. Thus, the risk of future type 2 diabetes appears to be related to the severity of the hypertensive disorder in pregnancy. With regard to hypertension, a recent meta-analysis showed that women with history of preeclampsia were three times more likely to develop chronic hypertension compared to women who had normotensive pregnancies (pooled relative risk 3.1(95% C.I.) 2.5–3.9)] [188, 189]. Recurrent preeclampsia entails a sixfold higher risk of developing hypertension [190]. Such an increased risk is more evident within the first 5 years after pregnancy, although the absolute excess risk persists and may grow along the years, as shown by the US Nurses' Health Study II, in which, four decades after first pregnancy, 146 excess cases of hypertension were recorded every 1000 women who had preeclampsia in their first pregnancy.

It has been shown that women who will later develop preeclampsia tend to have higher baseline BP with respect to women who will have normotensive pregnancies [188], thus leading to speculate that preeclampsia may be a marker of a pre-existing predisposition to cardiovascular disease, rather than a causal factor in itself, an issue not fully resolved yet [188]. It must be borne in mind that most studies rely on diagnostic criteria based on the older classifications, and it would be interesting to ascertain whether the recently proposed classifications by ACOG and ISSHP will carry the same association with cardiovascular risk as the older definitions [29, 35, 39, 188].

## References

1. Poppas A, Shroff SG, Korcarz CE et al (1997) Serial assessment of the cardiovascular system in normal pregnancy: role of arterial compliance and pulsatile arterial load. Circulation 95:2407–2415
2. Chapman AB, Abraham WT, Zamudio S et al (1998) Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. Kidney Int 54:2056–2063
3. Sanghavi M, Rutherford JB (2014) Cardiovascular physiology of pregnancy. Circulation 130:1003–1008
4. Maynard SE, Karumanchi SA, Thadhani R (2015) Hypertension and kidney disease in pregnancy. In: Skorecki K, Chertow GM, Marsden PA, Maarten WT, ASL Y (eds) Brenner and Rector's the kidney, 10th edn. Elsevier, London, pp 1792–1824

5. Odutayo A, Hladunevitch M (2012) Obsteric nephrology: renal hemodynamic and metabolic physiology in normal pregnancy. Clin J Am Soc Nephrol 7:2073–2080
6. Clapp JF 3rd, Capeless E (1997) Cardiovascular function before, during, and after the first and subsequent pregnancies. Am J Cardiol 80:1469–1473
7. Mahendru AA, Everett TR, Wilkinson IB et al (2014) A longitudinal study of maternal cardiovascular function from preconception to the postpartum period. J Hypertens 32:849–856
8. Greenwood JP, Scott EM, Stoker JB et al (2001) Sympathetic neural mechanisms in normal and hypertensive pregnancy in humans. Circulation 104:2200–2220
9. Elsheikh A, Creatsas G, Mastorakos G et al (2001) The renin-aldosterone system during normal and hypertensive pregnancy. Arch Gynecol Obstet 264:182–185
10. Khraibi AA (2002) Renal interstitial hydrostatic pressure and sodium excretion in hypertension and pregnancy. J Hypertens Suppl 20:S21–S27
11. Davison JM (1997) Edema in pregnancy. Kidney Int Suppl 59:S90–S96
12. Gant NF, Chand S, Whalley PJ et al (1974) The nature of pressor responsiveness to angiotensin II in human pregnancy. Obstet Gynecol 43:854
13. McGuane JT, Debrah JE, Debrah DO et al (2009) Role of relaxin in maternal systemic and renal vascular adaptations during gestation. Ann N Y Acad Sci 1160:304–312
14. Sherwood OD (2005) An "old hand's" perspective of Relaxin 2004's place along the relaxin trail. Ann N Y Acad Sci 1041:29–35
15. Ervasti M, Kotisaari S, Heinonen S, Punnonen K (2008) Elevated serum erythropoietin concentration is associated with coordinated changes in red blood cell and reticulocyte indices of pregnant women at term. Scand J Clin Lab Invest 68:160–165
16. Castro LC, Hobel CJ, Gornbein J (1994) Plasma levels of atrial natriuretic peptide in normal and hypertensive pregnancies: a meta-analysis. Am J Obstet Gynecol 171:1642–1651
17. Robson SC, Hunter S, Moore M, Dunlop W (1987) Haemodynamic changes during the puerperium: a Doppler and M-mode echocardiographic study. Br J Obstet Gynaecol 94:1028–1039
18. Brunton PJ, Arunachalam S, Russel JA (2008) Control of neurohypophysial hormone secretion, blood osmolality and volume in pregnancy. J Physiol Pharmacol 59(suppl 8):27–45
19. Oelkers W (2002) Antimineralocorticoid activity of a novel oral contraceptive containing drospirenone, a unique progestogen resembling natural progesterone. Eur J Contracept Reprod Health Care 7(suppl 3):19–26
20. Lumbers ER, Pringle KG (2014) Roles of the circulating renin-angiotensin aldosterone system in human pregnancy. Am J Physiol Regul Integr Comp Physiol 306:R91–R101
21. Baker PN, Broughton Pipkin F, Symonds EM (1990) Platelet angiotensin II binding and plasma renin concentration, plasma renin substrate and plasma angiotensin II in human pregnancy. Clin Sci (Lond) 79:403–408
22. Dunlop W (1981) Serial changes in renal haemodynamics during normal human pregnancy. Br J Obstet Gynaecol 88:1–9
23. Bader RA, Bader ME, Rose DF, Braunwald E (1955) Hemodynamics at rest and during exercise in normal pregnancy as studies by cardiac catheterization. J Clin Invest 34:1524–1536
24. Robson SC, Hunter S, Boys RJ, Dunlop W (1989) Serial study of factors influencing changes in cardiac output during human pregnancy. Am J Phys 256(pt 2):H1060–H1065
25. Hunter S, Robson SC (1992) Adaptation of the maternal heart in pregnancy. Br Heart J 68:540–543
26. Canada H (2004) Special report on maternal mortality and severe morbidity in Canada – enhanced surveillance: the path to prevention. Minister of Public Works and Government Services Canada, Ottawa
27. Centre for Maternal and Child Enquiries (CMACE) (2011) Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–08. The eighth report on confidential enquiries into maternal deaths in the United Kingdom. BJOG 118(Suppl 1):1–203
28. Tranquilli AL, Dekker G, Magee L et al (2014) The classification diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. Pregnancy Hypertens 4:97–104
29. American College of Obstetricians and Gynecologists: Task Force on Hypertension in Pregnancy (2013) Hypertension in pregnancy. Report of the American College of

Obstetricians and Gynecologists' task force on hypertension in pregnancy. Obstet Gynecol 122:1122–1131
30. Von Dadelszen P, Magee LA, Roberts JM (2013) Subclassification of pre-eclampsia. Hypertens Pregnancy 22:143–148
31. Sibai BM (2011) Evaluation and management of severe preeclampsia before 34 weeks' gestation. Am J Obstet Gynecol 205:191–198
32. Chancellor J, Thorp JM Jr (2008) Blood pressure measurement in pregnancy. BJOG 115:1076–1077
33. Pickering TG, Hall JE, Appel LJ et al (2005) Recommendations for blood pressure measurement in humans and experimental animals: a statement for professionals from the Subcommittee of Professional and Public education of the American Heart Association Council on high blood pressure research. Hypertension 45:142–161
34. Cote AM, Firoz T, Mattman A et al (2008) The 24-hour urine collection: gold standard or historical practice? Am J Obstet Gynecol 199:625–626
35. Magee LE, Pels A, Helewa MD et al (2015) The hypertensive disorders of pregnancy (29.3). Best Pract Research Clin Oobstet Gynecol 29:643–657
36. Poon LC, Kametas N, Strobl I et al (2008) Inter-arm blood pressure differences in pregnant women. BJOG 115:1122–1130
37. Shennan A, Gupta M, Halligan A et al (1996) Lack of reproducibility in pregnancy of Korotkoff phase IV as measured by mercury sphygmomanometry. Lancet 347:139–142
38. Reinders LW, Mos CN, Thornton C et al (2006) Time poor: rushing decreases the accuracy and reliability of blood pressure measurement technique in pregnancy. Hypertens Pregnancy 25:81–91
39. Lowe SA, Bowyer, Lust K et al (2014) The SOMANZ guideline for the management of hypertensive disorders of pregnancy. http://www.somanz.org/
40. Lo C, Taylor RS, Gamble G et al (2002) Use of automated home blood pressure monitoring in pregnancy: is it safe? [see comment]. Am J Obstet Gynecol 187:1321–1328
41. Stergiou GS, Giovas PP, Gkinos CP, Tzamouranis DG (2008) Validation of the a&D UM-101 professional hybrid device for office blood pressure measurement according to the international protocol. Blood Press Monit 13:37–42
42. NCGCNational Clinical Guideline Center, BHS (2011) Clinical management of primary hypertension in adults. NICE Clinical Guideline 127, London
43. Head GA, McGrath BP, Mihailidou AS et al (2012) Ambulatory blood pressure monitoring in Australia: 2011 consensus position statement. J Hypertens 30:253–266
44. Bellomo G, Narducci PL, Rondoni F et al (1999) Prognostic value of 24-hour blood pressure in pregnancy. JAMA 282:1447–1452
45. Brown MA, Mangos G, Davis G, Homer C (2005) The natural history of white coat hypertension during pregnancy. BJOG 112:601–606
46. Brown MA, Davis GK, McHugh L (2012) The prevalence and clinical significance of nocturnal hypertension in pregnancy. J Hypertension 19(8):1437–1444
47. Magee LA, Ramsay G, von Dadelszen P (2008) What is the role of out-of-office BP measurement in hypertensive pregnancy? Hypertens Pregnancy 27:95–101
48. Magee LA, von Dadelszen P, Chan S et al (2007) The control of hypertension in pregnancy study pilot trial. BJOG 114:770.e13–770.e20
49. Pickering TJ (1991) Ambulatory monitoring and blood pressure variability. Science Press Ltd, London, England
50. Brown MA, Roberts LM, Mackenzie C et al (2011) A prospective randomized study of automated versus mercury blood pressure recordings in hypertensive pregnancy (PRAM study). Hypertens Pregnancy 31:107–119
51. Brown MA, Robinson A, Bowyer L, Buddle ML et al (1998) Ambulatory blood pressure monitoring in pregnancy: what is normal? Am J Obstet Gynecol 178:836–842
52. Martin JN Jr, May WL, Magann EF et al (1999) Early risk assessment of severe preeclampsia: admission battery of symptoms and laboratory tests to predict likelihood of subsequent significant maternal morbidity. Am J Obstet Gynecol 180:1407–1414

53. Lee-Ann Hawkins T, Brown MA, Mangos GJ, Davis GK (2012) Transient gestational hypertension: not always a benign event. Pregnancy Hypertens 2:22–27
54. Reinders A, Cuckson AC, Lee JT, Shennan AH (2005) An accurate automated blood pressure device for use in pregnancy and preeclampsia: the microlife 3BTO-A. BJOG 112:915–920
55. Villar J, Say L, Shennan A et al (2004) Methodological and technical issues related to the diagnosis, screening, prevention, and treatment of pre-eclampsia and eclampsia. Int J Gynaecol Obstet 85(Suppl 1):S28–S41
56. Rey E, Morin F, Boudreault J et al (2009) Blood pressure assessments in different subtypes of hypertensive pregnant women: office versus home patient-or nurse measured blood pressure. Hypertens Pregnancy 28:168–177
57. Hermida RC, Ayala DE, Iglesias M (2003) Circadian rhythm of blood pressure challenges office values as the "gold standard" in the diagnosis of gestational hypertension. Chronobiol Int 20:135–156
58. Sibai BM (2002) Chronic hypertension in pregnancy. Obstet Gynecol 100:369–377
59. Vanek M, Sheiner E, Levy A, Mazor M (2004) Chronic hypertension and the risk for adverse pregnancy outcome after superimposed preeclampsia. Int J Gynecol Obstet 86:7–11
60. Lawler J, Osman M, Shelton JA, Yeh J (2007) Population based analysis of hypertensive disorders of pregnancy. Hypertens Pregnancy 26:67–76
61. Hutcheon JA, Lisonkova S, Joseph KS (2011) Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol 25:391–403
62. Roberts CL, Algert CS, Morris JM et al (2005) Hypertensive disorders in pregnancy: a population-based study. Med J Aust 182:332–335
63. Ahmad AS, Samuelsen SO (2012) Hypertensive disorders in pregnancy and fetal death at different gestational lengths: a population study of 2 121 371 pregnancies. BJOG 119: 1521–1528
64. Seely E, Ecker J (2011) Chronic hypertension in pregnancy. N Engl J Med 365:439–446
65. Rey E, Couturier A (1994) The prognosis of pregnancy in women with chronic hypertension. Am J Obstet Gynecol 171:410–416
66. McCowan LM, Buist RG, North RA, Gamble G (1996) Perinatal morbidity in chronic hypertension. Br J Obstet Gynaecol 103:123–129
67. Chappell LC, Enye S, Seed P et al (2008) Adverse perinatal outcomes and risk factors for preeclampsia in women with chronic hypertension. Hypertension 51:1002–1009
68. Catov JM, Nohr EA, Olsen J, Ness RB (2008) Chronic hypertension related to risk for preterm and term small for gestational age births. Obstet Gynecol 112:290–296
69. Bateman BT, Huybrechts KF, Fischer MA et al (2015) Chrobic hypertension in pregnancy and the risk of congenital malformations: a cohort study. Am J Obstet Gynecol 212:e1–e14
70. Xie RH, Guo Y, Krewski D et al (2013) Trends in using beta-blockers and methyldopa for hypertensive disorders during pregnancy in a Canadian population. Eur J Obstet Gynecol Reprod Biol 171:281–285
71. Caton AR, Bell EM, Druschel CM et al (2009) Antihypertensive medication use during pregnancy and the risk of cardiovascular malformations. Hypertension 54:63–70
72. Yakoob MY, Bateman BT, Ho E et al (2013) The risk of congenital malformations associated with exposure to beta-blockers early in pregnancy: a meta-analysis. Hypertension 62:375–381
73. Finer LB, Henshaw SK (2006) Disparities in unintended pregnancy in the United States, 1994 and 2001. Perspect Sex Reprod Health 38:90–96
74. Magee LA, von Dadelszen P, Rey E et al (2015) Less-tight versus tight control of hypertension in pregnancy. N Engl J Med 372:407–417
75. Publications Committee SMFM (2015) SMFM statement: benefit of antihypertensive therapy for mild to moderate hypertension during pregnancy remains uncertain. Am J Obstet Gynecol 213:3–4
76. Tabacova S, Kimmel CA, Wall K, Hansen D (2003) Atenolol development toxicity: animal-to-human comparisons. Birth Defects Res A Clin Mol Teratol 67:181–192
77. Collins R, Yusuf S, Peto R (1985) Overview of randomised trials of diuretics in pregnancy. Br Med J (Clin Res Ed) 290:17–23

78. Brent RL, Beckman DA (1991) Angiotensin converting enzyme inhibitors, an embryopathic class of drugs with unique properties: information for clinical teratology counselors. Teratology 43:543–546
79. Gersak K, Cvijic M, Cerar LK (2009) Angiotensin II receptor blockers in pregnancy: a report of five cases. Reprod Toxicol 28:109–112
80. Serreau R, Luton D, Macher MA et al (2005) Developmental toxicity of the angiotensin II type 1 receptor antagonists during human pregnancy: a report of 10 cases. BJOG 112: 710–712
81. Pergament E, Schechtman AS, Roth K (1996) Calcium channel blockers and pregnancy. fetal-exposure.org 5(1)
82. Duley LMS, Jones L (2013) Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database Syst Rev 7:CD001449. doi:10.1002/14651858.CD001449.pub3
83. Hutcheon JA, Lisonkova S, Joseph KS (2011) Epidemiology of preeclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynecol 25:391–403
84. Duley L (2009) The global impact of pre-eclampsia and eclampsia. Semin Perinatol 33:130–137
85. Fong A, Chau CT, Pan D, Ogunyemi DA (2013) Clinical morbidities trends and demographics of eclampsia: a population –based study. Am J Obstet Gynecol 209:e1–e7
86. Abalos E, Cuesta C, Grosso AL, Chou D, Say L (2013) Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol 170:1–7
87. van Oostwaard MF, Langenfeld J, Schuit E et al (2015) Recurrence of hypertensive disorders of pregnancy. Am J Obstet Gynecol 212:e1–e17
88. Hlimi T (2015) Association of anemia, pre-eclampsia and eclampsia with seasonality: a realistic systematic review. Health Place 31:180–192
89. Melo B, Amorim M, Katz L et al (2014) Hypertension, pregnancy and weather: is seasonality involved? Rev Assoc Med Braz 60:105–110
90. Hernandez-Diaz S, Toh S, Cnattingius S (2009) Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. BMJ 338:b2255
91. Mogren I, Hogberg U, Winkvist A, Stenlund H (1999) Familial occurrence of pre-eclampsia. Epidemiology 10:518–522
92. Robillard PY, Hulsey TC, Alexander GR et al (1993) Paternity patterns and risk of preeclampsia in the last pregnancy in multiparae. J Reprod Immunol 24:1–12
93. Dekker G, Robillard PY, Roberts C (2011) The etiology of preeclampsia: the role of the father. J Reprod Immunol 89:126–132
94. Hartikainen AL, Aliharmi RH, Rantakillo PT (1998) A cohort study of epidemiologic associations and outcomes of pregnancies with hypertensive disorders. Hypertens Pregnancy 17:31–41
95. Ros HS, Cnattingius S, Lipworth L (1998) Comparison of risk factors for pre-eclampsia and gestational hypertension in a population-based cohort study. Am J Epidemiol 147:1062–1070
96. Katsi V, Felekos I, Siristatidis C et al (2015) Preeclampsia: what does the father have to do with it? Curr Hypertens Rep 17:576–577
97. Mathiesen ER, Ringholm L, Feldt-Rasmussen B et al (2012) Obstetric nephrology: pregnancy in women with diabetic nephropathy--the role of antihypertensive treatment. Clin J Am Soc Nephrol 7:2081–2088
98. Mission JF, Marshall NE, Caughey AB (2015) Pregnancy risks associated with obesity. Obstet Gynecol Clin N Am 42:335–353
99. Duckitt K, Harrington D (2005) Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ 330:565
100. Carr DB, Epplein M, Johnson CO et al (2005) A sister's risk: family history as a predictor of preeclampsia. Am J Obstet Gynecol 193:965–972
101. Eskenazi B, Fenster L, Sidney S (1991) A multivariate analysis of risk factors for preeclampsia. JAMA 266:237–241
102. Mostello D, Catlin TK, Roman L et al (2002) Preeclampsia in the parous woman: who is at risk? Am J Obstet Gynecol 187:425–429

103. Zetterstrom K, Lindeberg SN, Haglund B et al (2005) Maternal complications in women with chronic hypertension: a population-based cohort study. Acta Obstet Gynecol Scand 84:419–424
104. Palmer SK, Moore LG, Young D et al (1999) Altered blood pressure course during normal pregnancy and increased preeclampsia at high altitude (3100 meters) in Colorado. Am J Obstet Gynecol 180:1161–1168
105. Krotz S, Fajardo J, Ghandi S et al (2002) Hypertensive disease in twin pregnancies: a review. Twin Res 5:8–14
106. Ness RB, Markovic N, Bass D et al (2003) Family history of hypertension, heart disease, and stroke among women who develop hypertension in pregnancy. Obstet Gynecol 102:1366–1371
107. Clowse MEB, Jamison M, Myers E et al (2008) A national study of the complications of lupus in pregnancy. Am J Obstet Gynecol 199(2):121–127
108. Weiss JL, Malone FD, Emig D et al (2004) Obesity, obstetric complications and cesarean delivery rate—a population-based screening study. Am J Obstet Gynecol 90:1091–1097
109. DeVader SR, Neeley HL, Myles TD et al (2007) Evaluation of gestational weight gain guidelines for women with normal prepregnancy body mass index. Obstet Gynecol 110:745–751
110. Michikawa T, Morokuma S, Fukushima K et al (2015) A register-based study of the association between air pollutants and hypertensive disorders of pregnancy in the Japanese population. Environ Res 142:644–650
111. Strevens H, Wide-Svensson D, Hansen A et al (2003) Glomerular endotheliosis in normal pregnancy and preeclampsia. BJOG 110:831–836
112. Romero R, Dey SK, Fisher SJ (2014) Preterm labor: one syndrome, many causes. Science 345:760–765
113. Fisher SJ (2015) Why is placentation abnormal in preeclampsia? Am J Obstet Gynecol 213(suppl 4):s115–s122
114. Shah D, Khalil RA (2015) Bioactive factors in uteroplacental and systemic circulation link placental ischemia to generalized vascular dysfunction in hypertensive pregnancy and preeclampsia. Biochem Pharmacol 95:211–226
115. Levine RJ, Lam C, Qian C et al (2006) Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. N Engl J Med 355:992–1005
116. Goulopoulou S, Davidge ST (2015) Molecular mechanisms of maternal vascular dysfunction in preeclampsia. Trends Mol Med 21:88–97
117. Young BC, Levine RJ, Karumanchi AS (2010) Pathogenesis of preeclampsia. Annu Rev Pathol Mech Dis 5:173–192
118. Agarwal I, Karumanchi A (2011) Preeclampsia and the anti-angiogenic state. Pregnancy Hypertens 1:17–21
119. Kendall RL, Thomas KA (1993) Inhibition of vascular endothelial cell growth factor activity by an endogenously encoded soluble receptor. Proc Natl Acad Sci U S A 90:10705–10709
120. George EM, Palei AC, Granger JP et al (2012) Endothelin as a final common pathway in the pathophysiology of preeclampsia: therapeutic implications. Curr Opin Nephrol Hypertens 21:157–162
121. Naljayan MV, Karumanchi AS (2013) New developments in the pathogenesis of preeclampsia. Adv Chronic Kidney Dis 20:265–270
122. Knock GA, Poston L (1996) Bradykinin-mediated relaxation of isolated maternal resistance arteries in normal pregnancy and preeclampsia. Am J Obstet Gynecol 175:1668–1674
123. Kenny LC, Baker PN, Kendall DA et al (2002) Differential mechanisms of endothelium-dependent vasodilator responses in human myometrial small arteries in normal pregnancy and pre-eclampsia. Clin Sci (Lond) 103:67–73
124. Bobst SM, Day MC, Gilstrap LC 3d et al (2005) Maternal autoantibodies from preeclamptic patients activate angiotensin receptors on human mesangial cells and induce interleukin-6 and plasminogen activator inhibitor-1 secretion. Am J Hypertens 18: 330–336
125. Herse F, LaMarca B (2013) Angiotensin II type 1 receptor autoantibody (AT1-AA)-mediated pregnancy hypertension. Am J Reprod Immunol 69:413–418

126. Cotechini T, Graham CH (2015) Aberrant maternal inflammation as a cause of pregnancy complications: a potential therapeutic target? Placenta 36:960–966
127. Borzychowski AM, Sargent IL, Redman CW (2006) Inflammation and pre-eclampsia. Semin Fetal Neonatal Med 11:309–316
128. Regal JF, Gilbert JS, Burwick RM (2015) The complement system and adverse pregnancy outcomes. Mol Immunol 67:56–70
129. Burger D, Shock S, Thompson CS et al (2013) Microparticles: biomarkers and beyond. Clin Sci (Lond) 124:423–441
130. Schoofs K, Grittner U, Engels T et al (2014) The importance of repeated measurements of the sFlt-1/PlGF ratio for the prediction of preeclampsia and intrauterine growth restriction. J Perinat Med 42:61–68
131. Zeisler H, Llurba E, Chantraine F et al (2016) Predictive value of the sFlt-1:PlGF in women with suspected preeclampsia. N Engl J Med 374:13–22
132. Bramham K, Seed PT, Lightstone L et al (2016) Diagnostic and predictive biomarkers for pre-eclampsia in patients with established hypertension and chronic kidney disease. Kidney Int 89:874–885
133. Bellomo G (2012) Serum uric acid and pre-eclampsia: an update. Exp Rev Cardiovasc Ther 10:701–705
134. Bellomo G, Venanzi S, Saronio P et al (2011) Prognostic significance of serum uric acid in women with gestational hypertension. Hypertension 58:704–708
135. Jardim LL, Rios DR, Perucci LO et al (2015) Is the imbalance between pro-angiogenic and anti-angiogenic factors associated with preeclampsia? Clin Chim Acta 447:34–38
136. Garovic VD (2014) The role of the podocyte in preeclampsia. Clin J Am Soc Nephrol 9:1337–1340
137. Spencer K, Cowans NJ, Chefetz I et al (2007) First-trimester maternal serum PP-13, PAPP-A and second-trimester uterine artery Doppler pulsatility index as markers of preeclampsia. Ultrasound Obstet Gynecol 29:128–134
138. Alpoim PN, Godoi LC, Freitas LG et al (2013) Assessment of L-arginine asymmetric 1 dimethyl (ADMA) in early-onset and late-onset (severe) preeclampsia. Nitric Oxide 1(33):81–88
139. Pozharny Y, Lambertini L, Clunie G et al (2010) Epigenetics in women's health care. Mt Sinai J Med 77(2):225–235
140. Pineles BL, Romero R, Montenegro D et al (2007) Distinct subsets of microRNAs are expressed differentially in the human placentas of patients with preeclampsia. Am J Obstet Gynecol 196:261.e1–261.e6
141. Pillar N, Yoffe L, Hod M, Shomron N (2015) The possible involvement of microRNAs in pre-eclampsia and gestational diabetes mellitus. Best Pract Res Clin Obstet Gynaecol 29:176–182
142. Uddin MN, Allen SR, Jones RO et al (2012) Pathogenesis of pre-eclampsia: marinobufagenin and angiogenic imbalance as biomarkers of the syndrome. Transl Res 160:99–113
143. Williamson R, O'Keeffe GW, Kenny LC (2015) Activin signaling and preeclampsia: ff rom genetic risk to pre-symptomatic biomarker. Cytokine 71:360–365
144. Barati M, Shahbazian N, Ahmadi L et al (2014) Diagnostic evaluation of uterine artery Doppler sonography for the prediction of adverse pregnancy outcomes. J Res Med Sci 19:515–519
145. Kleinrouweler CE, Cheong-See FM, Collins GS et al (2016) Prognostic models in obstetrics: available, but far from applicable. Am J Obstet Gynecol 214:79–90
146. Sibai BM, Stella CL (2008) Diagnosis and management of atypical preeclampsia-eclampsia. Am J Obstet Gynecol 200:481e1–481.e7
147. Sibai BM (2003) Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol 102:181–192
148. Douglas KA, Redman CW (1994) Eclampsia in the United Kingdom. BMJ 309:1395–1400
149. Knight M, UKOSS (2007) Eclampsia in the United Kingdom 2005. BJOG 114:1072–1078
150. Martin JN Jr, Rose CH, Briery CM (2006) Understanding and managing HELLP syndrome: the integral role of aggressive glucocorticoids for mother and child. Am J Obstet Gynecol 195:914–934

151. Shainker SA, Edlow JA, O'Brien K (2015) Cerebrovascular emergency in pregnancy. Best Pract Res Clin Obstet Gynaecol 29:721–731
152. Singhal A (2004) Postpartum angiopathy with reversible posterior leukoencephalopathy. Arch Neurol 61:411–416
153. Singhal AB, Kimberly WT, Schaefer PW et al (2009) Case 8-2009: a 36-year-old woman with headache, hypertension, and seizure 2 weeks post partum. N Engl J Med 360:1126–1137
154. Singhal AB, Hajj-Ali RA, Topcuoglo MA et al (2011) Reversible cerebral vasoconstriction syndromes: analysis of 139 cases. Arch Neurol 68:1005–1012
155. Fugate JE, Ameriso SF, Ortiz G et al (2012) Variable presentations of postpartum angiopathy. Stroke 43:670–676
156. Ursell MR, Marras CL, Farb R et al (1998) Recurrent intracranial hemorrhage due to postpartum cerebral angiopathy: implications for management. Stroke 29:1995–1998
157. Ducros A (2012) Reversible cerebral vasoconstriction syndrome. Lancet Neurol 11:906–917
158. Garcia-Reitboeck P, Al-Memar A (2013) Reversible cerebral vasoconstriction after pre-eclampsia. N Engl J Med 369:–364
159. Singhal, Aneesh B, Bernst in RA (2005) Postpartum angiopathy and other cerebral vasoconstriction syndromes. Neurocrit Care 3:91–97
160. Fugate JE, Claassen DO, Cloft HJ et al (2014) Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. Mayo Clin Proc 85:427–432
161. Ducros A, Boukobza M, Sarov M et al (2007) The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. Brain 130:3091–3101
162. Bateman BT, Schumacher HC, Bushnell CD et al (2006) Intracerebral hemorrhage in pregnancy: frequency, risk factors, and outcome. Neurology 67:424–429
163. James AH, Bushnell CD, Jamison MG et al (2005) Incidence and risk factors for stroke in pregnancy and the puerperium. Obstet Gynecol 106:509–516
164. Fakhouri F, Vercel C, Frémeaux-Bacchi V (2012) Obstetric nephrology: AKI and thrombotic microangiopathies in pregnancy. Clin J Am Soc Nephrol 7:2100–2106
165. Prakash J, Niwas SS, Parekh A et al (2010) Acute kidney injury in late pregnancy in developing countries. Ren Fail 32:309–313
166. Stratta P, Besso L, Canavese C et al (1996) Is pregnancy-related acute renal failure a disappearing clinical entity? Ren Fail 18:575–584
167. Arora N, Mahajan K, Jana N, Taraphder A (2010) Pregnancy-related acute renal failure in eastern India. Int J Gynaecol Obstet 111:213–216
168. Prakash J, Vohra R, Wani IA, Murthy AS et al (2007) Decreasing incidence of renal cortical necrosis in patients with acute renal failure in developing countries: a single-centre experience of 22 years from eastern India. Nephrol Dial Transplant 22:1213–1217
169. Prakash J, Tripathi K, Pandey LK et al (1995) Spectrum of renal cortical necrosis in acute renal failure in eastern India. Postgrad Med J 71:208–210
170. Grunfeld JP, Ganeval D, Bournerias F (1980) Acute renal failure in pregnancy. Kidney Int 18:179–191
171. Chugh KS, Singhal PC, Sharma BK et al (1976) Datta BN: acute renal failure of obstetric origin. Obstet Gynecol 48:642–646
172. Too G, Hill JB (2013) Hypertensive crisis during pregnancy and postpartum period. Semin Perinatol 37:280–287
173. Dennis AT, Chambers E, Serang K (2015) Blood pressure assessment and first-line pharmacological agents in women with eclampsia. Int J Obstet Anesth 24:247–251
174. Wacker JR, Wagner BK, Briese V et al (2006) Antihypertensive therapy in patients with pre-eclampsia: a prospective randomized multicentre study comparing dihydralazine with urapidil. Eur J Obstet Gynecol Reprod Biol 127:160–165
175. Magee LA, Yong PJ, Espinosa V et al (2009) Expectant management of severe preeclampsia remote from term: a structured systematic review. Hypertens Pregnancy 28:312–347
176. Koopmans CM, Bijlenga D, Groen H et al (2009) Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet 374:979–988

177. Rosenstein MG, Snowden JM, Cheng YW, Caughey AB (2014) The mortality risk of expectant management compared with delivery stratified by gestational age and race and ethnicity. Am J Obstet Gynecol 211:e1–e8
178. Thadhani R, Hagmann H, Schaarschmidt W et al (2016) Removal of soluble Fms-like tyrosin kinase-1 by dextran sulfate apheresis in preeclampsia. J Am Soc Nephrol 27:903–913
179. Bujold E, Roberge S, Nicolaides KH (2014) Low-dose aspirin for prevention of adverse outcomes related to abnormal placentation. Prenat Diagn 34:642–648
180. Duley L, Henderson-Smart DJ, Meher S et al (2007) Antiplatelet agents for preventing preeclampsia and its complications. Cochrane Database Syst Rev 2:CD004659
181. Kozer E, Nikfar S, Costei A et al (2002) Aspirin consumption during the first trimester of pregnancy and congenital anomalies: a meta-analysis. Am J Obstet Gynecol 187:1623–1630
182. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA (2007) Antiplatelet agents for prevention of preeclampsia: a meta-analysis of individual patient data. Lancet 369:1791–1798
183. Hofmeyr GJ, Lawrie TA, Atallah AN et al (2014) Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev 6:CD001059
184. Perez Lopez F, Pasupuleti V, Mezones Holguin E et al (2015) Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controller trials. Fertil Steril 103:1278–1288
185. Edison RJ, Muenke M (2004) Mechanistic and epidemiologic considerations in the evaluation of adverse birth outcomes following gestational exposure to statins. Am J Med Genet 131:287–298
186. Cleary KL, Roney K, Costantine M (2014) Challenges of studying drugs in pregnancy for off-label indications: pravastatin for preeclampsia prevention. Semin Perinatol 38:523–527
187. Costantine MM, Cleary K, Hebert MF et al (2016) Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high risk pregnant women: a pilot randomized controlled trial. Am J Obstet Gynecol 214:720.e1–720.e17
188. Seely EW, Tsigas E, Rich-Edwards JW (2015) Preeclampsia and future cardiovascular disease in women: how good are the data and how can we manage our patients? Semin Perinatol 39:276–283
189. Bellamy L, Casas JP, Hingorani AD, Williams DJ (2007) Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. Br Med J 335:974–979
190. Brown MC, Best KE, Pearce MS et al (2013) Cardiovascular disease risk in women with preeclampsia: systematic review and meta-analysis. Eur J Epidemiol 28:1–19
191. Sandvik MK, Leigul E, Nygard O et al (2013) Preeclampsia in healthy women and endothelial dysfunction 10 years later. Am J Obstet Gynecol 209:e1–e101
192. Habli M, Eftekhari N, Wiebracht E et al (2009) Long-term maternal and subsequent pregnancy outcomes 5 years after hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. Am J Obstet Gynecol 201:385e1–385e5

# Blood Pressure Trends in Children and Adolescents: Predictors of Blood Pressure Elevation in Children and Adolescents

45

Stella Stabouli

## 45.1 Introduction

Hypertension beginning in childhood may accelerate adverse cardiovascular outcomes shifting clinical events in early adulthood [1, 2]. Cohort studies have demonstrated a positive association between BP levels at childhood and subclinical target organ damage in adulthood [3, 4], while observational studies provide evidence that target organ damage is already present in hypertensive children [5, 6]. Moreover, BP tracks from childhood and adolescence into adulthood [7]. For these reasons, identification and management of hypertension in childhood are gaining increasing interest for the prevention of future cardiovascular disease.

Analysis of secular BP trends in childhood and recognition of predictors for early incidence or sustained BP elevation at population level could provide critical information for the future of cardiovascular disease in adulthood [8, 9]. Trends and patterns of environmental risk factors may not be static over time and induce changes in BP tracks at population level. Understanding temporal interactions between risk factors in a time frame may well provide a window to the future and define optimal time frame for population-based approaches to reduce burden of future hypertension.

Although hypertension is increasing in US adults, BP levels in population level are lower, maybe because of increasing awareness and therapeutic innervations [10]. Antihypertensive medication or other therapeutic interventions are unlikely to affect secular BP trends in childhood and adolescence. Environmental factors, mainly diet and physical activity, are the most targeted modifiable risk factors in public health policies. Monitoring changing patterns of these factors in parallel to BP could be a tool to guide interventions to reduce the prevalence of hypertension.

S. Stabouli, M.D., Ph.D.
First Department of Pediatrics, Aristotle University Thessaloniki, Thessaloniki, Greece
e-mail: sstaboul@auth.gr



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_45

## 45.2 Secular BP Trends in Children and Adolescents Around the World

The US National Health and Nutrition Examination Surveys (NHANES) have provided significant information on secular BP trends in children and adolescents. A series of publications, during the last decades, have systematically assessed changes in BP and have attempted to identify possible covariates to explain them (Table 45.1). Significant assets of these publications are the use of nationally representative samples of noninstitutionalized children and adolescents, in successively conducted cross-sectional studies, and the standardized BP measurement protocol. Ford et al. [11], using data from the third NHANES (1988–1994) and the NHANES 1999–2000, found that mean systolic BP increased by 2.2 mmHg among children and adolescents, 8–17 years of age. Similarly, Muntner et al. [12] found greater by 1.4 mmHg mean systolic BP and by 3.3 mmHg mean diastolic BP after adjustment for differences in age, race, and sex in the NHANES 1999–2000 compared with the NHANES 1988–1994. Further adjustment for body mass index (BMI) accounted for 29 and 12 percentage decreases in systolic and diastolic BP, respectively. Din-Dzietham et al. [13] analyzed NHANES data from 1962 to 2002 with the main aim to determine secular BP trends in 8–17-year-old children in association with the rise in obesity. They found that age-adjusted high BP prevalence (>95th percentile) presented decreasing trends from 1962 up to 1988–1994, significantly greater for diastolic BP (8.4 mmHg) than for systolic BP (1.3 mmHg). Beyond 1994 high BP prevalence presented increasing trends. The increase in high BP occurred one decade after a sharp increase in obesity during 1980–2002. However, BP levels decrease during the first 32 years could be attributed to the fact that there were differences in BP measurement protocol mainly between NHANES I and II and those beyond NHANES III [14]. Ostchega et al. [15] estimated trends in elevated and pre-elevated BP based on data from NHANES 1988–1994, 1999–2002, and 2003–2006. They reported an increased likelihood of having elevated BP in girls in NHANES 2003–2006 compared to NHANES 1989–1994. For the same time period, the likelihood of having elevated BP was decreased in adolescent boys. The prevalence of elevated or pre-elevated BP did not change for the total sample among the three surveys. Obese boys and girls were more likely to have elevated or pre-elevated BP. Rosner et al. [16] found an 1.27 times increased likelihood of elevated BP (>90th percentile) in children 8–17 years old in NHANES 2007–2008 compared to NHANES III (1988–1994) after adjustment for age, sex, race/ethnicity, body mass index, waist circumference, and sodium intake. It should be pointed out that in this study, elevated BP was assessed using normative values based on normal-weight children resulting in higher rates of high BP. Kit et al. [17] found a decrease in pre-high and high BP prevalence between 1999–2000 and 2010–2012, analyzing seven periods (NHANES 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012). However, when combining the prevalence of high and pre-high BP, the trends were stable for the total period. Further period-to-period analysis showed that high BP prevalence increased until 2006 and gradually decreased thereafter, resulting in similar prevalence at 1999–2000 and 2011–2012. Yang et al. [18] examine trends in

**Table 45.1** Studies reporting secular BP trends in children and adolescents: characteristic and methodological aspects

| | Study/time period | No. of subjects | Ages (years) | Ethnicity | Definition for high BP | Methodology (device/cuff/ Korotkoff sound for DBP/no. of BP readings/position) | Comments on methodology | Covariate effect |
|---|---|---|---|---|---|---|---|---|
| *USA* | | | | | | | | |
| Ford et al. [11] | NHANES III (1988–1994) to NHANES 1999–2000 | 6489<br>2410 | 8–17 | Non-Hispanic Black, White, Mexican American | – | Mercury gravity sphygmomanometer/child, adult, large-arm cuff/K5/average of last two BPs available/sitting | – Different no. of readings among subjects (three BP readings for NHANES III, up to four for NHANES 1999–2000) | |
| Muntner et al. [12] | NHANES III (1988–1994) to NHANES 1999–2000 | 3496<br>2086 | 8–17 | Non-Hispanic Black, White, Mexican American | – | Mercury gravity sphygmomanometer/appropriate cuff size/ K5/average of three BP readings/sitting | – Oversample of Mexican Americans, non-Hispanic Blacks | Adjustment for BMI attenuated changes in BP |
| Din-Ditziem et al. [13] | NHES II (1963–1965), NHES III (1966–1970), NHANES I (1971–1975), NHANES II (1976–1980), HHANES (1982–1984), NHANES III (1988–1994), continuous NHANES (1999–2002) | 29,176 | 8–17 | Non-Hispanic Black, White, Mexican American | NHBPEP | Mercury gravity sphygmomanometer/appropriate cuff size/ K4 or K5/average of all available BP readings/sitting | – Appropriate cuff size use percentage differ among surveys<br>– Shift in the ethnic distribution between studies | Adjustment for BMI or waist circumference attenuated changes in BP |

(continued)

**Table 45.1** (continued)

| | Study/time period | No. of subjects | Ages (years) | Ethnicity | Definition for high BP | Methodology (device/cuff/ Korotkoff sound for DBP/no. of BP readings/position) | Comments on methodology | Covariate effect |
|---|---|---|---|---|---|---|---|---|
| Ostchega et al. [15] | NHANES III (1988–1994), NHANES (1999–2002), NHANES (2003–2006) | 4673<br>5110<br>4662 | 8–17 | Non-Hispanic Black, White, Mexican American | NHBPEP | Mercury gravity sphygmomanometer/appropriate cuff size/ K5/average of all available BP readings/sitting | – Appropriate cuff size use percentage differ among surveys<br>– Oversampling of youth aged 12–19 years, Mexican Americans, and Blacks | BP changes persisted after controlling for all covariates including BMI |
| Rosner et al. [16] | NHANES III (1988–1994) NHANES 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008 | 3248<br>8388 | 8–17 | Non- Hispanic Black, White, Mexican American | BP percentiles based on normal-weight children | Mercury gravity sphygmomanometer /–/–/average of three BP readings or of all available readings/sitting | – Different no. of readings among subjects<br>– Shift in the ethnic distribution between studies | – Adjustment for BMI attenuated changes in BP<br>– Adjustment for Na intake strengthened changes in BP |
| Kit et al. [17] | NHANES 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008 2009–2010, 2011–2012 | 2362<br>2486<br>2187<br>2242<br>1620<br>1696<br>1665 | 8–17 | Non-Hispanic White, Black, Mexican American, non-Hispanic Asian | NHBPEP | Mercury gravity sphygmomanometer/appropriate cuff sizes/K5/average of up to three BP readings/sitting | – Different no. of readings among subjects | Discordant BP and obesity trends |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Yang et al. [18] | NHANES 1988–1994, 1999–2002, 2003–2006, 2007–2012 | 14,844 | 12–19 | Non-Hispanic White, Black, Mexican American, non-Hispanic Asian | – | Mercury sphygmomanometer/ appropriate cuff sizes/K5/ averages of three or four BP measurements or one BP reading/sitting | – Adjustment for different no. of readings among subjects | Adjustments for smoking, physical activity, healthy eating index—2010, poverty-income ratio, waist-to-height ratio, and BMI did not changed BP trends |
| Okosun et al. [19] | 1999–2000, 2001–2002, 2003–2004, 2005–2006, and 2007–2008 (NHANES) | 4095 male<br>4035 female | 12–17 | Non-Hispanic White, Black, Mexican American, multiracial American | – | Mercury sphygmomanometer/ appropriate cuff sizes/K5/ averages of three BP readings/ sitting | – Adjustment for changes in average BP were studied | |
| Luepker et al. [22] | 1986 to 1995–1996 in Minneapolis, Minnesota, public schools | 8222 (4239 male, 3983 female), 10,241 (5232 male, 5018 female) | 10–14 | White, African-American, native American, Hispanic, Southeast Asian | – | Standard sphygmomanometer/ appropriate cuff size/average of K4 and K5/average of two BP readings/sitting | Shift in the ethnic composition from 1986 to 1996 | Adjustments for weight and height or BMI and arm circumference resulted in reductions in adjusted SBP |

(continued)

**Table 45.1** (continued)

| | Study/time period | No. of subjects | Ages (years) | Ethnicity | Definition for high BP | Methodology (device/cuff/ Korotkoff sound for DBP/no. of BP readings/position) | Comments on methodology | Covariate effect |
|---|---|---|---|---|---|---|---|---|
| Gidding et al. [20] | Bogalusa Heart Study, two cohorts: first 1973–1981 and second 1984–1992 | 417<br>235 | 7–9<br>15–17 | White, African-American | – | Mercury sphygmomanometer/ cuff sizes, child, adult, obese/ K4/average of six readings/ sitting | Second cohort older | Despite increase in weight, SBP levels were lower in the second cohort |
| Freedman et al. [21] | Bogalusa Heart Study surveys from 1974–1977 to 1992–1994 | 11,478 | 5–17 | White, African-American | ≥90th pc of NHBPEP | Mercury sphygmomanometer/ cuff sizes, child, adult, obese/ K5/average of six readings/ sitting | – The proportion of African-Americans increased over the two decades<br>– Most children were examined multiple times | Discordant BP and obesity trends |
| McCrindle et al. [23] | 2002–2008 in public and Catholic schools, Canada | 20,719 | 14–15 | – | NHBPEP | –/appropriate cuff size/–/1 BP reading if BP ≥135/85 average of three readings/sitting | Different no. of readings among subjects | Family history, low levels of physical activity, sedentary behaviors, poor nutrition, and lower socioeconomic status were all independently and negatively associated with elevated BP |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *Europe* | | | | | | | | | |
| Watkins et al. [25] | 1989–1990 to 1999–2001 in postprimary schools | 1015<br>2017 | 12 or 15 | Northern Ireland | – | UK random-zero Hawksley sphygmomanometer/standard cuff size/Korotkoff IV for participants aged 12 and Korotkoff V for participants aged 15/averages of two readings in 1989–1990 and one reading in 1999–2000/– | – | Different no. of reading among studies—response rate for the second study was lower than that for the first | Adjustment for body mass index, age, height, physical activity score, self-reported smoking, or additional adjustment for social class, pubertal status, birth weight, and infant feeding did not change BP trends |
| McCarron et al. [24] | Health screening on Glasgow University 1948–1968 | 12,412 | 19.9 in males and 19.2 in females | Glasgow | JNC VI | –/–/–/–/– | | | Adjustment for age, height, body mass index, smoking, father's social class, and age of menarche in women did not change BP trends |

(continued)

**Table 45.1** (continued)

| | Study/time period | No. of subjects | Ages (years) | Ethnicity | Definition for high BP | Methodology (device/cuff/ Korotkoff sound for DBP/no. of BP readings/position) | Comments on methodology | Covariate effect |
|---|---|---|---|---|---|---|---|---|
| Peters et al. [26] | 1980–2008: 1970 British birth cohort (1980), Brompton (1984–1985), two towns study (1991) | 25,501: 12,093 774 1293 1356 | 9–11 | White European | – | Mercury sphygmomanometer, Dinamap 1846 and 8100, Omron 907/different cuff sizes among studies/–/1–3 BP readings, average of the first two readings was used in analysis/sitting | – Different ages and BP measurement methodology among studies | Adjustment for height and BMI attenuated changes in BP<br>The BMI/SBP association weakened over time |
| | National Study of Health and Growth (NSHG) 1992–1994 | 3363 | | | | | | |
| | Ten towns (1994), HSE 1995–1998, HSE 2002 | 3083 1172 | | | | | | |
| | CHASE 2005 | 1382 | | | | | | |
| | HSE 2006–2008 | 985 | | | | | | |
| Haas et al. [27] | PEP Family Heart Study 1994–2003 in first grade schools | 2228 | 6 | German children | – | –/–/–/–/– | BP not adjusted for height | No significant BP or obesity trend |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Kollias et al. [28] | 2004–2007 in high schools Karlovassi, Samos, Greece | 446<br>558 | 12–17 | White European | NHBPEP | Automated oscillometric device/three different cuffs/–/average of three measurements/sitting | –<br>– | Small sample<br>BP not adjusted for height despite statistically significant differences between 2004 and 2007 | After adjustment for age and BMI, differences in BP, levels remained significant |
| Smpokos et al. [29] | 1992–1993 to 2006–2007 in first grade schools Crete, Greece | 606<br>361 | 5.7–7.8 | Caucasian | – | Mercury sphygmomanometer/appropriate cuff size/–/three BP readings, average of last two used in the analysis/sitting | –<br>– | Small sample<br>BP not adjusted for height despite statistically significant differences between cohorts | Higher BP prevalence in obese at both periods |
| Viikari et al. [30] | 1980–2001 | 3596<br>2285 | 3–18 | Finn children | – | Random-zero mercury sphygmomanometer/–/K5/average of three BP readings/– | – | Lower participation of subjects in follow-up studies | Discordant BP and obesity trends |
| *Asia* | | | | | | | | | |
| Liang et al. [37] | 1991, 1993, 1997, 2000, 2004, Chinese National Surveys on Students' Constitution and Health (CNSSCH) in seven provinces (Jiangsu, Shandong, Henan, Hubei, Hunan, Guangxi, Guizhou) | 1936<br>1710<br>1988<br>1602<br>1111<br>Total 8247 | 6–17 | Chinese children | Age and sex pc in Chinese children | Mercury sphygmomanometer/appropriate cuff size/K5/average of three BP readings/sitting | – | BP pc not adjusted for height | Similar BP and obesity trends |

(continued)

**Table 45.1** (continued)

| | Study/time period | No. of subjects | Ages (years) | Ethnicity | Definition for high BP | Methodology (device/cuff/ Korotkoff sound for DBP/no. of BP readings/position) | Comments on methodology | Covariate effect |
|---|---|---|---|---|---|---|---|---|
| Dong et al. [34] | 1985, 1995, 2000, 2005, 2010, Chinese National Surveys on Students' Constitution and Health (CNSSCH) | 1, 010, 153 | 8–17 | Chinese children of Han nationality | NHBPEP | Mercury sphygmomanometer/ appropriate cuff size/K5/ average of three BP readings/ sitting | | Adjustment for average BMI did not change the trends in BP |
| Zhang et al. [36] | 2000, 2005, 2010, Chinese National Surveys on Students' Constitution and Health (CNSSCH) in Shandong | 7776<br>7878<br>6894<br>Total 22,548 | 7–17 | Chinese children | Age and sex percentile in Chinese children | Mercury sphygmomanometer/ appropriate cuff size/K5/ average of two BP readings/ sitting | – BP pc not adjusted for height | Similar BP and obesity trends |
| Dong et al. [35] | 2005, 2010, Chinese National Surveys on Students' Constitution and Health (CNSSCH) | 391,982 | 7–17 | Chinese children of Han nationality | – | Mercury sphygmomanometer/ appropriate cuff size/K5/ average of three BP readings/ sitting | | Adjustment for BMI attenuated changes in BP |
| Lin et al. [38] | 1996–2006 in junior high schools in Tapei | 1354<br>1203 | 12–14 | Taiwanese children | NHBPEP | Auscultatory method/ appropriate cuff size/K5/ average of two BP readings/ sitting | | Similar BP and obesity trends in boys |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Kouda et al. 2010 | Annual screenings from 1993–2008 in public schools in Iwata City, Japan | 14,872 | 10–11 | Japanese children | – | Oscillometric device/ appropriate cuff size/–/1–3 readings per participant, the lowest value was used in the analysis/sitting | – Different no. of readings among subjects<br>– Different readings used per participant | Discordant BP and obesity trends |
| Shirasawa et al. [31] | 1994–2010 in schools in Ina, Saitama Prefecture, Japan | 10,894 | 9–13 | Japanese children | – | Mercury sphygmomanometer/9-cm and 12-cm cuffs/–/1–3 reading, the last one was recorded/– | Different no. of readings among subjects<br>– Different readings used per participant | Discordant BP and obesity trends |
| Khang et al. [32] | Korean National Health and Nutrition Examination Surveys 1998, 2001, 2004, 2007–2008 | 5909 | 10–19 | Korean children | NHBPEP | Mercury sphygmomanometer/ appropriate cuff size/K5/ average of two BP readings for first and second survey and three for the rest/average of first two readings used in the analysis/sitting | Response rates different among surveys | Trends remained significant after adjustment for body mass index and waist circumferences, cigarette smoking and physical activity, nutritional factors, psychological and sociodemographic factors |
| Agirbasli et al. [39] | 1989–1990 in one Ankara school to 2004–2005 in Istanbul school | 673<br>640 | 15–17 | Turkish children | NHBPEP | Mercury sphygmomanometer/22–32 cm cuff/K5/ average of last 2/3 BP readings/sitting | Measurements in single schools and small samples | Discordant BP and obesity trends |

(continued)

**Table 45.1** (continued)

| | Study/time period | No. of subjects | Ages (years) | Ethnicity | Definition for high BP | Methodology (device/cuff/ Korotkoff sound for DBP/no. of BP readings/position) | Comments on methodology | Covariate effect |
|---|---|---|---|---|---|---|---|---|
| Agirbasli et al. [40] | 1989; 2008 in schools | 1385<br>1746 | 8–12 | Turkish children | NHBPEP | – | | Similar BP and obesity trends |
| Chiolero et al. [41] | 1998–2006 annual school-based surveys in Seychelles | 12,467 | 4–18 | African descent | NHBPEP | Oscillometric device/ appropriate cuff size/–/ average of two BP readings/ sitting | – Most children were examined multiple times | – Discordant BP and obesity trends<br>– The relationship between BMI and BP weakened slightly over time |

*BMI* body mass index, *BP* blood pressure, *NHBPEP* National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, *JNC VI* The sixth report of the Joint National Committee of Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

pre-high BP and high BP among adolescents, aged 12–19 years, by body weight category during 1988–2012 using NHANES data from 1988–1994, 1999–2002, 2003–2006, and 2007–2012. Adjusted for age, sex and ethnicity mean systolic and diastolic BP levels did not change significantly from 1988 to 2012. They reported that the prevalence of high BP decreased and pre-high BP did not change in both lean and overweight adolescents. The trend for high BP increased from 1988–1994 to 1999–2006 and then declined during 2007–2012 for lean adolescents, while the trend was continuously decreasing for obese adolescents. In contrast to previous studies based on NHANES, Okosun et al. [19] found consecutive decreases in mean BP for both genders in 12–17-year-old adolescents for the period between 1999–2000 and 2007–2008.

Regional studies from the USA and Canada showed relatively different results. In the Bogalusa area, comparison of two cohorts of children, each one examined at two time points, 7–9 years and again at 15–17 years (first cohort 1979–1981 and second cohort 1984–1992), demonstrated lower systolic BP after adjustment for age, both at baseline and follow-up surveys, despite higher weight in the second cohort [20]. In a most recent publication from the Bogalusa Heart Study, including seven cross-sectional examinations of schoolchildren 5–17 years old between 1974 and 1993, it was shown that mean systolic BP levels did not change, while mean diastolic BP levels decreased by 2 mmHg, despite large increases in obesity prevalence during this period [21]. BP was measured in two cross-sectional surveys in Minneapolis, Minnesota, in school-aged children, aged 10–14 years, at 1986 and 1996. During the 10-year period, systolic BP decreased at all ethnic and sex groups. However, adjustment for age, height, and weight resulted in decrease or elimination of differences in systolic BP among surveys [22]. In Canada, 20,719 adolescents, 14–15 years old, were screened between 2002 and 2008 during the Healthy Heart Schools' Program in the Niagara Peninsula [23]. Minimal changes were reported upward for systolic and downward for diastolic BP. The prevalence of prehypertension significantly decreased from 11 to 8 percentage, while the prevalence of hypertension remained stable over time.

In Europe most of the studies were performed in the UK (Table 45.1). The older study comes from the Glasgow University Students' screening during the years 1948–1968 [24]. Although methodology issues may have influenced the results as measurement protocols were not the same during the studied period, significant strengths of the study are the large number of participants, the assessment of possible confounders, and the investigation of BP trends in those born in the first half of the twentieth century. During the 50 studied years, substantial declines in BP were documented for both sexes in young adults 16–25 years. Watkins et al. [25] examined secular trends of BP over a 10-year period in two cohorts of adolescents, 12–15 years old, in Northern Ireland. The 1999–2001 cohort presented significant lower systolic and diastolic BP compared to the 1989–1990 cohort. Results were adjusted for height and other possible confounders, but were not unambiguously comparable. Korotkoff IV was used to identify diastolic BP in 12-year-old participants and V for those aged 15 years. Moreover, the mean of two measurements was used in the first study compared to one reading in each participant in the second

cohort. In addition, sample size despite lower respond rate was double in the second cohort. Using data from seven population-based studies conducted in the UK during 1980–2008, an upward trend in systolic BP (1980–2008) was documented significantly greater in girls than in boys [26]. The estimated annual increase in systolic BP was 0.51 mmHg and 0.45 mmHg per year among girls and boys, respectively. Similar but less steep trends were found for diastolic BP. The aforementioned study differs from previous standardized BP surveys as it combines data from separate observational studies. There were differences in methodology among studies with regard to participant ages, ethnicity, cities, and country regions included, BP measurement device (mercury sphygmomanometer vs. three different oscillometric devices), cuff size, number of readings, and period of rest. To account for the above differences, the investigators focused only on White European children aged 9–11 years and performed several statistical adjustments. Trends for systolic BP were found similar and marginally lower, when data from annual national studies (Health Survey for England) for 9–11 years old children were examined separately [26]. The study assessed secular trends on BMI during the same period, which also went upward, but the increase was steeper and could explain only 15 percentage of the BP trend, while association between BMI and BP weakened overtime.

Scarce are the data available from the rest of Europe. Haas et al. [27] examined the prevalence of metabolic syndrome components in first graders, aged 6 years, from 1994 to 2003, and found significant decreases in SBP (−3.8 and −4.1 percentage, in boys and girls, respectively) and DBP (−10.2 and −9.7 percentage, in boys and girls, respectively). In the small city of Karlovasi in Samos island, Greece, a large increment in BP levels was reported in a considerably small sample of adolescents, aged 12–17 years, during a 3-year period [28]. A standardized BP measurement protocol was used in both 2004 and 2007 surveys. However, BP was not adjusted for height, despite statistically significantly higher height of participants in the 2007 survey, which may have resulted in the overestimation of the trends. In another study from Greece, a significant decline in BP has been reported among children, aged 5.7–7.8 years, living in the island of Crete, over a 15-year period, despite the significant concurrent increase in obesity [29]. Blood pressure levels of a cohort in Finland followed up for 21 years with serial cross-sectional studies from childhood to adulthood presented significant decreases in all subjects [30]. The authors justified part of this decrease in the lower participation of subjects in the follow-up studies, supposing that the least healthy subjects were more prone to drop out earlier.

In Asia secular BP trends in childhood have been systematically examined in Japan, China, and Korea (Table 45.1). The National Health and Nutrition Surveys conducted by the Japanese Ministry of Health, Labor, and Welfare in 1996 and 2009 showed a reduction in systolic BP by 2 mmHg in 15–19-year-old adolescent boys and by 4 mmHg in girls from 1996 to 2009 [31]. Kouda et al. [31] analyzed data from annual population screenings in 10-year-old children from all public schools in the city of Iwata, Japan, during 1993–2008. There was a negative correlation between 95th, 50th, and 5th BP percentiles (calculated for each year) in the population for both sexes and calendar year from 1998 to 2003. This trend was diverging

the BMI trend, as both overweight and underweight in the population were increased during the same period. A significant limitation of the study was the unequal number of BP measurements among subjects, since BP assessment was repeated, if it exceeded the cutoff value. Data from the annual population screenings during 1994–2010 in Ina, another Japanese city, showed similar decreasing trends for both systolic and diastolic BP in 9–10-year-old and 12–13-year-old boys and girls [32]. A standardized BP measurement protocol was used, but, as discussed in the aforementioned study, the number of measurements was not equal in all subjects. Moreover, a significant proportion of subjects were reexamined, and this may have affected the results because of regression to mean. The BP trends were independent of obesity in 9–10-year-old children, but not in 11–12-year-old ones. Intriguingly, a decreasing trend for BMI has been reported in this study opposite to other Japanese studies.

The Korean National Health and Nutrition Examination Surveys (KNHNES) were first conducted in 1998 and then at 2001, 2005, and 2007–2008 [33]. Data available for 5909 participants, aged 10–19 years, showed decreasing secular age- and height-adjusted systolic BP trends, by 8.7 mmHg in boys and 10 mmHg in girls, for the 10-year period. Decreasing diastolic BP trends were also noticed in both sexes, when analysis was limited to those with DBP z score $\geq 0$ to account for discrepancies among surveys, as in earlier ones fourth Korotkoff instead of fifth was used to define diastolic BP. These declines resulted in 52 and 86 percentage reduction of prehypertension and hypertension in the population. The significant strength of this study was the assessment of potential risk factors that could explain the observed trends. Obesity and self-reported health behaviors, including physical activity and smoking, nutritional factors, psychological factors, and sociodemographic factors, had minimal influence on the BP trends. The BP trends opposed those of obesity, which during the same decade presented an increase in boys.

In China decreasing BP trends were documented between 1985 and 2005, which shifted upward from 2005 to 2010 [34]. Data are based on standardized successive Chinese National Surveys on Students' Constitution and Health (CNSSCH). The main strengths of the report are the huge representative nationwide sample size and the standardized protocol among surveys. There was a positive, relative steady association between BP and BMI among surveys. Focusing on the 2005 and 2010 surveys, mean systolic BP increased by 1.5 mmHg for boys and 1.1 mmHg for girls. Similarly diastolic BP increased by 1.2 mmHg and 1.0 mmHg for boys and girls, respectively. These increments decreased by 40.5 percentage for systolic BP and by 26.9 percentage for diastolic BP after adjustment for BMI [35]. In the province of Shandong, comparison of BP levels during the 2000, 2005, and 2010 Students' Constitution and Health Surveys showed steady increases in high BP prevalence [36]. Similar findings were reported from Students' Constitution and Health Survey data for seven provinces during the period 1991–2004 [37]. It should be noted that the last two studies provide regional trends compared to the nationwide trends in children of Han nationality by Dong et al. [34]. Moreover, results are not comparable as they were not adjusted for height, and Chinese reference BP values by age and sex were used compared to the US National High Blood Pressure Education

Program (NHBPEP) Working Group in Children and Adolescents used in the Dong et al. studies [34, 35]. One study from Taiwan examined BP trends from 1996 to 2006 in adolescents from high schools living in the city of Taipei and showed upward trends of both pre-high and high BP [38]. The prevalence of high BP increased in all genders and weight groups (normal weight and overweight), despite stable trends of overweight in girls.

In Turkey decreasing trends of BP levels have been reported in adolescent boys and girls, aged 15–17 years, despite increasing overweight and obesity, based on two cross-sectional studies from 1989–1990 to 2004–2005 [39]. The study however presented significant limitations as the two studies were conducted in different cities and schools and by different investigators. The same investigators reported conflicting results examining a more recent time period finding that the prevalence of elevated BP has been increased in 2008 compared to 1989 in Turkish adolescents [40].

Only one study examined secular BP trends in the African region. Data from annual school-based surveys in Seychelles, including a wide range of ages, 4–18 years, showed discordant trends between BP levels and obesity [41]. In this rapidly developing country, obesity was steadily increasing from the 1998 to 2000 surveys presenting 50 percentage relative increase between the 2004 and 2006 surveys. During the same period, prevalence of elevated BP presented 19 percentage decrease. Mean age- and height-adjusted systolic BP presented a 3.0 mmHg in boys and a 2.8 mmHg decrease in girls, while no substantial changes were observed for diastolic BP. In a recent update on BP trends in Seychelles, it is reported that the prevalence of elevated BP increased from 2005 to 2012, reaching to 14.5 percentage, accompanying the continuing increase in overweight and central obesity [42].

## 45.3 Differences in Secular BP Trends in Childhood

Comparisons of secular trends around the world may offer a better understanding of the development of hypertension in childhood and guidance for future studies [9]. Secular BP trends among studies from the different regions, and in some cases from the same country, do not show homogeneity (Table 45.1). A systematic review of BP trends in childhood has shown that BP increased in the 94 percentage of the studies, based on reports form 13 countries [43]. Notably studies on BP trends are not available from all regions, and pool data or comparisons could not provide a global estimate. Moreover, significant discrepancies in trends may not be real, but could be artifacts, due to differences in methodological issues, including BP measurement methodology, sample size, population, age, ethnicity, and other characteristics or statistical adjustments performed during the analysis. Furthermore, studies comparing two or three time points or short period of time may not be adequate to assess secular trends and might account for the inconsistency of reporting among studies. Therefore, safe conclusions could not be reached, unless there are standardized protocols over time and across the countries.

Studies in the USA seem to report conflicting results (Table 45.1). However, careful observation of the NHANES data taking into account the time period of

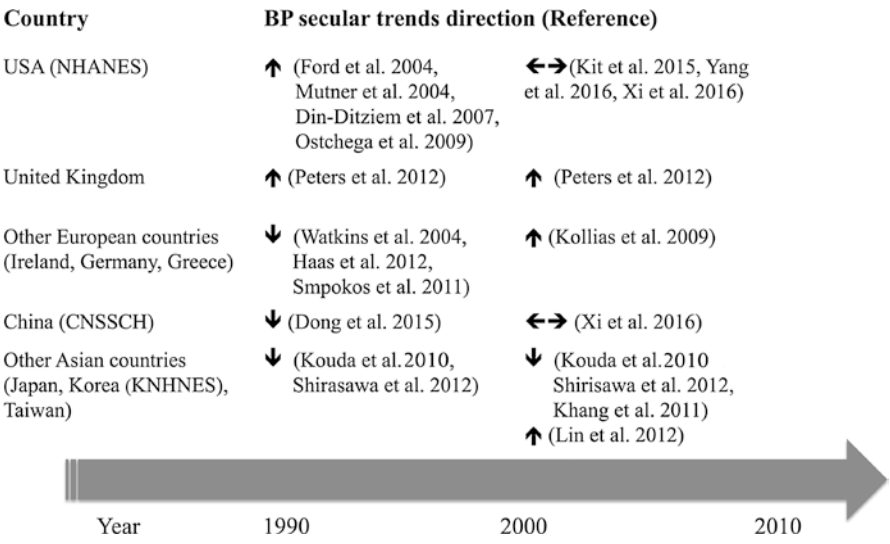



**Fig. 45.1** BP trends in children and adolescents during the last two decades. Reported trends are based on national surveys, where available, or regional studies

reported trends may crudely suggest upward trends since the late 1980s until the middle 2000s, [11–13, 15], while afterward BP levels are slightly decreasing [17] resulting in rather stable trends between 1999 and 2012 [17, 18, 42] (Fig. 45.1). Observed differences in high BP prevalence or in the magnitude of BP changes over time could be attributed to differences in sample size or ethnic sampling. These national trends are diverging to those in the Bogalusa area where trends went downward since the 1970s, but significant methodological differences do not allow safe comparisons [21].

In Europe during the 1990s, BP trends were decreasing in Ireland, Germany, and Greece [25, 27, 29], while BP increased in the UK [26] (Fig. 45.1). The upward BP trends persisted in the UK during the next decade, when similar trends were reported from Greece [28]. In Asia different trends were reported from national surveys among countries. In Korea trends were continuously decreasing during the 2000s, while in China trends increased until the middle 2000s and went downward thereafter, resulting in stable trends for the decade [33, 34, 42]. Reported regional trends for the same period were downward in Japan, similar to Korean ones [31, 32], and upward in Taiwan, similar to China ones [38].

One published study has attempted an international comparison of BP trends among four countries from American, Asian, and African region [42]. Studies were comparable with regard to age ranges, calendar years, cutoffs used to define elevated BP, and general and central obesity. Standardized BP measurement protocols were used in all studies, but they were not identical. A mercury sphygmomanometer was used in three of them, while an oscillometric device was used in the fourth one. In addition the number of BP readings per subject differed among studies. The interesting finding of the study was that BP trends for the same time period differed

among countries, while obesity trends went on the same direction, upward, suggesting that covariates that determine BP trends in different populations, having either protective or deleterious effect, may modify the effect of risk factors. Finally, genetic differences among populations and environmental interactions need to be investigated [44].

## 45.4 Predictors of BP Elevation

Many studies assessing BP trends in childhood also studied association with well-known risk factors for adverse cardiovascular outcomes. However, direct, solid evidence has not been established by the available studies for obesity, salt, or other environmental factors. Most of the earlier studies did not concurrently study changes in risk factors for elevated BP. Potential explanations for the BP trends were discussed on the basis of epidemiological data available for possible risk factors from national demographic records [26, 31, 33, 41, 45]. Few studies have assessed simultaneous secular trends in risk factors for elevated BP, mainly overweight and obesity. Contrary to BP prevalence studies, which show strong associations of BP elevation with increasing BMI, low physical activity, smoking, or low birth weight at a particular time point, reports on the effect of these factors on secular BP trends are inconsistent.

### 45.4.1 Overweight and Obesity

Obesity has been the most commonly environmental risk factor associated with the development of hypertension. However, population-based studies assessing simultaneously changes in BP and obesity over time did not consistently show parallel changes in both trends as it may be expected [45]. On the contrary, in many occasions it has been shown that BP trends are decreasing, while obesity is rising [21, 33]. Even in those studies that obesity and BP are both increasing, only part of the BP levels increase could be attributed to obesity [12, 13, 16, 26]. In some studies there was a weakening association between obesity and BP over time [26, 43]. Moreover, upward trends were more pronounced in children without overweight or obesity [26]. Both in developed and developing countries, obesity could not explain all the BP changes [43, 45]. BP trends seem to be affected by secular changes in other factors, which remain to be determined.

A comparison of secular trends in BP from 1997–2000 to 2011–2012 in four countries, the USA, Korea, China, and Seychelles, is confirming the heterogeneity of the effect of rising prevalence of obesity on BP trends [42]. Elevated BP in all countries was significantly more frequent among adolescents with overweight or central obesity than in adolescents with normal weight or no central obesity. Nevertheless, the prevalence of elevated BP decreased in Korea, remained stable in the USA and China, and increased in Seychelles. It is interesting that in Seychelles elevated BP prevalence was decreasing until 2005, but increment in BP levels beyond 2005

overlapped this decrease and finally resulted in significant increase at 2011–2012 compared to 1997–2000. Whether persisting high rates of obesity could affect BP trends in the future as suggested by high BP prevalence rise in the USA during the late 1980s and 1990s, which lagged about 10 years behind the increase in obesity rates, remains a significant concern [13].

### 45.4.2 Salt

Dietary sodium has been shown to be a causal factor for high BP. A meta-analysis of controlled trials in children showed that a modest reduction in salt intake causes immediate reductions in BP [46]. The BP reductions were higher if interventions on salt intake were performed in infancy. The importance of very early intervention is supported by the results of follow-up data on Dutch children, who took part in a double-blind salt reduction study during the first 6 months of life, in whom BP remained lower at 15 years of age [47]. The strongest indirect evidence in support of the role in salt intake on BP trends in children and adolescents comes from Japan. The nationwide campaign to reduce population salt intake starting in the 1950s may be associated with continuous BP decreases in children in the 2000s compared to 1990s, consistently found in all studies assessing BP trends in Japan [31, 32]. These BP downward trends occurred in parallel with decreases on national daily salt intake of Japanese children from 11.4 g in 1996 to 9.7 g in 2006 [31]. Rosner et al. [16] found that children with sodium intake >3.450 mg (≥1.5 of reference daily intake (RDI) per 2000 calories) vs. <2.300 mg (<RDI) presented an increased likelihood by 36 percentage of elevated BP in NHANES 1999–2008 compared to NHANES III, even after controlling for age, sex, race, BMI, and waist circumference. Notably, the percentage of children with sodium intake ≥1.5 RDI significantly decreased among both boys and girls, while the prevalence of moderate increased sodium intake (≥RDI but <1.5 RDI) increased during the same period, and consequently sodium intake could explain only part of differences between the surveys.

### 45.4.3 Other Dietary Factors, Physical Activity, and Smoking

Studies assessing the effect of dietary factors on BP trends are based on 24-h recall. Total calorie, protein, and fat intakes did not explain BP changes in Korean children [33]. Moreover, in the same study, there was no effect of potassium (a possible marker of fruit and vegetable consumption) on secular changes in BP. Rosner et al. [16] compared nutrient intake between NHANES 1999–2008 and NHANES III in relation with the RDI in the group of children who were above the RDI for potassium, calcium, magnesium, fiber, total fat, saturated fat, protein, carbohydrate, and total caloric intake by survey and sex. They found no association between the prevalence of elevated BP and the above nutrient intake. Similarly, Yang et al. [18] found no effect of healthy index eating on temporal BP trends using data from NHANES from 1988 to 2012. Other dietary habits or duration of breastfeeding also did not show significant

associations with the BP trends [25, 28, 48]. Physical activity along with smoking has been assessed by questionnaires in the US, Korean, and Irish studies and were consistently found to have minimal or no effect on BP trends [18, 25, 33]. Finally, in a small study, cardiorespiratory fitness was assessed as a covariate for changes in BP during a 15-year period without presenting any significant association [29].

### 45.4.4 Sociodemographic Factors

In the Glasgow University study during the 1950s and 1960s, social class did not show any association with BP changes over time [24]. Similar results were reported from Ireland during the 1990s [25]. Total annual family income, a socioeconomic status proxy, was used to calculate the poverty-income ratio among US adolescents from 1988 to 2012 [18]. The trends in pre-high and high BP prevalence remained unchanged after adjustments for the poverty-income ratio. In the Korean NHANES, annual household income and family size were studied as sociodemographic factors. BP trends were found similar in both low- and high-income groups [33].
Limited data are available from developing countries [34, 41]. Rapid urbanization may be accompanied by changes in lifestyle, diet, and physical activity. Reported BP secular trends are similar to those in developed countries [49]. Dong et al. [50] studied BP trends in children based on data from 1985 to 2010 Chinese National Surveys on Students' Constitution and Health in an attempt to explore urban-rural disparities. Urban children presented higher prevalence of obesity but lower BP levels over the 25-year period. This urban-rural disparity in BP decreased over time, reflecting the rapid westernization and improvement of parental education and knowledge on health behaviors in the rural areas.

### 45.4.5 Birth Weight

Since the Barker's hypothesis of fetal origin of adult disease, increased notion has been focused on low birth weight as a marker of intrauterine growth retardation [51]. Mzayek et al. [52] assessed retrospectively birth data from 2275 participants from the Bogalusa study conducted between 1973 and 2001, including seven cross-sectional surveys of children aged 5–17 years and seven cross-sectional surveys of young adults aged 18–44 years. They reported that for every 1-kg increase in birth weight, systolic BP decreased by 1.9 mmHg and diastolic BP by 0.7 mmHg in mid-adulthood. The association was independent of ethnicity and socioeconomic factors. Chen et al. [53] reported that the association between birth weight and longitudinal changes is modulated by genetic variations in *â*-AR genes in White and Black adults enrolled in the Bogalusa study.
Most studies on secular BP trends in children and adolescents have not investigated the effect of birth weight on the trends, and comparisons with national birth data failed to institute a strong hypothesis. Birth weight tended to increase in the UK [54] and, therefore, is an improbable explanation of the increasing trends in

childhood BP during the same time period. In Korea, a country with decreasing trends in childhood BP, average birth weight has been decreased based on national birth certificate data from 1993 [33]. Lower birth weight could not be the explanation for the decreasing trends. Finally, Chiolero et al. [41] found no changes in birth weight for the period 1998–2006, in which BP trends were assessed in Seychelles.

## 45.5 Perspectives

Secular BP trends among studies globally do not show homogeneity as significant discrepancies exist among different countries and ethnic populations. Beyond difficulties in international comparisons, identifying different patterns in BP tracks over time among countries could be instructive about the effect of environmental risk factors on different genetic backgrounds. It should be pointed out that BP trend reports do not actually report trends on hypertension as BP measurements are obtained in a single visit. Current definition of hypertension in children and adolescents requires repeated BP measurements on at least three separate occasions to avoid overdiagnosis of hypertension [1, 2]. Moreover, measurement of risk factors may not be precise as in most of the studies are based on questionnaires. Despite the limitations, childhood BP secular trend studies may well offer an epidemiological perspective to guide public health approaches for BP control.

## References

1. National High Blood Pressure Education Program (NHBPEP) Working Group on High Blood Pressure in Children and Adolescents (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 114(2 Suppl 4th Report):555–576
2. Lurbe E, Agabiti-Rosei E, Cruickshank JK et al (2016) 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens 34(10):1887–1920
3. Raitakari OT, Juonala M, Kahonen M et al (2003) Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the cardiovascular risk in Young Finns Study. JAMA 290(17):2277–2283
4. Li S, Chen W, Srinivasan SR, Berenson GS (2004) Childhood blood pressure as a predictor of arterial stiffness in young adults: the Bogalusa Heart study. Hypertension 43(3):541–546
5. Stabouli S, Kotsis V, Zakopoulos N (2007) Ambulatory blood pressure monitoring and target organ damage in pediatrics. J Hypertens 25(10):1979–1986
6. Kollias A, Dafni M, Poulidakis E et al (2014) Out-of-office blood pressure and target organ damage in children and adolescents: a systematic review and meta-analysis. J Hypertens 32(12):2315–2331. discussion 2331
7. Chen X, Wang Y (2008) Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. Circulation 117(25):3171–3180
8. Lurbe E (2013) Childhood blood pressure: trends and future tracks. Hypertension 62(2):242–243
9. Daniels SR (2011) International differences in secular trends in childhood blood pressure: a puzzle to be solved. Circulation 124(4):378–380

10. Cutler JA, Sorlie PD, Wolz M et al (2008) Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988-1994 and 1999-2004. Hypertension 52(5):818–827
11. Ford ES, Mokdad AH, Ajani UA (2004) Trends in risk factors for cardiovascular disease among children and adolescents in the United States. Pediatrics 114(6):1534–1544
12. Muntner P, He J, Cutler JA et al (2004) Trends in blood pressure among children and adolescents. JAMA 291(17):2107–2113
13. Din-Dzietham R, Liu Y, Bielo MV, Shamsa F (2007) High blood pressure trends in children and adolescents in national surveys, 1963 to 2002. Circulation 116(13):1488–1496
14. Falkner B (2007) What exactly do the trends mean? Circulation 116(13):1437–1439
15. Ostchega Y, Carroll M, Prineas RJ et al (2009) Trends of elevated blood pressure among children and adolescents: data from the National Health and Nutrition Examination Survey1988–2006. Am J Hypertens 22(1):59–67
16. Rosner B, Cook NR, Daniels S, Falkner B (2013) Childhood blood pressure trends and risk factors for high blood pressure: the NHANES experience 1988-2008. Hypertension 62(2):247–254
17. Kit BK, Kuklina E, Carroll MD et al (2015) Prevalence of and trends in dyslipidemia and blood pressure among US children and adolescents, 1999-2012. JAMA Pediatr 169(3):272–279
18. Yang Q, Zhong Y, Merritt R, Cogswell ME (2016) Trends in high blood pressure among United States adolescents across body weight category between 1988 and 2012. J Pediatr 169:166–173. e3
19. Okosun IS, Seale JP, Boltri JM, Davis-Smith M (2012) Trends and clustering of cardiometabolic risk factors in American adolescents from 1999 to 2008. J Adolesc Health 50(2):132–139
20. Gidding SS, Bao W, Srinivasan SR, Berenson GS (1995) Effects of secular trends in obesity on coronary risk factors in children: the Bogalusa Heart study. J Pediatr 127(6):868–874
21. Freedman DS, Goodman A, Contreras OA et al (2012) Secular trends in BMI and blood pressure among children and adolescents: the Bogalusa Heart study. Pediatrics 130(1):e159–e166
22. Luepker RV, Jacobs DR, Prineas RJ, Sinaiko AR (1999) Secular trends of blood pressure and body size in a multi-ethnic adolescent population: 1986 to 1996. J Pediatr 134(6):668–674
23. McCrindle BW, Manlhiot C, Millar K et al (2010) Population trends toward increasing cardiovascular risk factors in Canadian adolescents. J Pediatr 157(5):837–843
24. McCarron P, Okasha M, McEwen J, Smith GD (2001) Changes in blood pressure among students attending Glasgow University between 1948 and 1968: analyses of cross sectional surveys. BMJ 322(7291):885–889
25. Watkins D, McCarron P, Murray L et al (2004) Trends in blood pressure over 10 years in adolescents: analyses of cross sectional surveys in the Northern Ireland Young Hearts project. BMJ 329(7458):139
26. Peters H, Whincup PH, Cook DG et al (2012) Trends in blood pressure in 9 to 11-year-old children in the United Kingdom 1980-2008: the impact of obesity. J Hypertens 30(9):1708–1717
27. Haas GM, Bertsch T, Schwandt P (2012) Trends of components of the metabolic syndrome in German first graders throughout 10 years: the PEP Family Heart Study. Cholesterol 2012:231962
28. Kollias A, Antonodimitrakis P, Grammatikos E et al (2009) Trends in high blood pressure prevalence in Greek adolescents. J Hum Hypertens 23(6):385–390
29. Smpokos EA, Linardakis M, Papadaki A, Kafatos A (2011) Secular changes in anthropometric measurements and blood pressure in children of Crete, Greece, during 1992/93 and 2006/07. Prev Med 52(3–4):213–217
30. Viikari JS, Juonala M, Raitakari OT (2006) Trends in cardiovascular risk factor levels in Finnish children and young adults from the 1970s: the cardiovascular risk in Young Finns Study. Exp Clin Cardiol 11(2):83–88
31. Kouda K, Nakamura H, Nishio N et al (2010) Trends in body mass index, blood pressure, and serum lipids in Japanese children: Iwata population-based annual screening (1993-2008). J Epidemiol 20(3):212–218

32. Shirasawa T, Ochiai H, Nishimura R et al (2012) Secular trends in blood pressure among Japanese schoolchildren: a population-based annual survey from 1994 to 2010. J Epidemiol 22(5):448–453
33. Khang YH, Lynch JW (2011) Exploring determinants of secular decreases in childhood blood pressure and hypertension. Circulation 124(4):397–405
34. Dong B, Wang Z, Song Y et al (2015) Understanding trends in blood pressure and their associations with body mass index in Chinese children, from 1985 to 2010: a cross-sectional observational study. BMJ Open 5(9):e009050
35. Dong B, Wang HJ, Wang Z et al (2013) Trends in blood pressure and body mass index among Chinese children and adolescents from 2005 to 2010. Am J Hypertens 26(8):997–1004
36. Zhang YX, Zhao JS, Sun GZ et al (2012) Prevalent trends in relatively high blood pressure among children and adolescents in Shandong, China. Ann Hum Biol 39(3):259–263
37. Liang YJ, Xi B, Hu YH et al (2011) Trends in blood pressure and hypertension among Chinese children and adolescents: China Health and Nutrition Surveys 1991-2004. Blood Press 20(1):45–53
38. Lin FH, Chu NF, Hsieh AT (2012) The trend of hypertension and its relationship to the weight status among Taiwanese young adolescents. J Hum Hypertens 26(1):48–55
39. Agirbasli M, Tanrikulu B, Arikan S et al (2008) Trends in body mass index, blood pressure and parental smoking habits in middle socio-economic level Turkish adolescents. J Hum Hypertens 22(1):12–17
40. Agirbasli M, Adabag S, Ciliv G (2011) Secular trends of blood pressure, body mass index, lipids and fasting glucose among children and adolescents in Turkey. Clin Obes 1(4–6):161–167
41. Chiolero A, Paradis G, Madeleine G et al (2009) Discordant secular trends in elevated blood pressure and obesity in children and adolescents in a rapidly developing country. Circulation 119(4):558–565
42. Xi B, Bovet P, Hong YM et al (2016) Recent blood pressure trends in adolescents from China, Korea, Seychelles and the United States of America, 1997-2012. J Hypertens 34(10):1948–1958
43. Roulet C, Bovet P, Brauchli T et al (2016) Secular trends in blood pressure in children: a systematic review. J Clin Hypertens (Greenwich) 19(5):488–497. doi:10.1111/jch.12955
44. Jafar TH (2009) Children, obesity, and high blood pressure: Asian populations at high risk. Am J Hypertens 22(1):6–7
45. Chiolero A, Bovet P, Paradis G, Paccaud F (2007) Has blood pressure increased in children in response to the obesity epidemic? Pediatrics 119(3):544–553
46. He FJ, MacGregor GA (2006) Importance of salt in determining blood pressure in children: meta-analysis of controlled trials. Hypertension 48(5):861–869
47. Geleijnse JM, Hofman A, Witteman JC et al (1997) Long-term effects of neonatal sodium restriction on blood pressure. Hypertension 29(4):913–917
48. Xi B, Zhang T, Zhang M et al (2016) Trends in elevated blood pressure among US children and adolescents: 1999-2012. Am J Hypertens 29(2):217–225
49. Lurbe E, Grassi G (2012) Uncertainty in the assessment of trends in childhood blood pressure. J Hypertens 30(9):1697–1698
50. Dong B, Wang Z, Ma J (2016) Urban-rural disparity in blood pressure among Chinese children: 1985-2010. Eur J Pub Health 26(4):569–575
51. Barker DJ, Osmond C, Golding J et al (1989) Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ 298(6673):564–567
52. Mzayek F, Hassig S, Sherwin R et al (2007) The association of birth weight with developmental trends in blood pressure from childhood through mid-adulthood: the Bogalusa Heart study. Am J Epidemiol 166(4):413–420
53. Chen W, Srinivasan SR, Hallman DM, Berenson GS (2010) The relationship between birthweight and longitudinal changes of blood pressure is modulated by beta-adrenergic receptor genes: the Bogalusa Heart study. J Biomed Biotechnol 2010:543514
54. Power C (1994) National trends in birth weight: implications for future adult disease. BMJ 308(6939):1270–1271

# Hypertension in Children and Adolescents

# 46

Empar Lurbe

## 46.1 Introduction

During the last few decades, hypertension (HTN) in children and adolescents has gained ground in cardiovascular medicine, thanks to the progress made in several areas of pathophysiological and clinical research. The available data concerning childhood blood pressure (BP) has increased, and clinicians can use pediatric reference BP data to determine whether BP is in the normal range or is at a level that warrants evaluation or preventive intervention. It has also become possible to refine BP-derived parameters and to identify subclinical end-organ damage through measures and markers now far more sensitive than those available years ago.

## 46.2 Definition of Hypertension

In childhood and adolescents, BP increases during growth and maturation, and adolescence is a fast growth period during which body mass and BP change rapidly. These are the main reasons for why reference BP values over the last few decades have been referred to as ones specific to sex, age, and/or height in children and adolescents up to 18 years of age. Because of the persisting lack of European reference values that incorporate age, sex, and height throughout the entire pediatric age range, the normative data on auscultatory clinical measurements provided by the US Task Force [1] are recommended to be used as reference values [2, 3] although they should be considered the potential differences among countries and ethnicities.

E. Lurbe, M.D., Ph.D., F.A.H.A.
Department of Pediatrics, Consorcio Hospital General, University of Valencia,
Avda Tres Cruces s/n, 46014 Valencia, Spain

CIBER Fisiopatología Obesidad y Nutrición (CB06/03), Instituto de Salud Carlos III,
Madrid, Spain
e-mail: empar.lurbe@uv.es



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_46

**Table 46.1** Classification of hypertension in children and adolescents [3]

| | 0–15-year | 16-year and older |
|---|---|---|
| Category | SBP and/or DBP percentile | SBP and/or DBP values |
| Normal | <90th | <130/85 mmHg |
| High normal | ≥90th to <95th percentile | 130–139/85–89 mmHg |
| Hypertension | ≥95th percentile | ≥140/90 mmHg |
| Stage 1 hypertension | 95th percentile to the 99th percentile plus 5 mmHg | 140–159/90–99 mmHg |
| Stage 2 hypertension | >99th percentile plus 5 mmHg | 160–179/100–109 mmHg |
| Isolated systolic hypertension | SBP ≥95th percentile and DBP<90th percentile | ≥140/<90 mmHg |

In 2009 the European Society of Hypertension (ESH) Guidelines in children and adolescents were released [2]. The criteria to define BP categories were normal BP defined as systolic BP (SBP) and diastolic BP (DBP) less than 90th percentile for age, sex, and height; HTN is defined as SBP and/or DBP persistently 95th percentile or more, measured on at least three separate occasions with the auscultatory method. Children with average SBP or DBP 90th percentile or more but less than 95th percentile are classified as having high-normal BP.

Recently, the 2016 Guidelines [3] introduce a new criteria for boys and girls 16 or older since considering the 95th percentile for age, sex, and height as the definition of HTN; a 16-year-old boy in the 95th percentile for height would be defined as hypertensive by an office SBP of 137–140 mmHg, while a 16-year-old girl in the same height percentile by an office SBP of only 132 mmHg. One–two years later, no longer seen by a pediatrician, the girl will now be diagnosed as normotensive or high normal by the family physician on the basis of adult guidelines. Even greater differences in diagnosis will occur in adolescents shorter than the 95th height percentile. Due to these differences in diagnosis, a consensus in the 2016 Guidelines is given that for boys and girls aged 16 or older, the definition of HTN should no longer be based on the 95th percentile but on the absolute cutoff used for adults, which defines high normal (130–139/85–89 mmHg) and HTN (≥140/90 mmHg) [3].

The classification of hypertension in children and adolescents following the criteria of ESH Guidelines 2016 [3] is shown in Table 46.1.

## 46.3 Prevalence and Incidence

The prevalence in school-aged children appears to be increasing, perhaps as a result of the increased prevalence of obesity in the last years. The majority of these children have mild HTN, most often primary. A small group of children have much higher BPs, usually due to a secondary cause.

The prevalence of HTN in children and adolescents in Europe is reported to be ranging from 2.2 to 22% [4–9], depending on the demographic characteristics of the subjects analyzed, age, sex, body weight, as well as ethnicity. More specifically, it increases with age and in boys rather than in girls. Body weight has the greatest impact on the rate of HTN, and the body mass index is the strongest

determining factor of adolescent BP [5]. One study has reported a 27 and 47% in overweight or obese 6–18-year-old subjects [9]. A higher BP in Hispanic and African-Americans and a lower one in Asians, when either is compared to Caucasians, were observed [10].

Besides the characteristics of the subjects, the number of BP measurements is crucial in the prevalence of HTN. Statistically, 5% of children had a BP measurement above the 95th percentile during a single office visit; however, BP tended to normalize on subsequent measurements due to the accommodation of the child to the measurement procedure and to the statistical phenomenon of regression toward the mean [11]. Consequently, the prevalence of HTN decreased after repeated examination.

Clinically relevant are the studies in incidence that addressed the concern with progression from high-normal BP to HTN. In some groups of children, masked HTN, type 2 diabetes mellitus, obesity, or repaired aortic coarctation have an increased risk to progress. In contrast, in general population of adolescents, 10–19 years, the rate of progression from normotension to HTN was 0.4/100 subjects/year, and among those who had high normal, it was 1.1/100 subjects/year [12]. In normotensive children the risk is higher in boys than in girls [13].

## 46.4 Office and Out-of-Office Blood Pressure

Blood pressure variability and observer bias limit the reliability of office measurements that have the potential for inaccuracies [14]. Automated techniques of BP out-of-office measurement may overcome these limitations; therefore ambulatory BP monitoring, and also home BP measurements, became an established instrument for the diagnosis and follow-up of HTN in children and adolescents [15].

Ambulatory BP monitoring has the potential to obtain more accurate and reproducible BP values than does office BP, provides an estimation of circadian variability, and has become a recognized tool in evaluation and prognosis [16–18], overcoming many of the limitations associated with office BP measurements. Recommendations for the use of ambulatory BP and home BP measurements are presented in the recent 2016 Guidelines [3] (Table 46.2).

Office and ambulatory BP do not necessarily agree. The so-called white-coat HTN and masked HTN are conditions in which BP is discrepant from the majority of a person's BPs, depending on the setting. White-coat HTN is defined as elevated BP in an office setting, yet normal BP elsewhere. The reported frequency of white-coat HTN varies, perhaps as a result of the criteria used to establish the diagnosis, with values ranging from very low (1%) to as high as 44% [19]. Children with white-coat HTN tend to have an intermediate left ventricular mass (LVM) index between that of normotensive patients and patients with sustained hypertension, suggesting that white-coat HTN may be associated with hypertensive end-organ damage [20].

The inverse phenomenon, masked HTN, defined as normal BP in the office setting but elevated BP outside the office occurs in approximately 10% of children and adolescents [21–23]. The persistence and clinical significance of the phenomenon

**Table 46.2** Recommendations for 24-h ambulatory BP monitoring [3]

| |
|---|
| *During the process of diagnosis* |
| Confirm hypertension before starting antihypertensive drug treatment in order to avoid treatment of white-coat hypertension |
| Target-organ damage (LVH, microalbuminuria) and office BP normal (masked hypertension) |
| Type 1 and type 2 diabetes |
| Chronic kidney disease |
| Renal, liver, or heart transplant |
| Severe obesity with or without sleep-disordered breathing |
| Hypertensive response during the treadmill test |
| Discrepancy between office BP and home BP |
| *During antihypertensive drug treatment* |
| Evaluate for apparent drug-resistant hypertension |
| Assessment of BP control in children with target-organ damage |
| Symptoms of hypotension |
| *Clinical trials* |
| *Other clinical conditions* |
| Autonomic dysfunction |
| Suspicion of catecholamine-secreting tumors |

*LVH* left ventricular hypertrophy

was analyzed in a prospective study involving 234 adolescents [23]. In 40%, the abnormal elevation of the daytime ambulatory BP persisted over a minimum of 6 months. Adolescents with persistent masked HTN were more than twice as likely as those without it to have a parental history of HTN, higher ambulatory pulse rate, higher body mass index, and more frequently had left ventricular hypertrophy than did normotensive subjects. Alone or in combination, these findings were associated with a predisposition to the development of persistent hypertension and were linked to increased cardiovascular risk in later life [23].

Apart from the ability of ambulatory BP monitoring to obtain more accurate and reproducible BP values, another advantage of this method is the assessment of BP during sleep and, therefore, the estimation of circadian variability [24]. There is a physiological nocturnal fall of BP during sleep in response to the reduction of sympathetic tone. Patients with sympathetic overdrive renal disease and/or volume expansion are consistently found to have abnormalities in circadian BP variability with a high prevalence of the so-called non-dipping pattern, i.e., a blunted nocturnal fall. Although this may be related to the severity of hypertension, as in subjects with renovascular hypertension, in the majority of the other underlying causes, the degree of hypertension does not predict the amount of circadian variation.

## 46.5 Central Blood Pressure and the Case of Isolated Systolic Hypertension

Central BP values in the aortic root may be estimated by calculations from the pulse wave recorded in peripheral arteries, either radial or carotid. Central BP values are usually lower than those obtained from the brachial artery. The differences between central and peripheral values, the so-called amplification phenomenon, depend on

the elastic properties of the aorta and the large vessels, as well as the distance between the peripheral point of recording and the aortic root—the larger the distance, the greater the difference.

Elasticity of the great vessels is particularly relevant in adolescence and causes systolic BP to be considerably higher in upper limb arteries than in the ascending aorta and left ventricle. This phenomenon results in isolated systolic HTN, the main HTN subtype in youth. The presence of elevated brachial and radial systolic BP with normal central BP was first described by O'Rourke in six young male patients aged 14–23 years; the conclusions in that report were based on noninvasive methods for estimating central BP [25]. This phenomenon was described as "spurious systolic HTN" and has been attributed to exaggerated pulse pressure amplification from central to peripheral arteries as a result of increased vascular elasticity and has been considered most likely to be a benign condition. However, there is some lack of consensus among researchers. Recent data from the Anglo-Cardiff Collaborative Trial demonstrate that although pulse pressure amplification is moderately higher in young individuals with isolated systolic HTN compared with normotensive individuals, stroke volume is markedly higher [26]. This has potential clinical significance because elevated stroke volume associated with isolated systolic HTN in youth is highly likely to transform to sustained HTN. The clinical significance and prognostic value of isolated systolic HTN in youth are controversial, as longitudinal studies are lacking [27, 28].

In youth with isolated systolic HTN, the assessment of central BP may be crucial for identifying those individuals in whom antihypertensive treatment can be postponed for long periods of time, because their hemodynamic characteristics, arterial distensibility, and risk of developing sustained HTN may not differ from those of normotensive individuals. One longitudinal study demonstrated that isolated systolic HTN in young to middle-age persons implies a relatively low risk of developing HTN needing treatment when central BP is low [29]. Nevertheless, as it is not clear what the outcome will be, youth with isolated systolic HTN, even without elevated central BP, should be followed over time. The future need for antihypertensive treatment remains an open question [28].

## 46.6 Etiology

Pediatric HTN is associated with a broad spectrum of diseases that changes from childhood through adolescence. Definable causes of HTN are the rule in the early years of life, whereas essential hypertension is more common in adolescence. Consequently, techniques for the evaluation and diagnosis of hypertension differ, at least in part, among the different age groups.

Usually, sustained HTN in children and adolescents is classified as secondary with a specific cause that may be correctable or as essential and without an identifiable cause [2]. The most common causes of HTN can change during childhood. Essential HTN is rarely seen in infants and young children, but its prevalence increases significantly in adolescence [30]. A good general rule to follow is that the

likelihood of identifying a secondary cause of HTN is inversely related to the age of the child and directly related to the degree of BP elevation. Consequently, the evaluation of children with HTN, especially young children and those with severe HTN, should be comprehensive and aimed at identifying known causes of the disease.

The distribution of definable causes of HTN is associated with a broad spectrum of diseases and clearly varies with age. Renal parenchymal disorders predominate, accounting for a majority of secondary causes [31]. Renal parenchymal disorders with renovascular disease and coarctation of the aorta account for 70% [32] to 90% [33] of all cases. These figures vary depending not only on the age group but also on referral center and referral bias. Additionally, HTN is often related to prescribe drugs with hypertensive potential. Other infrequent causes of sustained HTN, tumors and central nervous and endocrine disorders, must be considered once more common causes of secondary HTN have been eliminated. An emerging cause of secondary HTN is a single-gene mutation that produces large changes in BP [3].

Hypertension in term or preterm neonates may be seen in up to 2% of all infants in modern neonatal intensive care units. Although the definition of HTN in this age group has not been completely standardized, useful data to this regard has been published [34] and may be used to facilitate the identification of such infants. As in older children, the causes of HTN in neonates are numerous, with the two largest categories being renovascular and parenchymal diseases. More specifically, umbilical artery catheter-associated thromboembolism affecting either the aorta or the renal arteries probably accounts for the majority of cases of HTN seen in the typical neonatal intensive care unit [35]. A careful history and physical examination will usually identify the cause in most cases, without the need for extensive laboratory or radiological testing.

In very young children (<6 years), HTN is most often the result of such renal parenchymal disease as glomerulonephritis, renal scarring, polycystic kidney diseases, and renal dysplasia. Renal artery stenosis and cardiovascular disorders like coarctation of the aorta, less frequent causes of HTN in this age group, are usually detected within the first decade of life. Late in the first decade and throughout the second, essential HTN is the most common cause of sustained HTN, particularly in those children with mild asymptomatic disease [36].

When confronted with an infant, child, or adolescent with HTN, the first question to be asked concerns the chronicity of the problem. Clearly, the most helpful information to have when one is attempting to establish the HTN chronicity are past BP readings. Unfortunately, these are by no means always available since routine BP measurements in children over 3 years of age are not yet uniformly obtained. In the absence of previous readings, one needs to look for the evidence of target-organ damage: left ventricular hypertrophy or an increase in urinary albumin excretion.

A diagnostic evaluation is based to some degree on the level of BP, age, sex, clinical findings, and family history. A significant number of children with secondary forms of hypertension, often renal ones, can be identified using a selective approach. Afterward, a careful selection of the necessary test often shortens the diagnostic process. The most common causes of HTN, according to age group, are shown in Table 46.3.

**Table 46.3** Age distribution of hypertension etiologies

| |
|---|
| *<1 month* |
| Renal arterial thrombosis |
| Congenital renal disease |
| Umbilical canalization |
| Bronchopulmonary dysplasia |
| *>1 month to <6 years* |
| Renal parenchymal disease |
| Coarctation of the aorta |
| Renovascular disease |
| *>6 years to 10 years* |
| Renal parenchymal disease |
| Renovascular disease |
| Essential hypertension |
| *>10 years* |
| Essential hypertension |
| Renal parenchymal disease |
| Exogenous hypertension (drugs) |
| Endocrine disorders |
| Coarctation of the aorta |
| Mendelian genetic disorders |

## 46.7 Target-Organ Damage and Consequences

Blood pressure level and the duration of arterial HTN result in target-organ damage. Heart failure, renal insufficiency, cerebral seizures, hemorrhagic stroke, visual impairment, encephalopathy, and posterior reversible leukoencephalopathy are complications associated with severe HTN in children and even in infants. Nowadays, these complications seldom occur in infants and children due to early diagnosis and efficient antihypertensive treatment.

Because overt morbid cardiovascular events are rare in the majority of hypertensive children, attention has focused on other markers of HTN injury, such as early renal damage, increased left ventricular mass index, and functional or organic vascular abnormalities. Cardiovascular damage develops in parallel to renal damage, although the cardiovascular sequelae of childhood onset HTN, such as left ventricular hypertrophy and dysfunction and atherosclerosis, may not become clinically relevant before adulthood. More recently, the study of early alterations of central nervous system functions has become a focus of interest.

### 46.7.1 Heart

The abnormal increase of left ventricular mass and/or geometry has been recognized as one of the most important markers of risk for HTN-induced cardiovascular morbidity and mortality in adults. In children and adolescents, left ventricular mass is normalized for height in meters raised to the allometric power of 2.7, in order to linearize the relation between LVM and height. The resulting LVM index (LVMI) is expressed in $g/m^{2.7}$. More recently reported definitions of left ventricular hypertrophy

(LVH) are suggested to improve the ability to identify abnormalities in LV geometry; these account for the inverse dependence of the LVMI with body size in infants and young children by using age- and sex-specific partition values for LVH [37].

Cross-sectional studies have indeed shown that the major determinants of left ventricular growth are body size and sex, with a smaller contribution made by BP [38–40]. The potential role of adiposity in the increment of left ventricular mass has been highlighted. Adiposity and left ventricular mass are related in childhood, and this association tracks and becomes stronger in young adulthood.

Studies of normal and hypertensive children have found that systolic BP and left ventricular mass index are positively associated across a wide range of BP values, with no clear threshold to predict a pathologically increased left ventricular mass index. The relationship between left ventricular mass index and systolic BP is more evident when BP is measured using 24-h ambulatory BP monitoring.

Operational thresholds for left ventricular mass have been established. Both the allometric definition of excessive mass (>51 g/m$^2$) and the percentile distribution of mass and geometry have been recommended [37]. Using these operational thresholds, a few studies have analyzed the prevalence of left ventricular hypertrophy in not only healthy but also hypertensive children and adolescents. In hypertensive children, the prevalence of left ventricular hypertrophy ranges from 24 to 40% in different pediatric studies [41–44]. In children with chronic kidney disease, left ventricular hypertrophy develops relatively early and becomes more prevalent as kidney function decreases [45].

Cardiac end-organ damage from HTN exists in children and left ventricular mass assessment seems to be important in the management of childhood HTN, since it is the most prominent evidence of target-organ damage in childhood HTN. The ESH Guidelines for BP in children has recommended performing echocardiography in all hypertensive children [2, 3]. The presence of left ventricular hypertrophy is an indication to initiate or intensify antihypertensive therapy. Studies assessing the effect of medical therapy of pediatric HTN on left ventricular mass need to be performed in the future to further reinforce the necessity of monitoring left ventricular mass.

### 46.7.2 Kidney

Evidence of the importance of BP values in the evolution of renal disease has come from several clinical studies in children with or without established renal insufficiency. In the post hoc analysis of a randomized multicenter study in children with chronic renal failure, renal survival was inversely associated with systolic BP [46], with a steeper decline of GFR in patients with office systolic BP above 120 mmHg. Further findings suggest that BP in the low-normal range should probably be targeted for patients with renal disease [47, 48]. Evidence for this concept was subsequently established in the prospective randomized ESCAPE Trial, which showed better 5-year renal survival in children with chronic kidney disease when strict BP control below the 50th percentile of mean arterial pressure was aimed for [17].

Increased urinary albumin excretion is considered a sensitive marker of hypertension-induced renal damage. Proteinuria indicates glomerular damage in primary and secondary glomerulopathies, and since proteinuria tends to increase with the duration and severity of hypertension, it should be targeted by lowering BP. Even small amounts of urinary albumin excretion (UAE), microalbuminuria, are correlated with the progression of nephropathy and linked to a higher cardiovascular risk. Initial information came from cross-sectional studies which demonstrated a clustering of cardiovascular risk factors and organ damage associated with even a subtle increase in UAE. The role of microalbuminuria in pediatrics, however, is limited to diabetic children and adolescents. The prevalence of elevated urinary albumin excretion is not prominent in obese children (2.4%), and when it is increased, it depends mainly on metabolic factors [49]. While the significance of microalbuminuria in pediatric essential hypertension has yet to be established, routine urinary albumin assessment is recommended by the ESH Guidelines [2, 3].

### 46.7.3 Vessels

Hypertension-induced abnormalities in arterial structure and function are important because they underlie many adverse effects. Assessment of vascular damage, however, received little attention prior to the advent of the advanced ultrasound technology which permits noninvasive study of vascular walls and lumen. Intima-media thickness measurement at the carotid artery is the most common of the methods to assess structural abnormalities. Since intima-media thickness is influenced by age and sex during childhood and adolescence [50], measured values should be related to percentiles or expressed as standard deviation scores.

Ultrasound examination of the carotid arteries with measurement of intima-media thickness and/or the presence of plaques has been shown to predict the occurrence of both stroke and myocardial infarction, independently of traditional CV risk factors [51]. In the few pediatric studies available, intima-media thickness tends to be increased in hypertensive children and adolescents compared to normotensive controls [52, 53], although one study did not observe differences among normotensives, white-coat, masked, or sustained hypertensives [22]. Moreover, a relationship between intima-media thickness and endothelial function has been established in the Cardiovascular Risk in Young Finns Study [54]. The impact of other cardiovascular risk factors besides HTN, such as cholesterol levels or smoking, needs to be considered in the interpretation of intima-media thickness levels, since these have been associated with intima-media thickness as well [55]. The International Childhood Cardiovascular Cohort Consortium demonstrated that individuals with persistently elevated BP from childhood to adulthood had increased risk of carotid atherosclerosis. This risk was reduced if elevated BP during childhood resolved by adult age [56]. Moreover, measurement is not trivial and subject to some observer bias. Hence, despite the increasing evidence for its predictive value in cardiovascular disease, carotid intima-media thickness assessments have not yet been recommended universally for routine clinical use [2, 3].

Finally, carotid-femoral pulse wave velocity is the "gold standard" for measuring aortic stiffness. In adults aortic stiffness has independent predictive value for fatal and nonfatal CV events in hypertensive patients [57]. Pulse wave velocity, a well-accepted surrogate marker and intermediate endpoint of cardiovascular morbidity, is increased in children and adolescents with elevated and even high-normal BP [58]. Notably obesity, the factor most frequently related to essential HTN in adolescents, blunts the expected increment in pulse wave velocity of hypertensive and high-normal subjects [58].

### 46.7.4 Central Nervous System

Traditional diagnostic procedures to assess early organ damage in the central nervous system included neurologic and ophthalmologic clinical evaluation, electroencephalography, and, in emergency cases, cranial magnetic resonance image to exclude intracranial hemorrhage or cerebral edema. Magnetic resonance imaging has largely replaced the computerized tomography scan, due to its better detection of small silent brain infarcts, micro-bleeds, and white matter lesions [2, 3].

As pediatric HTN is on the rise, there has been increased interest in evaluating its impact on neurocognitive function. There is now emerging evidence that children with HTN manifest neurocognitive differences when compared with normotensive controls, potentially representing early signs of hypertensive target-organ damage to the brain. Preliminary evidence suggests that children with hypertension may manifest deficits on measures of neurocognition. They have an increased prevalence of learning difficulties and have altered cerebrovascular reactivity. Children with HTN associated with obesity may be at increased risk for depression and anxiety in comparison to their normotensive and/or non-overweight peers [59]. Neurocognitive studies of children have focused principally on cognitive domains of attention and working memory, executive functions, and recall of newly learned information. However, pediatric reports to date have been limited to database and single-center studies [60]. The practical implications of the potential neurocognitive deficits associated with HTN in childhood are not clear. It is even less clear whether there would be any implications for longer-term cognitive reserve and ultimate cognitive decline in later life [61, 62]. Meanwhile, clinicians should be aware of these emerging concerns. Arterial hypertension should be ruled out routinely in children with deteriorating cognitive function, and referral for neurocognitive testing should be considered in children with HTN who are struggling academically.

## 46.8 Treatment Approach

The goal of treatment for hypertension is to decrease the short- and long-term risks of cardiovascular, neurological, and renal disease. Reducing BP alone is insufficient to obtain this objective; the issues of obesity, hyperlipidemia, smoking, and glucose intolerance must also be addressed if present.

Currently the initial treatment for children and adolescents with less severe hypertension and those with primary hypertension and no hypertensive target-organ damage involves lifestyle modifications: weight reduction, exercise, and dietary intervention [3]. Weight reduction has been shown to be an effective therapy for obese children with hypertension. Weight reduction in children, as in adults, however, is a goal that is difficult to achieve in the long run. Exercise helps to reduce systolic and diastolic BP levels as well as it does weight. Diets with a high intake of fruits, vegetables, low-fat dairy, and whole grains while reducing the intake of foods high in saturated fat and refined sugar are recommended. Dietary salt restriction has a very important place in the control of BP. The current recommendation for adequate daily sodium intake is only 1.2 g/day for 4–8-year-olds and 1.5 g/day for children older than that.

Although conservative measures clearly can reduce BP, these options are often insufficient for achieving the treatment goal, in part because of patient and of family compliance problems. The decision to initiate pharmacologic treatment in the first or the second decade in the absence of symptoms and in otherwise healthy individuals is not easy since the long-term consequences of untreated hypertension and the benefits of therapy remain unknown. For these reasons, a definitive indication for initiating pharmacologic treatment should be ascertained before medication is prescribed in a child or adolescent. The indications for antihypertensive therapy are symptomatic hypertension, secondary hypertension, hypertensive target-organ damage, diabetes, and persistent hypertension despite non-pharmacologic measures [3].

In making pharmacological treatment decisions for children, clinicians previously had to adapt the results of adult trials in selecting antihypertensive agents [51]. This approach, although possibly effective in lowering BP, is fraught with problems, especially the unknown differences in both the metabolism and adverse effect profiles of these drugs in children versus adults, as well as the unknown long-term effects of antihypertensive medications on the growth and development of children. Off-label use, with all of its implied risks, was often the only option available to physicians who treated children with hypertension.

Since 1998, many antihypertensive drugs have been successfully studied in children, and more studies are currently underway or planned. An ideal clinical trial would yield useful information and at the same time minimize the risks to the children participating in the study. Traditional methods of determining the safety and effectiveness of antihypertensive agents in adults may be modified to meet the challenges presented by pediatric patients. The advantages of ambulatory BP or home BP monitoring make it attractive for use in pediatric antihypertensive trials. This type of monitoring may avoid some of the practical difficulties normally encountered in trials in this age group, mainly those involving the eligibility of the subjects or the assessment of the endpoint trial. Ambulatory BP monitoring may play an even more important role than it does in adults because of the smaller number of children who have hypertension [63].

No particular class of antihypertensive drugs has been shown to be superior to another in terms of its effect in children. In some cases, the choice of

antihypertensive agent depends on the underlying cause. When choosing among the available therapies, the clinician must also consider efficacy, dosing availability and frequency, adverse effects, and cost. Taking into account that compliance is a very important issue if BP control can be achieved with a single drug that is taken once a day, it will improve the compliance and should be taken into consideration when the initial agent is chosen. If monotherapy is introduced, and after titration BP control is not achieved, the next step is to add a second drug. The choice of the drug to be added needs to look for additive antihypertensive activity and to buffer potential secondary effects.

Therapy must be monitored closely both for efficacy and for potential adverse effects. Efficacy in reducing BP values should be monitored by using both office and out-of-office BP measurements. The target BP goal in children with uncomplicated primary hypertension and no hypertensive target-organ damage should be <95th percentile for gender, age, and height, but it is probably wiser and safer to aim at a BP below the 90th percentile, provided this goal can be attained by well-tolerated treatment. For children with chronic renal disease, diabetes, or hypertensive target-organ damage, the goal BP should be <75th percentile [3]. After starting treatment, the frequency of office BP readings depends on the severity of hypertension and on the given BP goal. Stage 2 HTN or stage 1 in the presence of cardiac or renal failure needs to be monitored weekly until the goal is achieved. In subjects with diabetes or organ damage, a monthly check may be appropriate. At-home BP monitoring can help in long-term control and even improve compliance. Twenty-four hour ambulatory BP monitoring is recommended in cases of resistant hypertension, progression of organ damage despite an apparent good BP control and in those with frequent circadian variability abnormalities, chronic renal failure, and diabetes mellitus. Female patients of childbearing potential should be counseled about the need to use an effective method of contraception when treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker is indicated, because exposure to these drugs, even in the first trimester, may have adverse effects on the developing fetus [64].

The success of a given antihypertensive treatment, however, is difficult to estimate solely by the extent of BP reduction in part due to the impact of BP values on risk which depends on the existence of underlying organ damage and the coincident influence of other cardiovascular risk factors. Then, above and beyond BP values in an individual subject, it is necessary to monitor the impact of antihypertensive treatment in the development or regression of hypertension-induced early end-organ damage (left ventricular hypertrophy, urinary albumin excretion, intima-media wall thickness) or in a potential carbohydrate metabolism derangement [3]. Among the potential intermediate endpoints, left ventricular hypertrophy seems to be the most useful in this age group. Assessment and monitoring of these intermediate objectives may play an important role in providing scientific evidence for delineating the best antihypertensive treatment to apply. Although improvement in the intermediate endpoints may be followed by a substantial reduction of risk, the potential differences in success among the different classes of drugs are still a matter of debate.

The appropriate duration of treatment for a child or adolescent is unknown. Some patients require lifelong therapy, and others may experience an improvement or even a resolution to their hypertension. For these reasons, if BP is under excellent control and no organ system damage is present, medications can be tapered and even discontinued under careful observation if the underlying cause is corrected. BP should be monitored carefully upon follow-up, since a significant proportion of patients become hypertensive again in the future.

## References


1. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004) The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. Pediatrics 114:555–576
2. Lurbe E, Cifkova R, Cruickshank JK et al (2009) A management of high blood pressure in children and adolescents: recommendations of the European Society of Hypertension. J Hypertens 27:1719–1742
3. Lurbe E, Cruickshank JK, Dominiczak A et al (2016) 2016 European Society of Hypertension (ESH) guidelines for the management of high blood pressure in children and adolescents. J Hypertens 34:1887–1920
4. Chiolero A, Cachat F, Burnier M et al (2007) Prevalence of hypertension in schoolchildren based on repeated measurements and association with overweight. J Hypertens 25:2209–2217
5. Katona É, Zrínyi M, Lengyel S et al (2011) The prevalence of adolescent hypertension in Hungary—the Debrecen hypertension study. Blood Press 20:134–139
6. Ostrowska-Nawarycz L, Nawarycz T (2007) Prevalence of excessive body weight and high blood pressure in children and adolescents in the city of Łódź. Kardiol Pol 65:1079–1087
7. Akgun C, Dogan M, Akbayram S et al (2010) The incidence of asymptomatic hypertension in school children. J Nippon Med Sch 77:160–165
8. Maldonado J, Pereira T, Fernandes R et al (2011) An approach of hypertension prevalence in a sample of 5381 Portuguese children and adolescents. The AVELEIRA registry. "Hypertension in children". Blood Press 20:153–157
9. Flechtner-Mors M, Neuhauser H, Reinehr T et al (2015) APV initiative and the BMBF Competence Network Obesity. Blood pressure in 57,915 pediatric patients who are overweight or obese based on five reference systems. Am J Cardiol 115:1587–1594
10. Harshfield GA, Wilson ME (2004) Ethnic differences in childhood blood pressure. In: Portman RJ, Sorof JM, Ingelfinger JR (eds) Pediatric hypertension. Humana Press, Totowa, pp 293–305
11. Gardner LS, Heady JA (1973) Some effects of within-person variability in epidemiological studies. J Chronic Dis 26:781–795
12. Redwine KM, Acosta AA, Poffenbarger T et al (2012) Development of hypertension in adolescents with pre-hypertension. J Pediatr 160:98–103
13. Lurbe E, Thijs L, Torro MI et al (2013) Sexual dimorphism in the transition from masked to sustained hypertension in healthy youths. Hypertension 62:410–414
14. O'Brien E, Asmar R, Beilin L et al (2003) European Society of Hypertension Working Group on blood pressure monitoring. European Society of hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens 21:821–848
15. Ingelfinger JR (2014) The child or adolescent with elevated blood pressure. N Engl J Med 370:2316–2325
16. Lurbe E, Redon J, Kesani A et al (2002) Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. N Engl J Med 347:797–805
17. Wühl E, Trivelli A, Picca S, ESCAPE Trial Group et al (2009) Strict blood-pressure control and progression of renal failure in children. N Engl J Med 361:1639–1650

18. Ingelfinger JR (2009) Blood-pressure control and delay in progression of kidney disease in children. N Engl J Med 361:1701–1703
19. Lurbe E, Torró MI, Alvarez J (2013) Ambulatory blood pressure monitoring in children and adolescents: coming of age? Curr Hypertens Rep 15:143–149
20. Kavey RE, Kveselis DA, Atallah N, Smith FC (2007) White coat hypertension in childhood: evidence for end-organ effect. J Pediatr 150:491–497
21. Matsuoka S, Awazu M (2004) Masked hypertension in children and young adults. Pediatr Nephrol 19:651–654
22. Stabouli S, Kotsis V, Toumanidis S et al (2005) White-coat and masked hypertension in children: association with target organ damage. Pediatr Nephrol 20:1151–1155
23. Lurbe E, Torro I, Alvarez V et al (2005) Prevalence, persistence, and clinical significance of masked hypertension in youth. Hypertension 45:493–498
24. Parati G, Stergiou G, O'Brien E, European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability et al (2014) European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens 32:1359–1366
25. O'Rourke MF, Vlachopoulos C, Graham RM (2000) Spurious systolic hypertension in youth. Vasc Med 5:141–145
26. McEniery CM, Franklin SS, Wilkinson IB, Cockcroft JR (2013) Isolated systolic hypertension in the young: a need for clarity. J Hypertens 31:1911–1913
27. Lurbe E, Torro MI, Alvarez-Pitti J et al (2016) Central blood pressure and pulse wave amplification across the spectrum of peripheral blood pressure in overweight and obese youth. J Hypertens 34:1389–1395
28. Lurbe E, Redon J (2016) Isolated systolic hypertension in young people is not spurious and should be treated: con side of the argument. Hypertension 68:276–280
29. Saladini F, Santonastaso M, Mos L, HARVEST Study Group et al (2011) Isolated systolic hypertension of young-to-middle-age individuals implies a relatively low risk of developing hypertension needing treatment when central blood pressure is low. J Hypertens 29:1311–1319
30. Vogt BA (2001) Hypertension in children and adolescents: definition, pathophysiology, risk factors and long-term sequelae. Curr Ther Res 62:283–297
31. Goonasekera CDA, Dillon MJ (2000) Measurement and interpretation of blood pressure. Arch Dis Child 82:261–265
32. Arar MY, Hogg RJ, Arant BS, Seikaly MG (1994) Etiology of sustained hypertension in children in the Southwestern United States. Pediatr Nephrol 8:186–189
33. Lieberman E (1990) Hypertension in childhood and adolescence. In: Kaplan N (ed) Clinical hypertension, 5th edn. Williams and Wilkins, Baltimore, pp 407–433
34. Flynn J (2000) Neonatal hypertension: diagnosis and management. Pediatr Nephrol 14:332–341
35. Zubrow AB, Hulman S, Kushner H, Falkner B (1995) Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. J Perinatol 15:470–479
36. Kay JD, Sinaiko AR, Daniels SR (2001) Pediatric hypertension. Am Heart J 142:422–432
37. Khoury PR, Mitsnefes M, Daniels SR, Kimball TR (2009) Age-specific reference intervals for indexed left ventricular mass in children. J Am Soc Echocardiogr 22:709–714
38. Malcolm DD, Burns TL, Mahoney LT, Lauer RM (1993) Factors affecting left ventricular mass in childhood: the Muscatine Study. Pediatrics 92:703–709
39. de Simone G, Devereux RB, Daniels SR et al (1995) Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. J Am Coll Cardiol 25:1056–1062
40. Foster BJ, Gao T, Mackie AS, Zemel BS, Ali H, Platt RW, Colan SD (2013) Limitations of expressing left ventricular mass relative to height and to body surface area in children. J Am Soc Echocardiogr 26:410–418
41. Sivanandam S, Sinaiko AR, Jacobs DR Jr et al (2006) Relation of increase in adiposity to increase in left ventricular mass from childhood to young adulthood. Am J Cardiol 98:411–415

43. Litwin M, Niemirska A, Sladowska J et al (2006) Left ventricular hypertrophy and arterial wall thickening in children with essential hypertension. Pediatr Nephrol 21:811–819
44. Daniels SR, Loggie JM, Khoury P, Kimball TR (1998) Left ventricular geometry and severe left ventricular hypertrophy in children and adolescents with essential hypertension. Circulation 97:1907–1911
45. Kavey RE (2013) Left ventricular hypertrophy in hypertensive children and adolescents: predictors and prevalence. Curr Hypertens Rep 15:453–457
46. Wingen A, Fabian-Bach C, Schaefer F, Mehls O (1997) European study group for nutritional treatment of chronic renal failure in childhood. Randomized multicenter study of a low protein diet on the progression of chronic renal failure in children. Lancet 349:1117–1123
47. Toto RD (2005) Treatment of hypertension in chronic kidney disease. Semin Nephrol 25:435–439
48. Sarnak MJ, Greene T, Wang X, Beck G, Kusek JW, Collins AJ, Levey AS (2005) The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. Ann Intern Med 142:342–351
49. Lurbe E, Torro MI, Alvarez MI et al (2013) Prevalence and factors related to urinary albumin excretion in obese youths. J Hypertens 31:2230–2236
50. Jourdan C, Wühl E, Litwin M et al (2005) Normative values for intima-media thickness and distensibility of large arteries in healthy adolescents. J Hypertens 23:1707–1715
51. Mancia G, Fagard R, Narkiewicz K, Task Force Members et al (2013) 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 31:1281–1357
52. Sass C, Herbeth B, Chapet O et al (1998) Intima media thickness and diameter of carotid and femoral arteries in children, adolescents and adults from the Stanislas cohort: effect of age, sex, anthropometry and blood pressure. J Hypertens 16:1593–1602
53. Sorof JM, Alexandrov AV, Cardwell G, Portman RJ (2003) Carotid artery intimal-medial thickness and left ventricular hypertrophy in children with elevated blood pressure. Pediatrics 111:61–66
54. Juonala M, Viikari JSA, Laitinen T et al (2004) Interrelations between brachial endothelial function and carotid intima-media thickness in young adults. The cardiovascular risk in Young Finns Study. Circulation 110:2918–2923
55. Davis PH, Dawson JD, Riley WA, Lauer RM (2001) Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: the Muscatine Study. Circulation 104:2815–2819
56. Juhola J, Magnussen CG, Berenson GS et al (2013) Combined effects of child and adult elevated blood pressure on subclinical atherosclerosis: the International Childhood Cardiovascular Cohort Consortium. Circulation 128:217–224
57. Vlachopoulos C, Ioakeimidis N, Aznaouridis K et al (2014) Prediction of cardiovascular events with aortic stiffness in patients with erectile dysfunction. Hypertension 64:672–678
58. Lurbe E, Torro I, Garcia-Vicent C et al (2012) Blood pressure and obesity exert independent influences on pulse wave velocity in youth. Hypertension 60:550–555
59. Lande MB, Kupferman JC, Adams HR (2012) Neurocognitive alterations in hypertensive children and adolescents. J Clin Hypertens (Greenwich) 14:353–359
60. Lande MB, Adams HR, Kupferman JC et al (2013) A multicenter study of neurocognition in children with hypertension: methods, challenges, and solutions. J Am Soc Hypertens 7:353–362
61. Kupferman JC, Lande MB, Adams HR, Pavlakis SG (2013) Primary hypertension and neurocognitive and executive functioning in school-age children. Pediatr Nephrol 28:401–408
62. Marc Y, Gao J, Balavoine F et al (2012) Central antihypertensive effects of orally active aminopeptidase A inhibitors in spontaneously hypertensive rats. Hypertension 60:411–418
63. Lurbe E, Sorof JM, Daniels SR (2004) Clinical and research aspects of ambulatory blood pressure monitoring in children. J Pediatr 144:7–16
64. Cooper WO, Hernandez-Diaz S, Arbogast PG et al (2006) Major congenital malformations after first-trimester exposure to ACE-inhibitors. N Engl J Med 354:2443–2451

# Part X

# Management and Therapeutic Approaches

# 47 What Is New and What Is Different in Recent Guidelines on Antihypertensive Treatment? Looking Forward to Guidelines Reappraisal

Alberto Zanchetti

## 47.1 Approach to Guidelines

Guidelines on arterial hypertension management have an almost 40-year-long history, the first documents providing guides in the area being the Joint National Committee report on Detection, Evaluation and Treatment of High Blood Pressure published in 1977 [1] and the World Health Organization Technical Report on Arterial Hypertension published in 1978 [2]. Both the US Joint National Committee and the World Health Organization, the latter in conjunction with the International Society of Hypertension, have continued to issue guidelines at intervals of approximately 3–4 years, while the European Society of Hypertension (ESH) in collaboration with the European Society of Cardiology (ESC) published their first guidelines in 2003 [3]. This was a huge success as this European document received 3165 citations. In the 2 years after its publication (2004–2005), it was the top medical article for citations received, but an even greater success was met by the second edition of the ESH-ESC hypertension guidelines in 2007 [4, 5], which in the following years received as many as 5494 citations.

The second half of 2013 and the beginning of 2014 have seen a flowering of new hypertension guidelines, with the appearance of the third edition of the European Society of Hypertension—European Society of Cardiology guidelines in July [6, 7], the Practice Guidelines of the two European societies in October [8], the Evidence Based Guidelines of Members of the US Eighth Joint National Committee (JNC-8) [9] and the Clinical Practice Guidelines for the Management of Hypertension in the Community jointly issued by the American Society of Hypertension (ASH) and the International Society of Hypertension (ISH) [10, 11], which both appeared in January 2014.

A. Zanchetti
Emeritus Professor, University of Milan, Milano, Italy

Scientific Director, Istituto Auxologico Italiano IRCCS, Milano, Italy
e-mail: alberto.zanchetti@auxologico.it



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_47

In an editorial I wrote to accompany publication of the last document in the Journal of Hypertension, I commented: "When multiple guidelines are produced, the easiest temptation is to contrast them in order to provide ground for learned debates among experts" [12]. As a matter of fact, different guidelines being all prepared by groups of experts cannot substantially differ in those areas in which a clear body of evidence has been produced by adequate investigation. Fortunately, hypertension is an area of cardiovascular medicine in which evidence in favour of therapeutic intervention was searched for by randomized controlled trials long before the same methodology was applied to the treatment of other cardiovascular illnesses, such as myocardial infarction and heart failure [13]. When we have recently completed a meta-analysis of all blood pressure-lowering randomized controlled trials (versus placebo or less active therapy) from 1996 to 2014, we have compared our results to those of previous meta-analyses on a less extensive number of trials and noticed a substantially consistent reduction of all major cardiovascular outcomes [14]. When restricting analyses to those trials investigating all types of outcomes, we have calculated that a standardized systolic/diastolic blood pressure (SBP/DBP) reduction of 10/5 mmHg significantly decreases risk of stroke and heart failure to the greatest extent (by about 40%) but also significantly reduces risk of coronary heart disease events by about 20%, that of cardiovascular mortality by 22% and that of all cause death by 24% [15]. It is no surprise, therefore, that all guidelines strongly recommend blood pressure lowering in hypertension.

However, once the benefit of lowering blood pressure had been established by placebo-controlled (or more versus less intense treatment) trials, "most of the practical questions worth being investigated have remained substantially unexplored or insufficiently explored" [13]. Not that there have been few trials of antihypertensive treatment in the last 20 years or so, but most of them have focused on comparing the benefits of different antihypertensive regimens, with the intent to show specific benefits of new agents or, vice versa, the superiority of the older ones" [13]. These trials have certainly led to useful information, but recently, when we have surveyed trials head to head comparing different antihypertensive agents, we have identified as many as 50 trials for 58 two-drug comparisons in a total of 247,006 patients followed for an average of 4.17 years (1,029,768 patient-years) [16], probably too much effort to end up with the conclusion that what really matters is lowering blood pressure whatever the agents administered.

As a consequence, some of the questions the physician is confronted with daily have not received a definite answer by suitable intervention trials. Some of these questions are:

1. When should antihypertensive treatment be initiated, and, in particular, should grade 1 hypertensive individuals at low-to-moderate cardiovascular risk be treated?
2. What should the systolic/diastolic blood pressure targets of treatment be? Lower than 140 mmHg or lower than 130 mmHg for SBP? Lower than 90 mmHg or lower than 80 mmHg for DBP?
3. Should antihypertensive treatment differ in the elderly?

More than in the answers given to these questions, the various guidelines published in 2013–2014 differ in their approach to these questions, namely in the approach explicitly or tacitly followed in considering the fundamental problem: should guideline recommendations be based on evidence or wisdom [13]? The authors of the Joint National Committee eighth report [9] chose a very rigid approach, based on a very strict interpretation of evidence: for the US authors evidence exclusively consists not only of data provided by randomized controlled intervention trials, but only data derived from a limited number of trials the Committee judged of sufficiently high quality. Although strict criteria based on data quality may appear to confer high quality to the recommendations, nonetheless any selection is easily susceptible to bias. In the recent past, severe criteria of trial selection have often led to base guidelines predominantly on trials run by the guidelines authors themselves: something of this kind happened to the Joint National Committee Report 7 [17], predominantly based on results of the ALLHAT trial [18], and to the 2011 National Institute for Clinical Excellence (NICE) guidelines in the UK [19], largely based on the results of ASCOT [20].

The Joint National Committee Report 8 [9] proudly defines itself as evidence-based, but the decision of concentrating only in areas in which evidence was available necessarily limits the recommendations to the area of drug treatment, and to only nine major questions, of which one only receive Grade A (strong) recommendation, and as many as six receive the lowest Grade E recommendation (expert opinion). Admittedly, the Joint National Committee Report 8 has the merit of being short, only 14 pages, but even 14 pages may be too many for a single grade A recommendation.

The approach followed by the American Society of Hypertension and the International Society of Hypertension in preparing their Clinical Practice Guidelines [10, 11] has been, so to say, the opposite of that of the Joint National Committee Report 8 [9]. It is a concise document (13 pages) in which recommendations covering various aspects of hypertension management are given deliberately without mentioning whether these recommendations are supported by the weight of evidence or only based on expert opinion. This points to an unresolved issue about the format of guidelines.

> "Should any recommendation be supported by a detailed discussion of the weight of evidence upon which it is based, and practicing physicians instructed about the strength of each recommendation, and informed about which statement is supported by trial evidence and which by experts' wisdom only?... Or, vice versa, should guideline documents be short and agile, easy to read and, in particular, to follow in medical practice, mixing trial evidence with experts' wisdom, without exposing practicing physicians to the dilemma whether their decisions are evidence based or wisdom based only?"
>
> "The problem has been recurrent through the history of hypertension guidelines, as it results from two opposite, difficult to reconciliate requirements: to provide straightforward, simple recommendations and, on the same time, to inform the physicians not only about what they should do, but also about why they should follow any specific recommendations for the management of hypertension" [12].

Probably, the best realistic solution is that taken by the European Society of Hypertension and the European Society of Cardiology, whose 2013 guidelines for

the management of hypertension have been published in two formats, an extensive version with detailed explanations and citation of data supporting each recommendation [6, 7], and a concise one (defined Practice guidelines) focused on major recommendations [8], both versions, however, being accompanied by colour tables indicating the class of recommendations and the level of evidence upon which these were based.

## 47.2 Initiation of Antihypertensive Treatment

Recent hypertension guidelines, confronted with the question when to initiate antihypertensive treatment have acknowledged that trial-based evidence about the systolic blood pressure threshold deserving treatment is weak. The Eighth Report members of the Joint National Committee [9] recommend to "initiate pharmacologic treatment to lower blood pressure at systolic blood pressure ≥140 mmHg" only as expert opinion. The 2013 ESH-ESC guidelines [6] give a strong recommendation (Class I, Level A) to promptly initiate antihypertensive drug treatment "in individuals with grade 2 and 3 hypertension with any level of cardiovascular risk", but advise to consider "initiation of antihypertensive drug therapy in grade 1 hypertensive patients at low to moderate risk only when blood pressure is within this range at several repeated visits or elevated by ambulatory blood pressure criteria, and remain within this range despite a reasonable period with lifestyle measures" [6]. Despite all these precautions, this recommendation is classified only as class IIa (Conflicting evidence and or divergence of opinion) and level of evidence B (Fig. 47.1). The ASH/ISH clinical practice guidelines point out that in patients with stage (=grade) 1 hypertension, drug treatment can be delayed for some months if patients do not have evidence for abnormal cardiovascular findings or other risk factors, and suggest that, in settings in which healthcare resources are highly limited, "clinicians can consider extending the non-drug observation period in uncomplicated stage 1 hypertensive patients" [10]. Likewise, according to the 2011 NICE hypertension guidelines in the UK, antihypertensive drug treatment should be offered to people with stage 1 hypertension only when 10-year cardiovascular risk is equivalent to 20% or greater [19].

The issue about the poor level of evidence favouring active blood pressure lowering in individuals with SBP/DBP values within what is usually defined grade 1 (or stage 1) hypertension (SBP 140–159 mmHg and/or DBP 90–99 mmHg) was first raised in 2009 [21], when we called attention on the fact that the few trials conducted in the 1970–1980s on what was then defined as "mild" hypertension could not be taken as reliable evidence supporting treatment of grade 1 hypertension, as patients included in the "mild" hypertension trials had been recruited on the basis of DBP values only (often in a range much wider than the 90–99 mmHg range now used for grade 1 hypertension). Furthermore, in most of the "mild" hypertension trials SBP was not considered among recruitment criteria, and in some of them SBP could be as high as up to 200 mmHg.

| Recommendations | Class | Level |
|---|---|---|
| Prompt initiation of drug treatment is recommended in individuals with grade 2 and 3 hypertension with any level of CV risk, a few weeks after or simultaneously with initiation of lifestyle changes. | I | A |
| Lowering BP with drugs is also recommended when total CV risk is high because of OD, diabetes, CVD or CKD, even when hypertension is in the grade 1 range. | I | B |
| Initiation of antihypertensive drug treatment should also be considered in grade 1 hypertensive patients at low to moderate risk, when BP is within this range at several repeated visits or elevated by ambulatory BP criteria, and remains within this range despite a reasonable period of time with lifestyle measures. | IIa | B |
| In elderly hypertensive patients drug treatment is recommended when SBP is ≥160 mmHg. | I | A |
| Antihypertensive drug treatment may also be considered in the elderly (at least when younger than 80 years) when SBP is in the 140–159 mmHg range, provided that antihypertensive treatment is well tolerated. | IIb | C |
| Unless the necessary evidence is obtained it is not recommended to initiate antihypertensive drug therapy at high normal BP. | III | A |
| Lack of evidence does also not allow recommending to initiate antihypertensive drug therapy in young individuals with isolated elevation of brachial SBP, but these individuals should be followed closely with lifestyle recommendations. | III | A |

**Fig. 47.1** Initiation of antihypertensive drug treatment according to the 2013 European Society of Hypertension/European Society of Cardiology hypertension guidelines (from Mancia et al. [6], by courtesy of Journal of Hypertension). *BP* blood pressure, *CKD* chronic kidney disease, *CV* cardiovascular, *CVD* cardiovascular disease, *OD* organ damage, *SBP* systolic blood pressure

In 2012, a Cochrane collaboration tried to overcome this difficulty by making an individual patient meta-analysis of the "mild" hypertension trials including only data from those patients whose blood pressure values were in the grade 1 range [22]. This meta-analysis was unable to show a significant reduction in the risk of any cardiovascular outcome alone or in combination (Fig. 47.2a). Although based on a small number of patients and events (e.g. only 30 strokes) these negative results were widely publicized as warning against overtreating grade 1 hypertension, and obviously influenced the cautious attitude all guidelines had when discussing management of grade 1 hypertension.

Since 2013 new analyses of available data have been conducted [23]. The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) has made an attempt to increase the number of patients and events by including other individuals from other trials with baseline SBP/DBP in the grade 1 range [24]. As illustrated in Fig. 47.2b this extended meta-analysis showed significant reductions in stroke, major cardiovascular events, cardiovascular and all-cause mortality. The BPLTTC conclusions, however, were limited by the fact that about 50% of the added individuals were already under some blood pressure-lowering treatment at baseline and, therefore, could not be correctly defined as grade 1 hypertensive patients. Furthermore, most of the individuals added had diabetes with the consequence that the total cardiovascular risk in the placebo group of the BPLTTC meta-analysis (6.2% cardiovascular death in 10 years) was beyond the limits of low-to-moderate risk (which normally is <5%).

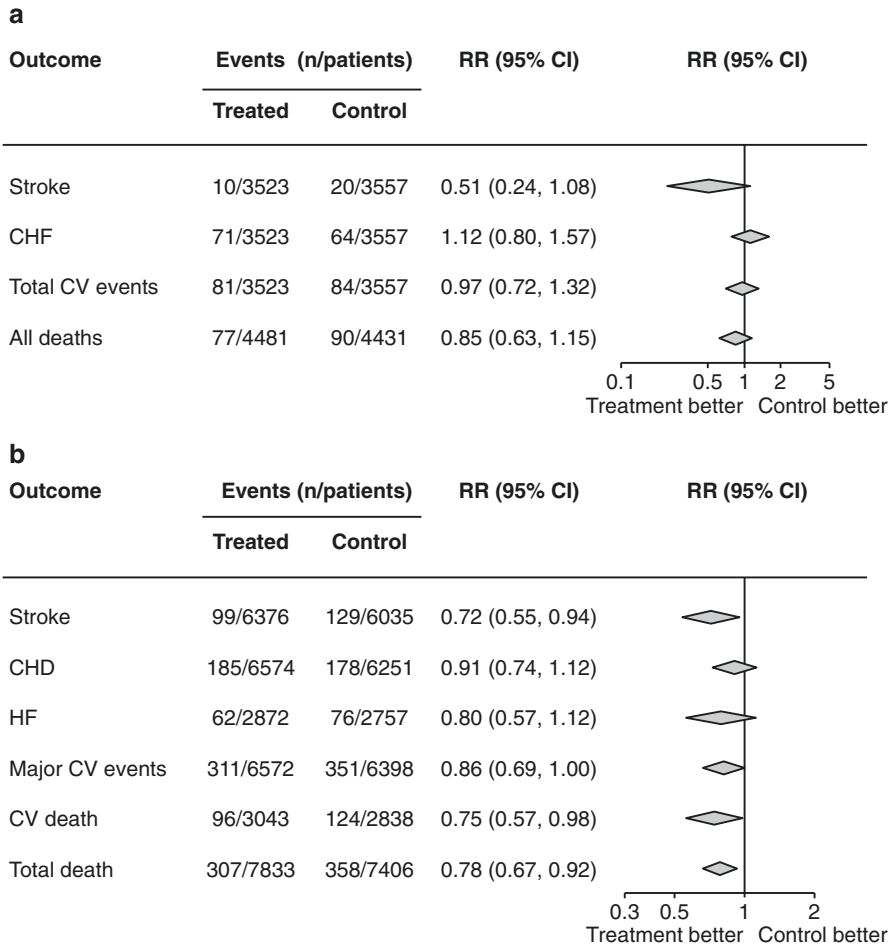



**Fig. 47.2** Effects of blood pressure lowering in grade 1 hypertension. Results from two meta-analyses of individual data. (**a**) Data from the Cochrane Collaboration Meta-analysis. (**b**) Data from the Blood Pressure Lowering Treatment Trialists' Collaboration meta-analysis. *CHD* coronary heart disease, *CI* confidence interval, *CV* cardiovascular, *HF* heart failure, *RR* risk ratio (redrawn from data in Diao et al. [22] and Sundström et al. [24]

Another, more powerful meta-analytical approach has recently been followed by our group. Among all blood pressure-lowering trials, we have chosen those in which patients had been randomized in the absence of current treatment, in order to avoid incorrectly labelling hypertension grade. We identified 32 trials (including 104,359 patients) that could be classified as investigating grade 1, 2 or 3 hypertension on the basis of the average baseline blood pressure in each trial [25]. Significant reductions of the risk of all major cardiovascular outcomes were found to be induced by blood pressure lowering at all grades of hypertension with no trend towards different relative risk reductions at different hypertension grades. In

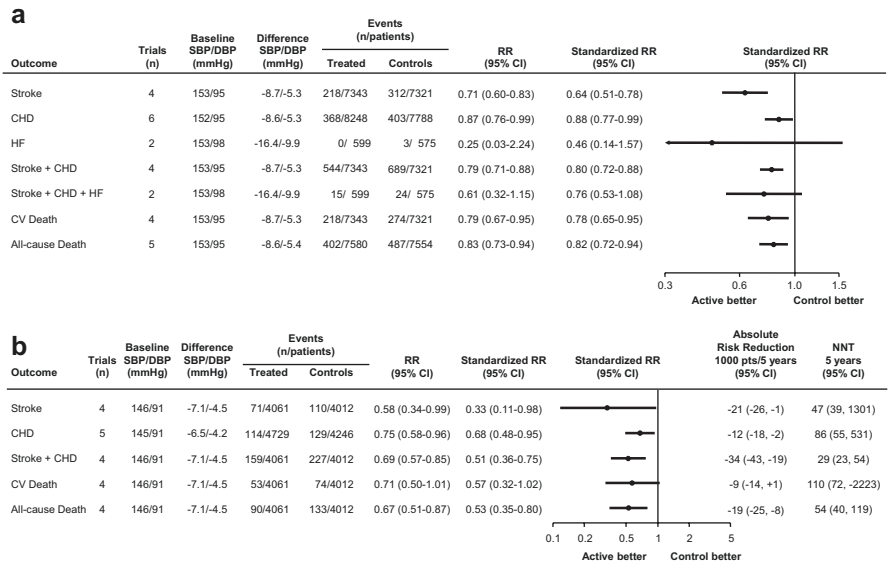



**Fig. 47.3** Effects of blood pressure lowering in trials of grade 1 hypertension. Meta-analyses of trials in which average baseline SBP/DBP were in the range 140–159/90–99 mmHg (all trials without or minimal baseline antihypertensive drugs at randomization). (**a**) All grade 1 trials independent of total cardiovascular risk. (**b**) Only grade 1 trials or trial subgroups at low-to-moderate risk. *CHD* coronary heart disease, *CI* confidence interval, *CV* cardiovascular, *HF* heart failure, *RR* risk ratios. Standardized RR is to a SBP/DBP difference of 10/5 mmHg (from Thomopoulos et al. [25], by courtesy of Journal of Hypertension)

particular, 6 trials in 16,036 individuals were classified as grade 1 hypertension, and their meta-analysis showed significant reductions in the risk of stroke, coronary events, the composite of stroke and coronary events, cardiovascular and all-cause deaths (Fig. 47.3a). As some of these trials included patients at high cardiovascular risk, another meta-analysis was done only including trials on trial subgroups with mean baseline SBP/DBP values in the grade 1 range and a low-to-moderate cardiovascular risk (<5% cardiovascular death in 10 years in the control groups). Also in the 8975 patients of this meta-analysis, blood pressure-lowering treatment significantly decreased the risk of stroke, coronary events, the composite of stroke and coronary events and all-cause death (Fig. 47.3b) absolute risk reduction was large, amounting to 21 strokes, 34 major cardiovascular events and 19 deaths prevented every 1000 patients treated for 5 years [25].

The results of this meta-analysis [25] have been further supported by the recently published results of the Heart Outcomes Prevention Evaluation (HOPE)-3 trial [26], which has shown a significant 27% reduction of major cardiovascular outcomes in patients at an intermediate level of cardiovascular risk with baseline SBP values higher than 143.5 mmHg (mean 154 mmHg), though no benefit of blood pressure-lowering treatment was seen in individuals with lower baseline blood pressure values (high-normal blood pressure).

On the whole, despite the absence of a large randomized placebo-controlled trial specifically investigating blood pressure-lowering treatment in patients with grade 1 hypertension at low-to-moderate cardiovascular risk, the data of our meta-analysis [25] and the results of the HOPE-3 subgroup analysis [26] provide a much stronger evidence-based support in favour of initiating active drug treatment in grade 1 low-to-moderate risk hypertensives [27] than the arguments that could be used in the 2013 ESH-ESC guidelines [6].

## 47.3 Blood Pressure Treatment Targets

Although the target values to which blood pressure should be brought by drug treatment to optimize treatment benefits is of prominent interest for the patients and the treating physicians, it is surprising that, among the large number of antihypertensive treatment trials (as many as 70), so few (only 14) have compared the effects of more versus less intense blood pressure-lowering treatment, and even less have investigated precise SBP or DBP targets [13].

When we first reviewed the subject in 2009 [21], we showed that the recommendation frequent in guidelines current at the time [4, 5, 17], namely, to lower SBP to less than 130 mmHg, particularly in patients with high cardiovascular risk (e.g. post-stroke or post-myocardial infarction) and in hypertensives with diabetes, was unsupported by trial evidence or supported by controversial evidence. As a consequence, the 2013 ESH-ESC guidelines [6] recommended a SBP target of less than 140 mmHg in most groups of hypertensive patients (those at low-to-moderate cardiovascular risk, those with diabetes, those with previous stroke or transient ischemic attack, those with coronary heart disease, those with diabetic or nondiabetic chronic renal disease), though with a different class of recommendation and a different level of available evidence (Fig. 47.4) [6]. Likewise, the JNC-8 report [9] expresses the "expert opinion" that hypertensive individuals younger than 60 years should be treated to a goal SBP <140 mmHg, and a similar recommendation is given in the American Society of Hypertension/International Society of Hypertension guidelines [10].

Since 2013 new data and new analyses have become available. In 2014 we published a meta-analysis of 32 blood pressure-lowering trials (including 128,232 individuals), showing that risk of all outcomes could be significantly reduced when SBP in the treated group was lowered to values less than 150 mmHg and compared to SBP values above 150 mmHg in the control group and when it was lowered to values less than 140 mmHg in the treated group and compared to values above 140 mmHg in the control group. However, when SBP values below were compared to SBP above the cut-off of 130 mmHg, only stroke and all-cause death were significantly reduced [25].

In November 2015, the results of a large National Institutes of Health (NIH)-sponsored trial comparing a SBP goal of less than 120 mmHg with the usual goal of less than 140 mmHg were published [28]. The Systolic Blood Pressure Intervention Trial (SPRINT) was stopped early because of a significant reduction of the primary

| Recommendations | Class | Level |
|---|---|---|
| A SBP goal <140 mmHg: | | |
| a) is recommended in patients at low–moderate CV risk; | I | B |
| b) is recommended in patients with diabetes; | I | A |
| c) should be considered in patients with previous stroke or TIA; | IIa | B |
| d) should be considered in patients with CHD; | IIa | B |
| e) should be considered in patients with diabetic or non-diabetic CKD. | IIa | B |
| In elderly hypertensives less than 80 years old with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. | I | A |
| In fit elderly patients less than 80 years old SBP values <140 mmHg may be considered, whereas in the fragile elderly population SBP goals should be adapted to individual tolerability. | IIb | C |
| In individuals older than 80 years and with initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg provided they are in good physical and mental conditions. | I | B |
| A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated. | I | A |

**Fig. 47.4** Blood pressure targets in hypertensive patients according to the 2013 European Society of Hypertension/European Society of Cardiology hypertension guidelines (from Mancia et al. [6], by courtesy of Journal of Hypertension). *CHD* coronary heart disease, *CKD* chronic kidney disease, *CV* cardiovascular, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *TIA* transient ischemic attack

endpoint in the group with more intense blood pressure-lowering treatment. The results of SPRINT have been received with obvious interest, but have also raised some perplexities. Among the latter, it has been found surprising that stroke, the cardiovascular outcome known to be most sensitive to blood pressure decrease, was not significantly reduced in SPRINT. The most important benefit of the lower blood pressure goal in SPRINT was a marked reduction in heart failure risk, which may have resulted from a larger use of diuretics and renin-angiotensin system blockers in the group with lower blood pressure [29]. The point has also been raised that the blood pressure measurements in SPRINT may be hardly comparable with those used in other trials (as well as in current medical practice), as in SPRINT blood pressure was measured by an automatic device in absence of a doctor or nurse and the reported values were likely lower than those to be expected by the use of conventional office blood pressure [30].

After the publication of SPRINT, we have updated our meta-analysis of blood pressure-lowering trials stratified according to the three different cut-offs of achieved SBP (below and above 150, 140 and 130 mmHg). The meta-analysis now includes 35 trials on 138,452 individuals and shows (Fig. 47.5) that lowering SBP below 130 mmHg can significantly reduce most types of outcomes (stroke, coronary events, cardiovascular and all-cause death); however, absolute outcome reduction was definitely smaller than at higher SBP cut-offs [31], and permanent treatment discontinuations for adverse events were significantly greater [32]. It should be underlined, however, that even for SBP values less than 130 mmHg, mean risk

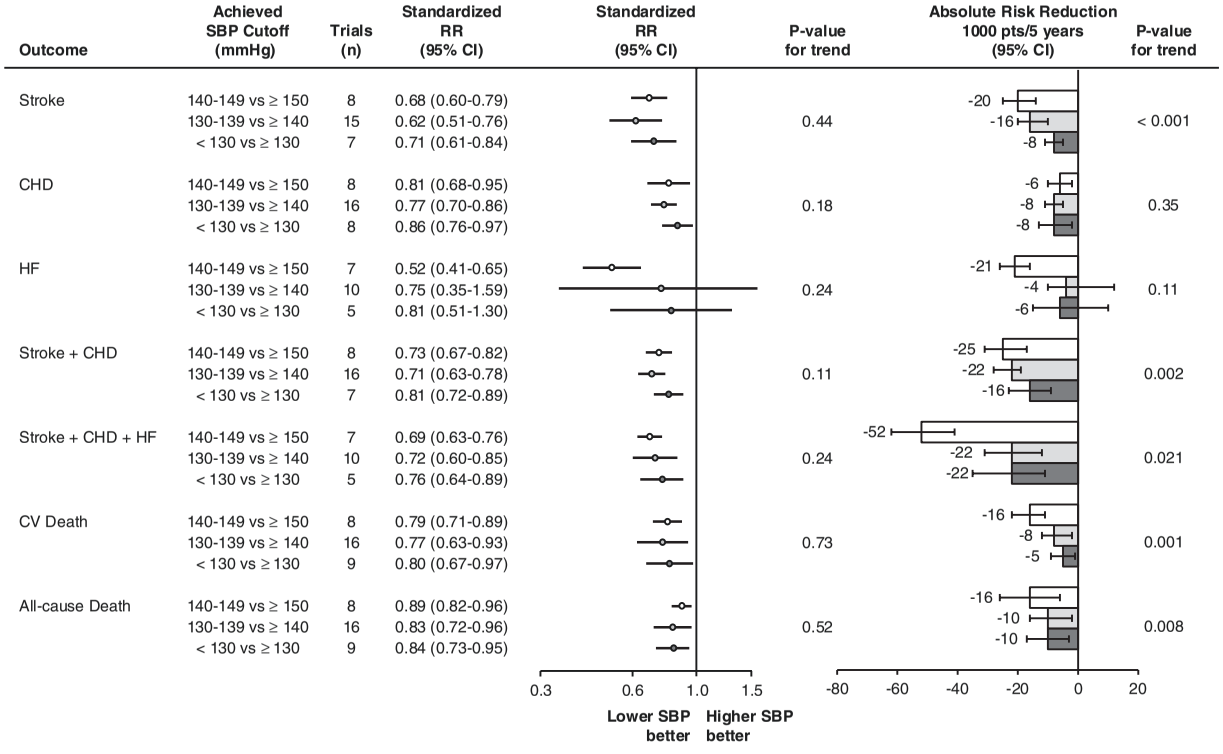



**Fig. 47.5** Effects of blood pressure-lowering treatment in trials stratified in three strata with mean SBP achieved by active or more intense treatment versus SBP achieved in the placebo or less intense treatment; 140–149 vs. ≥150 mmHg, 130–139 vs. ≥140 mmHg, <130 vs. ≥130 mmHg. Standardized RR is to a SBP/DBP difference of 10/5 mmHg. The histograms of the column Absolute risk reduction represent the number (and 95% CI) of events prevented every 1000 patients treated for 5 years. *BP* blood pressure, *CHD* coronary heart disease, *CI* confidence interval, *CV* cardiovascular, *HF* heart failure, *RR* risk ratio (from Thomopoulos et al. [31], by courtesy of Journal of Hypertension)

estimates of all outcomes were lower than one; hence there was no indication of a J-shaped relationship of the risk of any major outcome with achieved SBP, at least down to values several mmHg below 130.

In the various 2013 hypertension guidelines, recommendations are also given on DBP targets. All three major guidelines [6, 9, 10] suggest to achieve values below 90 mmHg in all hypertensive patients, with the ESH-ESC guidelines additionally recommending a target of below 85 mmHg in hypertensives with diabetes on the basis of evidence provided by the Hypertension Optimal Treatment (HOT) [33] and the United Kingdom Prospective Diabetes Study (UKPDS) [34] trials.

Since the publication of the 2013 guidelines, our meta-analyses have provided further evidence on the DBP target: both meta-analyses of trials in which achieved DBP were below 90 mmHg in the actively treated group and above 90 mmHg in the control group and below and above 80 mmHg showed significant reductions of all major outcomes [25, 31]. Admittedly, in trials in which achieved DBP values were below (versus above) 80 mmHg, also achieved SBP values were significantly lower values in the active versus the placebo treatment groups, and it is therefore difficult to ascribe the benefit of morbidity and mortality risk reduction to the lower DBP rather than to the lower SBP. In any case, our meta-analyses [25, 31] show that DBP values several mmHg lower than 80 mmHg are at least safe, being associated with a reduction rather than an increase in cardiovascular risk.

In conclusion, the recommendations given in 2013 by all major guidelines [6, 9, 10] to achieve SBP and DBP targets lower than 140 and, respectively, 90 mmHg can be placed now, thanks to new meta-analyses, on a much firmer ground and, therefore, with a greater strength. The additional recommendation can now be given that achieving SBP values lower than 130 mmHg and DBP values lower than 80 mmHg appear safe and can be associated with some further benefit provided that addition of drugs or dose increase are not incrementing adverse events and, consequently, the risk of permanent treatment discontinuation [32]. Whether these recommendations are valid for all phenotypes of hypertension, and particularly in the elderly or in secondary prevention, remains to be ascertained by further studies, such as the ongoing Stroke in Hypertension Optimal Treatment (SHOT) trial [35], and further analyses.

## References

1. (1977) Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. A co-operative study. JAMA 237:255–261
2. Report of a WHO Expert Committee (1978) Arterial hypertension. World Health Organ Tech Rep Ser 628:7–56
3. European Society of Hypertension-European Society of Cardiology Guidelines Committee (2003) 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 21:1011–1053
4. Mancia G, De Backer G, Dominiczak A et al (2007) 2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 25:1105–1187

5. Mancia G, De Backer G, Dominiczak A et al (2007) 2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 28:1462–1536
6. Mancia G, Fagard R, Narkiewicz K et al (2013) 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 31:1281–1357
7. Mancia G, Fagard R, Narkiewicz K et al (2013) 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 34:2159–2219
8. ESH/ESC Task Force for the Management of Arterial Hypertension (2013) 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC task force for the management of arterial hypertension. J Hypertens 31:1925–1938
9. James PA, Oparil S, Carter BL et al (2014) 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 311:507–520
10. Weber MA, Schiffrin EL, White WB et al (2014) Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. J Hypertens 32:3–15
11. Weber MA, Schiffrin EL, White WB et al (2014) Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. J Clin Hypertens 16:14–26
12. Zanchetti A (2014) What format for hypertension guidelines: a challenge for authors and users. J Hypertens 32:1–2
13. Zanchetti A (2011) Evidence and wisdom: recommendations for forthcoming guidelines. J Hypertens 29:1–3
14. Thomopoulos C, Parati G, Zanchetti A (2014) Effects of blood pressure lowering on outcome incidence in hypertension: 1. Overview, meta-analyses, and meta-regression analyses of randomized trials. J Hypertens 32:2285–2295
15. Thomopoulos C, Parati G, Zanchetti A (2016) Effects of blood pressure-lowering treatment: 6. Prevention of heart failure and new-onset heart failure—meta-analyses of randomized trials. J Hypertens 34:373–384
16. Thomopoulos C, Parati G, Zanchetti A (2015) Effects of blood pressure lowering on outcome incidence in hypertension: 5. Head-to-head comparisons of various classes of antihypertensive drugs. Overview and meta-analyses. J Hypertens 33:1321–1341
17. Chobanian AV, Bakris GL, Black HR et al (2003) Seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. Hypertension 42:1206–1252
18. ALLHAT officers and co-ordinators for the ALLHAT Collaborative Research Group (2002) Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 288:2981–2997
19. National Institute for Health and Clinical Excellence. Hypertension (CG127): clinical management of primary hypertension in adults. http://www.nice.org.uk/guidance/CG127
20. Dahlöf B, Sever PS, Poulter NR et al (2005) Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required vs. atenolol adding bendroflumethiazide as required in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) a multicentre randomised controlled trial. Lancet 366:895–906
21. Zanchetti A, Grassi G, Mancia G (2009) When should antihypertensive drug treatment be initiated and to what levels should systolic blood pressure be lowered? A critical reappraisal. J Hypertens 27:923–934

22. Diao D, Wright JM, Cundiff DK et al (2012) Pharmacotherapy for mild hypertension. Cochrane Database Syst Rev 8:CD006742
23. Zanchetti A (2015) Do we over treat mild hypertension? Expert Opin Pharmacother 16:1121–1126
24. Sundström J, Arima H, Jackson R et al (2015) Effects of blood pressure reduction in mild hypertension: a systematic review and meta-analysis. Ann Intern Med 162:184–191
25. Thomopoulos C, Parati G, Zanchetti A (2014) Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels. Overview and meta-analyses of randomized trials. J Hypertens 32:2296–2304
26. Lonn EM, Bosch J, López-Jaramillo P et al (2016) Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 374:2009–2020
27. López-Jaramillo P, Coca A, Sanchez R et al (2016) Hypertension guidelines: is it time to reappraise blood pressure thresholds and targets? Position of the Latin American Society of Hypertension. Hypertension 68:257–262
28. The SPRINT Research Group (2015) A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 373:2103–2116
29. Zanchetti A, Liu L, Mancia G et al (2016) Continuation of the ESH-CHL-SHOT trial after publication of the SPRINT: rationale for further study on blood pressure targets of antihypertensive treatment after stroke. J Hypertens 34:393–396
30. Kjeldsen SE, Lund-Johansen P, Nilsson PM et al (2016) Unattended blood pressure measurements in the systolic blood pressure intervention trial: implications for entry and achieved blood pressure values compared with other trials. Hypertension 67:808–812
31. Thomopoulos C, Parati G, Zanchetti A (2016) Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more versus less intensive blood pressure lowering and different achieved blood pressure levels—updated overview and meta-analyses of randomized trials. J Hypertens 34:613–622
32. Thomopoulos C, Parati G, Zanchetti A (2016) Effects of blood pressure lowering on outcome incidence in hypertension: 8. Outcome reductions versus discontinuations because of adverse drug events—meta-analyses of randomized trials. J Hypertens 34:1451–1463
33. Hansson L, Zanchetti A, Carruthers SG et al (1998) Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. HOT Study Group. Lancet 351:1755–1762
34. UK Prospective Diabetes Study Group (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 317:703–713
35. Zanchetti A, Liu L, Mancia G et al (2014) Blood pressure and LDL-cholesterol targets for prevention of recurrent strokes and cognitive decline in the hypertensive patient: design of the European Society of Hypertension- Chinese Hypertension League Stroke in Hypertension Optimal Treatment randomized trial. J Hypertens 32:1888–1897

# Place of Invasive Procedures in Blood Pressure Control

# 48

Costas Tsioufis, Alexandros Kasiakogias, Panayiotis Iliakis, and Vasilios Papademetriou

## Abbreviations

| | |
|---|---|
| BP | Blood pressure |
| dRHTN | Drug-resistant hypertension |
| HTN | Hypertension |
| RDN | Renal denervation |
| SBP | Systolic blood pressure |
| eGFR | Estimated glomerular filtration rate |

## 48.1 Introduction

The burden of uncontrolled hypertension (HTN) remains high worldwide, while a small proportion of patients presents with HTN resistant to multiple drug treatment even after undergoing a careful reevaluation and optimization of their regimen [1]. The knowledge of the central role of sympathetic activation in the pathophysiology of HTN and especially drug-resistant hypertension (dRHTN) coupled with advances in technology has led to the development and release of mechanical invasive treatments. Renal denervation (RDN) stands out of these new modalities as the most promising and with the most clinical efficacy and safety data and therefore will be the main issue of this chapter [2]. It is a minimally invasive procedure performed in order to cause ablation of the renal nerves with the use of a dedicated catheter reaching the renal arteries through a femoral approach.

C. Tsioufis (✉) • A. Kasiakogias • P. Iliakis
First Cardiology Clinic, Hippokration Hospital, University of Athens, Athens, Greece
e-mail: ktsioufis@hippocratio.gr

V. Papademetriou
Veteran Affairs Medical Center, Georgetown University, Washington, DC, USA



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_48

## 48.2 Pathophysiologic Background and Indications

Renal innervation consists of renal efferent sympathetic and afferent sensory nerves that travel through the adventitia of the renal arteries (Fig.48.1) [3]. Efferent sympathetic stimulation leads to increased renal tubular sodium reabsorption, increased renin secretion, water retention, and a reduction in blood flow as a consequence of renal vasoconstriction. The afferent sensory fibers regulate central sympathetic outflow and respond to various stimuli such as intrarenal pressure (renal mechanoreceptors), ischemia, and hypoxia (renal chemoreceptors). The concept of RDN is the disruption of the renal nerves that serve as the link between a heightened central sympathetic outflow and an impaired renal excretory function.

A number of expert documents have been published that have extensively discussed the population indicated for the procedure, the clinical steps before deciding RDN, and the various technical issues [1, 4]. Patients that have been considered as candidates for RDN based on clinical trial data are those with severe dRHTN defined by an office SBP ≥160 mmHg (≥150 mmHg in type 2 diabetes) despite treatment with at least three different types of antihypertensive drugs including a diuretic. Treatment resistance should be confirmed with out-of-office BP measurements and after management of contributing lifestyle factors, screening for secondary causes of HTN, and treatment optimization (Fig. 48.2). However, after the

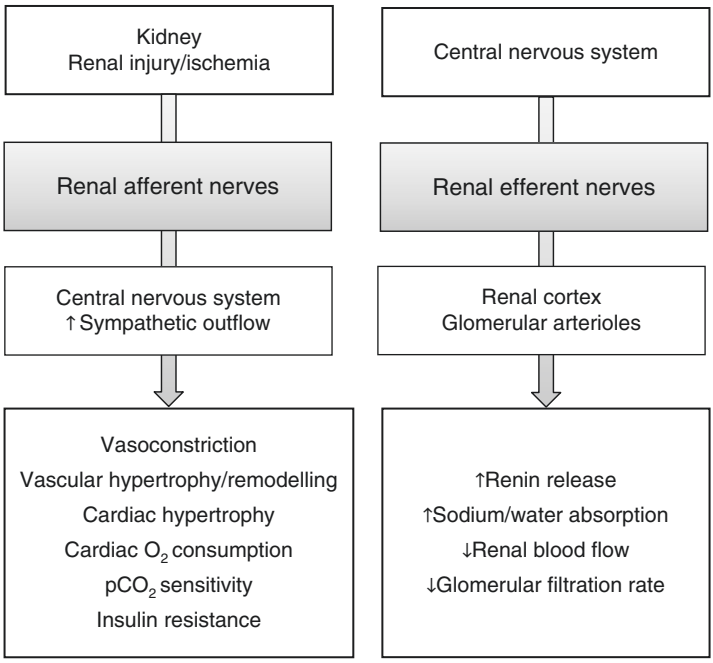



**Fig. 48.1** Effects of afferent and efferent renal nerves

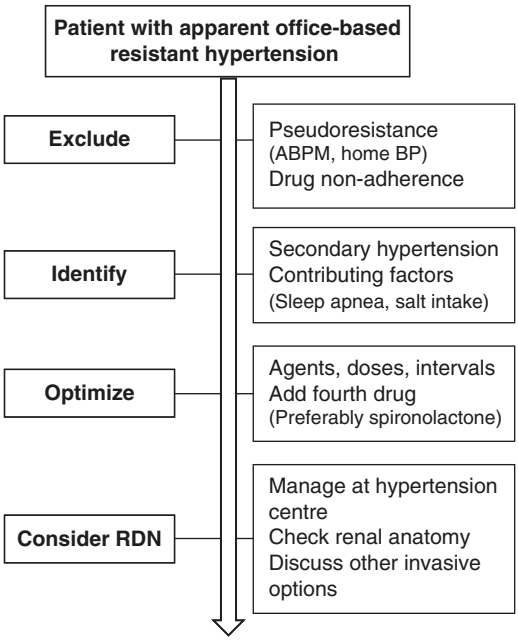



**Fig. 48.2** Management algorithm of a patient with resistant hypertension

recent conflicting data from randomized trials and the subsequent reevaluation of the method, inclusion criteria in the context of clinical trials are changing, principally with respect to inclusion of milder forms of HTN.

## 48.3 The Experimental Data on the BP Effects of RDN

There has been a series of experimental forms of HTN including models of rats, dogs, and pigs, in which it was shown that complete RDN by a combined surgical-pharmacological disruption of both afferent and efferent nerves delays the development of HTN or limits the increase in BP [3]. In spontaneously hypertensive rats, complete RDN was also associated with an increase in the fraction of the ingested sodium excreted in the urine, thus resulting in a "denervation natriuresis," while a subsequent development of HTN was accompanied by a return of renal tissue norepinephrine content toward normal (evidence of renal reinnervation) and a decrease in the fraction of the ingested sodium excreted in the urine. However, RDN does not affect the development of HTN in the Dahl NaCl-sensitive rat or in the canine HTN induced by nitric oxide synthase (NOS) inhibition. Thoracolumbar dorsal rhizotomy performed in order to produce selective afferent RDN attenuated the severity of HTN in rats with one-kidney, one-clip, and two-kidney one-clip Goldblatt HTN and in dogs with chronic aortic coarctation HTN but not in spontaneously hypertensive rats.

## 48.4 Effects of RDN on BP: Data from Clinical Trials

The first RDN proof-of-concept and safety study (Symplicity HTN-1), published in 2009 in *The Lancet*, included 45 patients with severe dRHTN (i.e., systolic office BP > 160 mmHg on three antihypertensive drugs including one diuretic) who underwent bilateral RDN with the use of a single-electrode radiofrequency ablation catheter inserted through the femoral artery, while five patients with inappropriate renal artery anatomy for RDN served as controls [5]. There was a gradual reduction in BP during follow-up, reaching a 27/17 mmHg drop at 1-year post-procedure, with no serious safety issues. At 36 months post-RDN, office BP fell further, and the rate of controlled (<140 mmHg) patients (140–159 mmHg) reached 50% [6].

EnligHTN I was the first-in-human, prospective, multicenter study designed to assess the safety and efficacy of a multielectrode radiofrequency ablation system (EnligHTN™) that can deliver lesions with a predetermined pattern [7]. Renal sympathetic denervation in 46 patients with dRHTN provided a rapid and significant office, ambulatory, and home BP reduction that was sustained through a follow-up period of up to 24 months [8]. Other studies were able to confirm the BP-lowering effect of RDN in patients with dRHTN using various energy modalities and catheters [9].

Randomized controlled RDN trials have provided conflicting results regarding the efficacy of RDN on BP reduction (Table 48.1) [10–13]. In the Symplicity HTN-2, 106 patients with dRHTN were randomly assigned either to RDN or to continuation of previous administered antihypertensive medication [10]. At 6 months post-RDN, office BP was significantly reduced by 32/12 mmHg, while there was interestingly no significant difference in the BP of the control group (change of only 1/0 mmHg).

PRAGUE-15 study, a prospective, randomized, open-label multicenter trial, evaluated the efficacy of catheter-based RDN (Symplicity, Medtronic) ($n = 52$) vs. intensified pharmacological treatment including spironolactone (if tolerated) ($n = 54$) in patients with dRHTN [11]. Chief assets of the study were 24-h ambulatory BP monitoring and confirmation of adherence to therapy by measurement of plasma antihypertensive drug levels. After 6 months, a comparable significant reduction in 24-h average systolic BP (−8.6 mmHg in RDN vs. −8.1 mmHg in the drug group) and systolic office BP (−12.4 mmHg in RDN vs. −14.3 mmHg in the drug group) was observed in both groups. PRAGUE-15 showed that RDN is not superior to intensified pharmacotherapy in dRHTN in reducing BP, but it is important to note that the average number of antihypertensive drugs used was significantly higher (+0.3 drugs, $P < 0.001$) and serum creatinine was significantly increased in the pharmacological group at 6 months post-RDN.

The small randomized Oslo study investigated the BP-lowering effect of RDN ($n = 9$, performed with the Symplicity catheter) vs. clinically adjusted drug treatment ($n = 10$) with the use of noninvasive integrated hemodynamic measurements of impedance cardiography with the HOTMAN System, in true dRHTN, after excluding patients with poor drug adherence [12]. The study was ceased earlier because at 6 months, the drug-adjusted group presented with significantly lower

**Table 48.1** Published randomized controlled studies of RDN

| | HTN-2 | OSLO RDN | PRAGUE-15 | DENERHTN |
|---|---|---|---|---|
| First author/ publication year | Esler [10]/2010 | Elmula [12]/2014 | Rosa [11]/2015 | Azizi [13]/2015 |
| Control group | Antihypertensive treatment | Clinically adjusted drug therapy with the HOTMAN system | Intensified pharmacological treatment including spironolactone if possible | Standardized stepped-care antihypertensive regimen |
| Total population (n) | 106 (52 vs. 54) | 19 (9 vs. 10) | 106 (52 vs. 54) | 106 (53 vs. 53) |
| Age (years) | 58 | 60 | 58 | 55 |
| 24-h BP monitoring | No | Yes | Yes | Yes |
| RDN device | Symplicity | Symplicity | Symplicity | Symplicity |
| Assessment of drug adherence | Diary | Witnessed intake | Plasma drug concentrations | Morisky score plus drug concentrations |
| Baseline office BP (mmHg) (RDN vs. control) | 178/97 vs. 178/98 | 156/91 vs. 160/89 | 159/92 vs. 155/89 | 159/93 vs. 155/91 |
| Change in office SBP (mmHg) (RDN vs. control) | −32 vs. +1 | −8 vs. −28 | −12.4 vs. −14.3 | −15.1 vs. −9.5 |
| Baseline 24-h BP (mmHg) (RDN vs. control) | NA | 151/89 vs. 149/85 | 149/86 vs. 147/84 | 151/90 vs. 146/88 |
| Changes in 24-h SBP (mmHg) (RDN vs. control) | −11/−3 | −10/−21 | −8.6 vs. −8.1 | −15.4 vs. −9.5 |

*RDN* renal denervation, *BP* blood pressure, *SBP* systolic blood pressure, *HTN-2* simplicity *HTN-2*, *DENERHTN* the renal denervation for hypertension

systolic and diastolic BP as well as larger absolute changes in SBP. Despite being small and underpowered, this study suggested that adjusted drug treatment has superior BP-lowering effects compared with RDN in patients with true dRHTN.

The Renal Denervation for Hypertension (DENERHTN) trial was a prospective, open-label randomized controlled trial with blinded endpoint evaluation in 106 patients with dRHTN from 15 French tertiary care centers specialized in HTN management [13]. Eligible patients received a standardized stepped-care antihypertensive treatment of indapamide 1.5 mg, ramipril 10 mg (or irbesartan 300 mg), and amlodipine 10 mg daily for 4 weeks to confirm treatment resistance by ambulatory BP monitoring before randomization. Patients were then randomly assigned (1:1) to receive either RDN plus the above mentioned standardized regimen (RDN group) or the same regimen alone (control group). The primary endpoint was met, with an observed mean change in daytime systolic BP at 6 months of −15.8 mmHg in the RDN group and −9.9 mmHg in the control group with a baseline-adjusted difference of −5.9 mmHg.

The Symplicity HTN-3 study was a prospective, randomized (2:1), masked (sham) procedure, single-blind study, which investigated the safety and efficacy of RDN in 535 resistant hypertensive patients in the USA [14]. Patients included were

similar to those of Symplicity HTN-1 and Symplicity HTN-2; drug-RHTN was further confirmed with ambulatory BP ≥135 mmHg, and before randomization, patients were under a stable antihypertensive regimen for at least 2 weeks of maximum tolerated doses of at least three antihypertensive drugs, including a diuretic. Office systolic BP at 6 months dropped by −14.1 mmHg in the RDN and −11.7 mmHg in the control (sham) group, respectively (difference of 2.39 mmHg, $p = 0.26$, with a 5 mmHg superiority margin). The change in ambulatory BP at 6 months was −6.7 mmHg in the RDN and −4.7 mmHg in the sham ablation arm (difference of −1.96 mmHg, $p = 0.98$, with a 2 mmHg superiority margin). The results of Symplicity HTN-3 trial limited the enthusiasm of the scientific community and industry toward RDN and have led to a thorough reappraisal of the procedure.

Another small, randomized, sham-controlled study from Germany by S. Desch examined the effectiveness of RDN with the Symplicity Flex catheter in patients ($n = 71$) with mild dRHTN (daytime systolic BP 135–149 and diastolic BP 90–94 mmHg on 24-h ambulatory measurement) [15]. In the intention to treat analysis, no significant difference between groups was observed in the reduction in the primary endpoint of 24-h systolic BP at 6 months, but in the per-protocol cohort, 24-h systolic BP was significantly reduced.

## 48.5 Safety of RDN

Safety data for RDN come from a few experimental studies, the clinical trials of the various RDN systems, and the RDN registries. Most evidence comes from studies using the Symplicity catheter, yet safety results seem comparable among different RDN systems. The Symplicity HTN-1 and Symplicity HTN-2 studies have reported the longest follow-up period of up to 3 years but unfortunately not on the respective entire initial cohorts.

Preclinical studies have shown that RDN acutely causes circumscribed transmural injury, thrombus formation, and cellular swelling [16, 17]. Longer-term findings are fibrosis of up to 25% of the total media and underlying adventitia and nerve fascicle replacement with fibrous connective tissue. Overall, a partial return to normal anatomy may be expected at least 6 months post-RDN. An optical coherence tomography study in 16 patients with dRHTN undergoing RDN showed that endothelial-intimal edema was found in 96% of cases after RDN and thrombus formation was a frequent finding, signifying the need for the use of antiplatelet therapy in patients undergoing the procedure [18].

Data from clinical trials have consistently shown that the procedure is safe. Rare periprocedural events include access site complications such as pseudoaneurysms and hematomas, renal artery dissections, hypotension, and vasovagal episodes. In Symplicity HTN-1, angiography showed focal renal artery irregularities right after radiofrequency energy delivery that were attributed to minor spasm or edema and were not flow-limiting. Short-term angiograms and 6-month magnetic resonance angiograms did not show any irregularities at the sites of treatment [5]. In the Symplicity HTN-3 trial, the overall number of adverse events was very low, and no

significant differences were noted between groups [14]. Rates of major adverse events did not significantly differ between the RDN group (1.4%) and the control group (0.6%). In the Global SYMPLICITY Registry, even though underreporting of adverse events may have been possible, there were only six periprocedural adverse events related to the procedure, including four vascular access site complications (0.34%) and two renal artery dissections that were stented [19].

Intraprocedural bradycardia may be considered only a self-limiting acute effect of the RDN procedure, since regulation of BP and chronotropic competence are well preserved at follow-up. Orthostatic hypotension has been a rather rare adverse event of RDN as documented in various patient series. In a study in 36 patients that underwent tilt-table testing before and 3 months after RDN, change in systolic BP and heart rate after tilting were not influenced by the procedure [20].

There have been concerns that application of radiofrequency thermal energy may cause structural damage and subsequently renal artery stenosis, even though in the various cohorts, stenosis has been a rare complication (<5%). Still, a series of case reports have documented the development of unilateral or bilateral significant stenosis as early as 2 months and as late as 2 years after RDN, usually associated with a relapse of high BP or deterioration of renal function [21–23]. Current contraindications for RDN include previous renal artery interventions and renal artery stenosis >50%, while energy delivery on atherosclerotic lesions should be avoided [4]. The few reports of development of renal artery stenosis highlight the importance of careful documentation of such events in RDN studies. A careful selection of the correct RDN catheter size (at least in the case of balloon-based devices) and the use of antiplatelet therapy to limit the risk of dissection and thrombus formation, respectively, are advised.

Development of acute or chronic renal damage has been one of the initial concerns regarding RDN, as a potential result of loss of autoregulatory mechanisms [24]. However, RDN has not been associated with significant deterioration of kidney function at least well beyond what is expected in patients of high cardiovascular risk by definition and with the progression of age. Overall, a relatively stable renal function during follow-up has been documented in RDN studies. On the other hand, in the 36-month report of the Symplicity HTN-1 registry, eGFR was shown to have decreased by 9.3 mL/min/1.73 $m^2$ [6]. A small decrease in eGFR was also shown in the 24-month report of the EnligHTN I trial [8]. Chronically uncontrolled HTN and the use of drugs such as diuretics, renin-angiotensin inhibitors, and aldosterone antagonists may have contributed to these findings. Careful long-term observation of patients undergoing RDN in large registries will provide a clearer picture of renal behavior.

## 48.6 Current and Future Perspectives of RDN

In the years following the first studies on RDN, our view on the technique has changed. RDN is a complex, specialized therapy with a number of unanswered questions with respect to renal nerve anatomy as well as the depth of ablation and time and amount of energy needed to provide the best results [2, 25]. Recent data

show that the highest average number of nerves is found in the proximal and middle segments of the renal artery and the mean distance from the lumen to the nerve is the longest in the proximal and the lowest in the distal segments [26]. Such findings indicate that asymmetric and most probably distal renal artery targeting is required to achieve effective ablation. Furthermore, a "dose-response" dependency between the number of ablation attempts and the efficacy of RDN has been proposed. Data from the Symplicity HTN-3 trial show that the BP response increased with an increasing number of ablations delivered and the successful delivery of circumferential (four quadrant) ablations. Nevertheless, there are still no reliable markers of procedural success recognized that could establish on time whether denervation has been completely achieved [27, 28]. Acute changes in renal hemodynamics and changes in BP after high-frequency stimulation in the renal artery have been studied as possible markers, but there is no consensus on their implementation [29].

The issue of regeneration of mainly renal efferent sympathetic fibers post-RDN was raised from experimental findings. Yet, whether reinnervation, functional or only anatomic, takes place in humans is uncertain [30]. However, data from clinical trials and registries indicate that changes in BP persist long term (at least up to 3 years) in patients with dRHTN after RDN. A sustained decrease in BP was observed after 36 months of follow-up in HTN-1 and after 24 months of follow-up in EnligHTN I.

With respect to study design, there have been some exploratory and hypothesis-generating findings that should be considered in future appropriately designed prospective studies. Medication stability and patient adherence are critical issues. Frequent drug changes and variable medication adherence in Symplicity HTN-3 may have affected the observed BP reduction after RDN [14]. Notably, in Symplicity HTN-3, 38% of patients had changes in their medications, while in the positive DENERHTN study, a standardized treatment protocol was followed. Accordingly, regarding ethnicity, in Symplicity HTN-3, among African-Americans there was a large drop in BP in the sham group (−17.8 mmHg), while in the non-African-American subgroup, a significant difference in office systolic BP was observed (−15.2 mmHg in the denervation and −8.6 mmHg in the control (sham) group, $p = 0.012$). Adherence rates among such groups may partially explain these unexpected effects in Symplicity HTN-3. European experts on RDN thus suggest that in future RDN trials, it is crucial to standardize antihypertensive therapy (preferentially all treated with the combination of a renin-angiotensin blocker, calcium channel blocker, and diuretic) with a stable run-in period of at least 4–8 weeks and to record drug adherence as a potential confounder of BP response with one of the available methods such as pill counting, use of electronic pill dispensers, or toxicological drug analysis.

There is a wide heterogeneity of BP response to RDN ranging from a clinically significant BP reduction to even an increase; that is however not surprising and should be considered in the general context of antihypertensive therapy. For comparison, the earlier procedures of sympathetic splanchnicectomy were accompanied by a significant BP reduction in 45% of the surgically treated patients [31]. After all, HTN is a multifactorial disease, and the wide experience from pharmaceutical trials

shows that inhibition of any pathway implicated in BP elevation is effective only in a certain percentage of patients (30–50%). It is therefore clear that predictors of BP response to RDN are much needed to identify the "right patient" for this interventional approach. Significantly, elevated BP (systolic >180 mmHg) has been associated with greater reductions of BP, but not all patients with largely elevated BP respond to RDN [19, 32]. Even though patients with evident sympathetic overactivity would intuitively be considered principal candidates for the procedure, clinically applicable measures of increased sympathetic activity are lacking. Interestingly, there is no clear established link between SNS activity and response to RDN, and more research is needed [33]. In any case, it is questionable whether older patients or patients with long-standing HTN may respond to RDN, compared to younger patients, given their commonly lower degree of SNS activation and their increased aortic stiffness [34].

Data from earlier RDN clinical trials showed that there was a disproportionally greater decrease in systolic office BP than in ambulatory BP [32]. The white-coat effect, which is very frequently encountered in dRHTN, might have contributed to this disparity. In an extended Symplicity protocol, at 6 months post-RDN, systolic ambulatory BP decreased by 10.2 mmHg in patients with true dRHTN, which is similar to the 24-h BP decline observed in Symplicity HTN-2; there was no effect on ambulatory BP monitoring in pseudoresistant patients, whereas office BP was reduced to a similar extent [35]. Ambulatory BP is less susceptible to bias, placebo effect, and day-to-day variability than office BP. In addition, it can easily be analysed blind to treatment allocation in controlled trials and allows correct selection of patients for RDN.

After the publication of the Symplicity HTN-3 trial, the earlier RDN trials underwent extensive scrutiny. An issue was raised that the observed BP reductions were due to the placebo and Hawthorne effects, the regression to the mean phenomenon, drug changes and adherence, the study population, or other biases. On the other hand, current evidence would not justify regarding the technology as a proven failure. There is a general agreement that a second chance is really needed to test the effectiveness of this modality. In this setting, a clinical consensus conference provided some considerations on future RDN clinical trials [36]. Patients with moderate HTN and HTN in earlier stages, rather than dRHTN, should be included in future trials, while patients with stiff large arteries (e.g., isolated systolic HTN) should be excluded. A washout period should be performed but only in highly experienced centers, and standardized concomitant antihypertensive therapy with monitored adherence should be pursued. Ambulatory BP should be the primary efficacy endpoint, while clinically easy accessible predictors for BP efficacy would ideally be discovered. The two initial trials of the ongoing SPYRAL HTN Global Clinical Trial Program (using the Symplicity Spyral multielectrode renal denervation catheter) focus on the effect of RDN in hypertensive patients in the absence (SPYRAL HTN-OFF MED) and presence (SPYRAL HTN-ON MED) of antihypertensive medications [37]. Hopefully, these two as well as other future appropriately designed trials will resolve all the uncertainties regarding the BP effects of RDN and help define its place in clinical practice. Until more evidence is available

concerning the long-term BP efficacy and safety of RDN, it is recommended that candidate cases are managed in HTN centers and procedures are performed by experienced operators.

## 48.7 Other Invasive Treatments for HTN

The baroreceptors of the carotid sinus are located at the bifurcation of the common carotid artery and are mechanosensitive nerve endings that respond to vascular distension as a result of elevated BP or increased intravascular volume [38]. Stimulation of these receptors activates the carotid baroreflex which eventually results in increased parasympathetic activity that decreases BP and lowers heart rate. Baroreceptor activation therapy has been represented by the first-generation bilaterally placed Rheos® carotid pacemaker system and the second-generation unilateral BAROSTIM NEO™ system (CVRx Inc., USA). Implantation of the system involves an operation under general anesthesia, where electrode wires are positioned around the carotid artery wall and a pacemaker generator is fitted in a subcutaneous pocket in the pectoral region [39]. Encouraging efficacy data have been gathered from the three trials on the device: the initial Rheos Feasibility Trial, the Device-Based Therapy of Hypertension Trial (DEBUT-HT), and the latest Rheos Pivotal Trial. The latter was a double-blind, randomized, prospective, multicenter, phase III clinical trial in 265 patients with dRHTN that received either carotid stimulation directly for 6 months (Group I) or delayed treatment after the 6-month visit (Group II) [40]. A decrease in systolic BP of 26 mmHg for Group I and 17 mmHg for Group II at 6 months was observed. However, safety issues are of principal concern as the Rheos Pivotal Trial failed the short-term safety endpoint. The newer BAROSTIM NEO™ system has been associated with significantly less adverse events. The ongoing Barostim Hypertension Pivotal Trial as well as trials using the more recently introduced MobiusHD™ device should provide further important data on the procedure.

The arteriovenous (AV) coupler is manufactured by ROX Medical and is used to create a central iliac AV anastomosis (initially with the scope of increasing venous oxygenation in chronic obstructive pulmonary disease patients) in order to reduce systemic vascular resistance and modulate autonomic activity among other effects [41]. The procedure involves catheterization of the common femoral artery and ipsilateral common femoral vein, placement of the coupler between the distal external iliac vein and artery, and dilation of the anastomotic passage to 4 mm. Promising data came from the ROX CONTROL HTN trial that was a multicenter, randomized controlled trial in 83 severely hypertensive patients; a 27/20 mmHg decrease in office BP and a 13.5/13.5 mmHg decrease in 24-h BP were documented in the active group while no change was observed in the control group [42]. Safety issues under investigation are high-output cardiac failure, venous stenosis, and ipsilateral lower limb swelling. Again, pending trials and registries will help clarify the effects and safety of the procedure.

## References


1. Mancia G, Fagard R, Narkiewicz K et al (2013) 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 31(7):1281–1357
2. Papademetriou V, Rashidi AA, Tsioufis C, Doumas M (2014) Renal nerve ablation for resistant hypertension: how did we get here, present status, and future directions. Circulation 129(13):1440–1451
3. DiBona GF (2005) Physiology in perspective: the wisdom of the body. Neural control of the kidney. Am J Physiol Regul Integr Comp Physiol 289(3):R633–R641
4. Schmieder RE, Redon J, Grassi G, Kjeldsen SE, Mancia G, Narkiewicz K et al (2013) Updated ESH position paper on interventional therapy of resistant hypertension. EuroIntervention 9(Suppl R):R58–R66
5. Krum H, Schlaich M, Whitbourn R et al (2009) Catheter-based renal sympathetic denervation for resistant hypertension: a multicenter safety and proof-of-principle cohort study. Lancet 373:1275–1281
6. Krum H, Schlaich MP, Sobotka PA et al (2014) Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. Lancet 383(9917):622–629
7. Worthley SG, Tsioufis CP, Worthley MI et al (2013) Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: the EnligHTN I trial. Eur Heart J 34(28):2132–2140
8. Tsioufis CP, Papademetriou V, Dimitriadis KS et al (2015) Catheter-based renal denervation for resistant hypertension: twenty-four month results of the EnligHTN I first-in-human study using a multi-electrode ablation system. Int J Cardiol 201:345–350
9. Sievert H, Schofer J, Ormiston J et al (2015) Renal denervation with a percutaneous bipolar radiofrequency balloon catheter in patients with resistant hypertension: 6-month results from the REDUCE-HTN clinical study. EuroIntervention 10(10):1213–1220
10. Esler MD, Krum H, Sobotka PA et al (2010) Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet 376(9756):1903–1909
11. Rosa J, Widimský P, Toušek P et al (2015) Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 study. Hypertension 65:407–413
12. FadlElmula FE, Hoffmann P, Larstorp AC et al (2014) Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. Hypertension 63(5):991–999
13. Azizi M, Sapoval M, Gosse P et al (2015) Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. Lancet 385(9981):1957–1965
14. Bhatt DL, Kandzari DE, O'Neill WW et al (2014) A controlled trial of renal denervation for resistant hypertension. N Engl J Med 370(15):1393–1401
15. Desch S, Okon T, Heinemann D et al (2015) Randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. Hypertension 65(6):1202–1208
16. Rippy MK, Zarins D, Barman NC et al (2011) Catheter-based renal sympathetic denervation: chronic preclinical evidence for renal artery safety. Clin Res Cardiol 100:1095–1101
17. Steigerwald K, Titova A, Malle C et al (2012) Morphological assessment of renal arteries after radiofrequency catheter-based sympathetic denervation in a porcine model. J Hypertens 30:2230–2239
18. Templin C, Jaguszewski M, Ghadri JR et al (2013) Vascular lesions induced by renal nerve ablation as assessed by optical coherence tomography: pre- and post-procedural comparison

with the simplicity catheter system and the EnligHTN multi-electrode renal denervation catheter. Eur Heart J 34:2141–2148. 2148b
19. Böhm M, Mahfoud F, Ukena C et al. (2015) First report of the Global SYMPLICITY Registry on the effect of renal artery denervation in patients with uncontrolled hypertension. Hypertension 65:766–774
20. Lenski M, Mahfoud F, Razouk A et al (2013) Orthostatic function after renal sympathetic denervation in patients with resistant hypertension. Int J Cardiol 169:418–424
21. Vonend O, Antoch G, Rump LC, Blondin D (2012) Secondary rise in blood pressure after renal denervation. Lancet 380:778
22. Kaltenbach B, Id D, Franke JC et al (2012) Renal artery stenosis after renal sympathetic denervation. J Am Coll Cardiol 60:2694–2695
23. JaénÁguila F, Mediavilla Garcia JD, Navarro EM et al (2014) Bilateral renal artery stenosis after renal denervation. Hypertension 63:e126–e127
24. Petidis K, Anyfanti P, Doumas M (2011) Renal sympathetic denervation: renal function concerns. Hypertension 58(4):e19
25. Papademetriou V, Tsioufis C, Doumas M (2014) Renal denervation and Symplicity HTN-3: "Dubium sapientiae initium" (doubt is the beginning of wisdom). Circ Res 115(2):211–214
26. Tzafriri AR, Mahfoud F, Keating JH et al (2014) Innervation patterns may limit response to endovascular renal denervation. J Am Coll Cardiol 64(11):1079–1087
27. Kandzari DE, Bhatt DL, Brar S et al (2015) Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. Eur Heart J 36(4):219–227
28. Tsioufis C, Mahfoud F, Mancia G et al (2014) What the interventionalist should know about renal denervation in hypertensive patients: a position paper by the ESH WG on the interventional treatment of hypertension. EuroIntervention 9(9):1027–1035
29. Tsioufis C, Papademetriou V, Dimitriadis K et al (2013) Catheter-based renal sympathetic denervation exerts acute and chronic effects on renal hemodynamics in swine. Int J Cardiol 168(2):987–992
30. Booth LC, Nishi EE, Yao ST et al (2015) Reinnervation of renal afferent and efferent nerves at 5.5 and 11 months after catheter-based radiofrequency renal denervation in sheep. Hypertension 65(2):393–400
31. Smithwick RH, Thompson JE (1953) Splanchnicectomy for essential hypertension; results in 1,266 cases. JAMA 152(16):1501–1504
32. Schmieder RE, Schmidt ST, Riemer T et al (2014) Disproportional decrease in office blood pressure compared with 24-hour ambulatory blood pressure with antihypertensive treatment: dependency on pretreatment blood pressure levels. Hypertension 64(5):1067–1072
33. Grassi G, Seravalle G, Brambilla G et al (2015) Blood pressure responses to renal denervation precede and are independent of the sympathetic and baroreflex effects. Hypertension 65(6):1209–1216
34. Ewen S, Ukena C, Linz D et al (2015) Reduced effect of percutaneous renal denervation on blood pressure in patients with isolated systolic hypertension. Hypertension 65(1):193–199
35. Mahfoud F, Ukena C, Schmieder RE et al (2013) Ambulatory blood pressure changes after renal sympathetic denervation in patients with resistant hypertension. Circulation 128(2):132–140
36. Mahfoud F, Böhm M, Azizi M et al (2013) Proceedings from the European clinical consensus conference for renal denervation: considerations on future clinical trial design. Eur Heart J 36(33):2219–2227
37. Kandzari DE, Kario K, Mahfoud F et al (2016) The SPYRAL HTN Global Clinical Trial Program: rationale and design for studies of renal denervation in the absence (SPYRAL HTN OFF-MED) and presence (SPYRAL HTN ON-MED) of antihypertensive medications. Am Heart J 171(1):82–91
38. Grassi G, Cattaneo BM, Seravalle G et al (1998) Baroreflex control of sympathetic nerve activity in essential and secondary hypertension. Hypertension 31(1):68–72
39. Victor RG (2015) Carotid baroreflex activation therapy for resistant hypertension. Nat Rev Cardiol 12(8):451–463

40. Bisognano JD, Bakris G, Nadim MK et al (2011) Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled Rheos Pivotal Trial. J Am Coll Cardiol 58(7):765–773
41. Brier TJ, Jain AK, Lobo MD (2015) Central arteriovenous anastomosis for hypertension: it is not all about sympathomodulation. Futur Cardiol 11(5):503–506
42. Lobo MD, Sobotka PA, Stanton A et al (2015) Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial. Lancet 385(9978):1634–1641

# Is Hypertension-Related Target Organ Damage Reversible/Preventable?

# 49

Enrico Agabiti Rosei and Maria Lorenza Muiesan

## 49.1 Introduction

Hypertension-induced mortality and morbidity is produced through the impact on the heart, the central nervous system, the arterial vessels, and the kidney. Evaluation of early target organ damage (TOD) in these organs is an important step in a risk stratification strategy to reduce cardiovascular and renal damage. The 2013 ESH-ESC Guidelines [1] encouraged the convenience of assessing target organ damage for global risk stratification and of repeating TOD assessment during the follow-up.

A panel of TOD is included in the 2013 ESH-ESC Guidelines, although some of them, such as the ankle-brachial index or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 $m^2$, indicate advanced organ damage. Others are not available for routine use. Based on availability, cost, and clinical significance, the evaluation of left ventricular hypertrophy (LVH) by electrocardiography and, possibly, the assessment of left ventricular mass (LVM) by echocardiography, urinary albumin excretion, and glomerular filtration rate are minimally recommended.

Several studies have shown that the regression of asymptomatic TOD occurring during treatment reflects the treatment-induced reduction of morbid and fatal CV events, thereby offering valuable information on whether patients are more or less effectively protected by the treatment strategies adopted (Fig. 49.1).

E.A. Rosei, M.D. (✉) • M.L. Muiesan, M.D.
Clinica Medica, Department of Clinical and Experimental Sciences, University of Brescia, 25100 Brescia, Italy
e-mail: enrico.agabitirosei@unibs.it



A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_49

| Marker of OD | Prognostic value | Sensitivity for change detection | Time |
|---|---|---|---|
| LVH (Electrocardiogram) | ++++ | + | > 6 months |
| LVH (Echocardiography) | ++++ | ++ | > 6 months |
| Albuminuria | ++ | +++ | Weeks-months |
| Estimated Glomerular Filtration Rate (eGFR) | (+) | ++ | Years |
| Pulse wave Velocity (PWV) | (+) | +++ | Weeks-months |
| Ankle Brachial Index (ABI) | – | + | – |
| Carotid wall thickness | – | –/+ | > 1 year |

**Fig. 49.1** Prognostic value of changes during treatment of markers of asymptomatic organ damage. *LVH* left ventricular hypertrophy, *OD* organ damage

## 49.2 Heart

Electrocardiographic LVH is a powerful marker of cardiovascular (CV) morbidity/mortality in the general population as well as in different clinical settings [2]. In hypertensive patients LVH may predict the occurrence of cardiovascular events, including myocardial infarction, stroke, sudden death, and heart failure [3, 4]. The incidence of atrial fibrillation and of renal events, such as creatinine doubling, estimated glomerular filtration rate <30 mL/min/1.73 $m^2$, or the need for end-stage renal disease, is also higher in the presence of LVH [5].

BP control, mainly measured during 24 h monitoring, and body mass index (BMI) are strictly associated to LVH development [6]. In addition metabolic syndrome, diabetes mellitus [7], hyperuricemia, and chronic neurohormonal activation may further influence LVH development; the risk of incident LVH is particularly relevant among women.

Antihypertensive treatment is associated with a significant reduction in ECG LVH and in LVM. The magnitude of the decrease is related to the baseline LVM. According to variability in LVM measurements by echocardiography, only changes >10–15% can be considered of biological relevance. The correlation between changes of LVM and changes in clinic BP is modest and increases when average of 24 h BP is considered [8].

Among all classes of antihypertensive drugs, ACE inhibitors (ACEi), angiotensin receptor blockers, and calcium antagonists seem to be more effective as compared with beta-blockers [9]. In most studies, however, patients were receiving a combination of drugs (usually with a diuretic) and not monotherapy, and therefore the efficacy of antihypertensive treatment in inducing adequate and long-term blood pressure control seems more important than the choice of a specific class.

A normalization of LVM is more difficult and cannot be always reached in women [5], obese or diabetic patients [10], elderly subjects with isolated systolic hypertension [11], or patients with coronary artery disease, despite adequate treatment. A normalization of LV geometry is also possible during antihypertensive treatment [12].

The improvement of systolic and/or diastolic function parameters in response to antihypertensive therapy is still controversial.

Regression of ECG LVH assessed by voltage and strain criteria may be induced by treatment [13–20]. Large changes in ECG voltage and strain result in improved prognosis [21, 22]. Changes in echocardiographic LVM and in renal function may also independently predict the occurrence of cardiovascular events [23].

During antihypertensive treatment, the modifications of LV geometry, of left atrial size, of midwall fractional shortening, and of diastolic dysfunction parameters have been also shown to be associated with the incidence of cardiovascular events, independently of LVM change [12, 24, 25].

Regression of LVH may have a prognostic significance independently of blood pressure values, even when measured by 24 h BP. The changes in electrocardiographically or echocardiographically LVH induced by treatment reflect the effects on cardiovascular events; however, a residual risk may be observed in patients with LVH regression, in whom LVM remains higher, although in the normal range, than in patients with persistently normal LVM [26].

## 49.3 Vascular Damage

### 49.3.1 Aortic Stiffness

In more recent years, it has become possible to evaluate the vascular aging process, i.e. the increase in arterial stiffness [27]. Arterial stiffness may be measured at systemic and local levels with non invasive technique. Regional and local arterial stiffness can be

measured directly and noninvasively, at various sites along the arterial tree, and they are based on direct measurements of parameters strongly linked to wall stiffness.

The 2013 ESH/ESC Guidelines have confirmed the importance of carotid-femoral pulse wave velocity (cfPWV) as a subclinical organ damage for a more accurate and precise cardiovascular (CV) risk stratification and have indicated a threshold greater than 10 m/s as an index of increased large artery stiffening [1]. Nuclear magnetic resonance may be the most appropriate method for the evaluation of less superficial vessels [1, 28, 29]. Several studies have documented a correlation between arterial stiffness measures (in particular aortic PWV) and CV risk factors, such as aging, arterial hypertension, diabetes mellitus, metabolic syndrome, hypercholesterolemia, as well as markers of chronic inflammation processes [28]. More importantly, an increase of aortic stiffness has been shown to predict the occurrence of CV events above and independently of traditional risk factors [30].

Arterial stiffness is associated with damage in other target organs (LVH [31], microalbuminuria, carotid intima-media thickening, endothelial dysfunction, and microvascular alterations [32]) and with clinical events.

Aging and BP are the main determinants of vascular stiffness, inducing a reduced synthesis and an increased degradation of elastin, in association with an increased synthesis and reduced degradation of type 1 and type 3 collagen [33]; calcification of the vessel wall may also occur, as frequently observed in elderly subjects and in hypertensive patients.

A large number of publications and several reviews have reported the various pathophysiological conditions associated with increased arterial stiffness and wave reflections, including arterial hypertension and in particular isolated systolic hypertension [34, 35].

In recent years numerous studies have reported an association between alterations of arterial stiffness or of pulsatile hemodynamic parameters and the occurrence of CV events [30]. The increase in cfPWV has been shown to predict all-cause mortality, CV mortality, fatal and nonfatal coronary artery events, and fatal stroke in different groups of patients, including those with arterial hypertension [36–38], with diabetes mellitus [39], with end-stage renal disease [40, 41], the elderly patients [42, 43], and in the general population [44–46]. Most importantly the prognostic significance of PWV is independent of brachial BP values, of major CV risk factors, and of the Framingham risk score [36], indicating that aortic stiffness has a better predictive value than each or the combination of the classical risk factors [47].

Data about prognostic significance of arterial stiffness measured at other arterial sites are less consistent. Carotid stiffness was predictive of CV events in a small number of patients with endstage renal disease (ESRD) [48] or following renal transplantation [49] and in a large prospective cohort with a high prevalence of insulin resistance [50], while no predictive value was demonstrated in a larger number of patients with manifest arterial disease [51].

Data on changes in PWV and occurrence of CV events are still limited. Guerin et al. [52] have demonstrated that in end-stage renal disease patients the persistence of elevated cfPWV was associated with a worse survival as compared to patients with a decrease of cfPWV, independently of brachial BP changes.

It remains to be demonstrated in hypertensive patients at lower CV risk that a reduction or a normalization of arterial stiffness is effective in reducing CV events beyond brachial BP reduction.

Exercise training, weight loss, low to moderate sodium diet, and moderate alcohol consumption but also dietary supplements may have a beneficial effect on changes in arterial stiffness.

The reduction of BP per se may induce a decrease of cfPWV [53]. Among antihypertensive classes of drugs, diuretics, beta-blockers, ACE inhibitors, angiotensin II type 1 receptor blocker (AT1 blockers), and calcium channel antagonists are able to reduce arterial stiffness [28, 54].

Some studies have also shown that a non-dihydropyridinic calcium antagonist (acute administration) or an ACE inhibitor [55, 56] or an angiotensin II receptor blocker [57] is able to reduce arterial stiffness and/or wave reflections independently of the reduction in brachial BP.

In addition a decrease in arterial stiffness has been determined in congestive heart failure patients by ACE inhibitors, nitrates, and aldosterone antagonists, as well as statins and antidiabetic drugs. The additional BP-independent effect of different pharmacological interventions remains to be further evaluated.

### 49.3.2 Carotid Arteries

High-resolution ultrasound assessment of the carotid arteries allows the measurement of intima-media (IMT) complex in the arterial wall, according to a validated method, and carotid IMT (C-IMT) is the most widely accepted noninvasive marker of subclinical atherosclerosis [58, 59].

Available data indicate that IMT >0.9 mm represents a risk of myocardial infarction and/or cerebrovascular disease [60–66]. A high heterogeneity in the assessment of C-IMT in the different studies may explain the different results related to risk prediction. The use of radiofrequency C-IMT measurements has been recently shown to have an additional stratification power for coronary artery disease, in addition to the Framingham risk score [67].

Ultrasound may also identify the presence of plaques, and ultrasonic plaque morphology may add useful information on plaque stability and may correlate with symptoms. More recently plaque volume assessment by three-dimensional reconstruction of ultrasound or nuclear magnetic resonance images has been proposed to better evaluate atherosclerotic lesion changes and to stratify patients' risk [68, 69].

Traditional risk factors, including aging, male sex, being overweight or obese, elevated blood pressure, diabetes, and smoking, are all positively associated with an increase in carotid IMT in observational and epidemiological studies. Hypertension, and particularly high systolic BP values, seems to have the greatest effect on IMT [70]. Patients with metabolic syndrome have higher IMT than patients with individual metabolic risk factors. Carotid IMT has also been found to be associated with preclinical cardiovascular alterations, in the heart, in the brain, in the kidney, and in the lower limb arteries.

Therapeutic double-blind trials have shown that antihypertensive drugs may have a more or less marked effect on carotid IMT progression. Compared with no treatment, diuretics/+ beta-blockers, or ACE inhibitors, calcium-channel blockers attenuate the rate of progression of carotid intima-media thickening [71]. The odds ratio for all fatal and nonfatal cardiovascular events in trials comparing active treatment with placebo reached statistical significance ($P = 0.007$).

Few studies have shown a lower thickness of intima-media during treatment with angiotensin II antagonists in respect to patients treated with beta-blockers [72].

Comparative studies assessing the effect of statin treatment on IMT progression have demonstrated a beneficial effect on common carotid mean IMT; the effect was greater in the setting of secondary prevention versus primary prevention, in younger patients versus older patients, and in studies with a greater proportion of male patients [73, 74].

A greater reduction of plaque volume with the long-term treatment with angiotensin II blocker in respect to the beta-blocker was demonstrated in a study (Multicenter Olmesartan Atherosclerosis Regression Evaluation (MORE)), with the use of the noninvasive 3D plaque measurement [75]. A significant change in 3D plaque volume was also observed during short-term treatment with a high dose of statin in a small group of 20 patients [75]. No significant changes in plaque composition were observed after 4 years of treatment with either lacidipine or atenolol [76].

It has not been demonstrated whether a decrease of IMT progression may be associated with a reduction of cardiovascular events and an improvement in prognosis [77, 78]. Changes in plaque composition characteristics seem to have additional prognostic significance [69].

### 49.3.3 Microvascular Structure

Essential hypertension is associated with the presence of structural alterations in the microcirculation [79, 80] that may be also the result of adaptive mechanisms to the increased blood pressure load. Since structural alterations might have hemodynamic consequences, their evaluation represents an important target, also in terms of cardiovascular risk stratification [81, 82].

The mechanisms underlying the development of microvascular structural alterations are only partially elucidated. The extent of structural alterations in subcutaneous small resistance arteries is particularly pronounced in hypertensive patients with type 2 diabetes mellitus [83, 84] or obesity [85, 86], suggesting that the association of several cardiovascular risk factors may have a synergistic, deleterious effect on the microcirculation.

The presence of an increased media-to-lumen ratio on the incidence of cardiovascular events was evaluated in three different studies [87–89] including patients at high or moderate global CV risk. It was shown that the media-to-lumen ratio was significantly associated to the occurrence of cardiovascular events, independently of other CV risk factors. These results strongly indicate a relevant prognostic significance of small resistance artery structural alterations in a high-risk population. More recently,

Buus NH et al. [90] have demonstrated a prognostic role of changes of small resistance artery structure during antihypertensive treatment. Antihypertensive treatment may induce the reversal of increased media-to-lumen ratio, and inhibitors of the renin-angiotensin system (RAS) (including ACE inhibitors, angiotensin II receptor antagonists, aliskiren) and calcium antagonist are more effective in this regard [91].

Other new techniques for evaluation of microvascular morphology in the retinal vasculature are presently used or under clinical investigation, representing a promising and interesting future perspective [92, 93].

## 49.4 Renal TOD

The 2013 ESH/ESC Guidelines recommend the assessment of serum creatinine and the calculation of estimated glomerular filtration rate (eGFR) to assess renal excretory function [1, 94]. In addition the measurement of urinary albumin excretion is considered a biomarker of early renal damage. Both measurements are low cost and easy to use. In hypertensive patients both GFR and urinary albumin excretion should be measured, in order to assess the presence of chronic kidney disease (CKD) and to better stratify cardiovascular risk [1, 66].

### 49.4.1 Albuminuria

Microalbuminuria has been related to the presence of increased blood pressure but also to insulin resistance, blood pressure, salt sensitivity, central obesity, and smoke; to an atherogenic lipid profile; and to early signs of extrarenal organ damage such as left ventricular hypertrophy, carotid atherosclerosis, and biomarkers of vascular endothelium damage [95]. Therefore, microalbuminuria has been referred as an integrated marker of cardiovascular risk, confirmed by the relationship between even modest increase in albuminuria and cardiovascular morbidity and mortality [96].

Redon et al. have shown that during antihypertensive treatment, albuminuria reaches normal values in about 50% of patients, while in about 10% of them, a progression toward more severe proteinuria occurs [97, 98]. The new development of microalbuminuria during treatment is independently related to poor blood pressure control and to a progressive increase in glucose plasma levels. Some caution should be taken when evaluating albuminuria changes during treatment; it has been suggested that a reliable change in albuminuria requires a regression or an increment of more than 50% of the initial value. The calculation of the average value of two different measurements performed in different days may reduce variability.

A recent meta-analysis of trials evaluating blood pressure targets with respect to proteinuria progression has shown that a more aggressive target (<130 mmHg vs. <140 mmHg) is associated with a lower prevalence of albuminuria [97].

Some randomized clinical trials have suggested that drugs acting on the renin-angiotensin-aldosterone system are more effective in reducing albuminuria in respect to placebo in individuals with diabetic or nondiabetic nephropathy and with

cardiovascular disease [98]. If a combination treatment is needed, then the association of two RAS blockers is not recommended.

In patients with resistant hypertension, the addition of a mineral corticoid receptor antagonist was associated with a further reduction of albuminuria in patients treated with ACE inhibitor or angiotensin receptor blocker monotherapy, possibly because of the greater efficacy in home blood pressure reduction.

The reduction of albuminuria during treatment may favorably affect cardiovascular and renal prognosis [99].

### 49.4.2 Glomerular Filtration Rate

Renal function, as assessed by glomerular filtration, declines with increasing age. In addition to age and excluding all diseases producing a direct renal damage, high blood pressure values, diabetes, and dyslipidemia represent the main factors accelerating the glomerular filtration rate over time [94].

According to the evaluation of eGFR, it is possible to define five different stages of renal dysfunction, and values below 60 mL/min/1.73 $m^2$ indicate the presence of chronic kidney diseases. CKD is observed in a significant proportion of hypertensive patients, mainly in older individuals, in women, and in diabetics. Few data have demonstrated that changes in eGFR may influence cardiovascular prognosis in hypertensive patients, despite the evidence that lower eGFR is associated with a higher risk for CV events [95].

The long-term control of BP values during antihypertensive treatment favors preservation of renal function and delays progression to end-stage renal disease in hypertensive patients with or without chronic nephropathy; however, it has been observed that a slight increase in serum creatinine, due to the transient renal hypoperfusion, may occur after initiation of treatment. Blood pressure targets with respect to CKD progression have shown that a more aggressive target (<130 mmHg vs. <140 mmHg) is not associated with a reduction in eGFR [100, 101]. However, recent data from the SPRINT study (Systolic Blood Pressure Intervention Trial) suggest that in patients with CKD who achieved during treatment a value of unattended blood pressure lower than 120 mmHg, the risk of cardiovascular events was lower [102].

In patients with even mild degree of CKD, a combination treatment is needed in order to reach adequate BP control. A RAS blocker may be associated to other classes of antihypertensive drugs. In the ACCOMPLISH study, the association of an ACE inhibitor and a calcium antagonist was more effective in preventing the progression to creatinine doubling and/or to the development of end-stage renal disease, as compared with the combination of an ACE inhibitor and a diuretic [103].

**Conclusions**

The 2013 ESH/ESC Guidelines recommend the measurement of serum creatinine, urine albumin excretion, and electrocardiographic LVH in all patients with hypertension both at baseline and during treatment. In addition echocardiographic left ventricular mass, ultrasonic carotid wall thickness, aortic PWV, and ankle-brachial

index measurements should be considered to better stratify the cardiovascular risk. In the future, more effort should be made to identify which combination of markers to measure, at what time points, in which patients, and with which consequence for a better clinical use of TOD during antihypertensive treatment.

## References


1. Mancia G, Fagard R, Narkiewicz K et al (2013) 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 31(7):1281–1357
2. Agabiti-Rosei E, Muiesan ML, Salvetti M (2006) Evaluation of subclinical target organ damage for risk assessment and treatment in the hypertensive patients: left ventricular hypertrophy. J Am Soc Nephrol 17(4 Suppl 2):S104–S108
3. Vakili BA, Okin PM, Devereux RB (2001) Prognostic implications of left ventricular hypertrophy. Am Heart J 141(3):334–341
4. Verdecchia P, Angeli F, Borgioni C et al (2003) Changes in cardiovascular risk by reduction of left ventricular mass in hypertension: a meta-analysis. Am J Hypertens 16(11 Pt 1):895–899
5. Tsioufis C, Kokkinos P, Macmanus C et al (2010) Left ventricular hypertrophy as a determinant of renal outcome in patients with high cardiovascular risk. J Hypertens 28(11):2299–2308
6. Peer M, Boaz M, Zipora M, Shargorodsky M (2013) Determinants of left ventricular hypertrophy in hypertensive patients: identification of high-risk patients by metabolic, vascular, and inflammatory risk factors. Int J Angiol 22(4):223–228
7. Wijkman M, Lanne T, Grodzinsky E et al (2012) Ambulatory systolic blood pressure predicts left ventricular mass in type 2 diabetes, independent of central systolic blood pressure. Blood Press Monit 17(4):139–144
8. Mancia G, Zanchetti A, Agabiti-Rosei E et al (1997) Ambulatory blood pressure is superior to clinic blood pressure in predicting treatment-induced regression of left ventricular hypertrophy. SAMPLE Study Group. Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation. Circulation 95(6):1464–1470
9. Fagard RH, Celis H, Thijs L, Wouters S (2009) Regression of left ventricular mass by antihypertensive treatment: a meta-analysis of randomized comparative studies. Hypertension 54(5):1084–1091
10. de Simone G, Devereux RB, Izzo R et al (2013) Lack of reduction of left ventricular mass in treated hypertension: the strong heart study 6. J Am Heart Assoc 2(3):e000144
11. Mancusi C, Gerdts E, De Simone G et al (2014) Impact of isolated systolic hypertension on normalization of left ventricular structure during antihypertensive treatment (the LIFE study). Blood Press 23(4):206–212
12. Muiesan ML, Salvetti M, Monteduro C et al (2004) Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients. Hypertension 43(4):731–738
13. Okin PM, Devereux RB, Harris KE et al (2007) Regression of electrocardiographic left ventricular hypertrophy is associated with less hospitalization for heart failure in hypertensive patients. Ann Intern Med 147(5):311–319
14. Prineas RJ, Rautaharju PM, Grandits G, Crow R (2001) Independent risk for cardiovascular disease predicted by modified continuous score electrocardiographic criteria for 6-year incidence and regression of left ventricular hypertrophy among clinically disease free men: 16-year follow-up for the multiple risk factor intervention trial. J Electrocardiol 34(2):91–101
15. Levy D, Salomon M, D'Agostino RB et al (1994) Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. Circulation 90(4):1786–1793

16. Mathew J, Sleight P, Lonn E et al (2001) Reduction of cardiovascular risk by regression of electrocardiographic markers of left ventricular hypertrophy by the angiotensin-converting enzyme inhibitor ramipril. Circulation 104(14):1615–1621
17. Okin PM, Devereux RB, Jern S et al (2003) Regression of electrocardiographic left ventricular hypertrophy by losartan versus atenolol: the Losartan Intervention for Endpoint reduction in Hypertension (LIFE) Study. Circulation 108(6):684–690
18. Okin PM (2009) Serial evaluation of electrocardiographic left ventricular hypertrophy for prediction of risk in hypertensive patients. J Electrocardiol 42(6):584–588
19. Okin PM, Wachtell K, Devereux RB et al (2006) Regression of electrocardiographic left ventricular hypertrophy and decreased incidence of new-onset atrial fibrillation in patients with hypertension. JAMA 296(10):1242–1248
20. Wachtell K, Okin PM, Olsen MH et al (2007) Regression of electrocardiographic left ventricular hypertrophy during antihypertensive therapy and reduction in sudden cardiac death: the LIFE Study. Circulation 116(7):700–705
21. Bang CN, Devereux RB, Okin PM (2014) Regression of electrocardiographic left ventricular hypertrophy or strain is associated with lower incidence of cardiovascular morbidity and mortality in hypertensive patients independent of blood pressure reduction—a LIFE review. J Electrocardiol 47(5):630–635
22. Okin PM, Devereux RB, Jern S et al (2004) Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. JAMA 292(19):2343–2349
23. Salvetti M, Muiesan ML, Paini A et al (2012) Left ventricular hypertrophy and renal dysfunction during antihypertensive treatment adversely affect cardiovascular prognosis in hypertensive patients. J Hypertens 30(2):411–420
24. Wachtell K, Gerdts E, Palmieri V et al (2010) In-treatment midwall and endocardial fractional shortening predict cardiovascular outcome in hypertensive patients with preserved baseline systolic ventricular function: the Losartan Intervention For End point reduction study 3. J Hypertens 28(7):1541–1546
25. Kurt M, Wang J, Torre-Amione G, Nagueh SF (2009) Left atrial function in diastolic heart failure 3. Circ Cardiovasc Imaging 2(1):10–15
26. Angeli F, Reboldi G, Poltronieri C et al (2015) The prognostic legacy of left ventricular hypertrophy: cumulative evidence after the MAVI study. J Hypertens 33(11):2322–2330
27. Nilsson PM, Boutouyrie P, Cunha P et al (2013) Early vascular ageing in translation: from laboratory investigations to clinical applications in cardiovascular prevention. J Hypertens 31(8):1517–1526
28. Laurent S, Cockcroft J, Van Bortel L et al (2006) Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 27(21):2588–2605
29. Van Bortel LM, Laurent S, Boutouyrie P et al (2012) Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens 30(3):445–448
30. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C (2010) Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J 31(15):1865–1871
31. Asmar R, Safavian A, Tual JL, Safar ME (1995) Arterial and cardiac changes in hypertension in the elderly. Blood Press Suppl 3:31–37
32. Muiesan ML, Salvetti M, Rizzoni D et al (2013) Pulsatile hemodynamics and microcirculation: evidence for a close relationship in hypertensive patients. Hypertension 61(1):130–136
33. Cliff WJ (1970) The aortic tunica media in aging rats. Exp Mol Pathol 13(2):172–189
34. Asmar R (2015) Effects of treatment on arterial stiffness and central blood pressure—points to consider 23. J Clin Hypertens (Greenwich) 17(2):105–106
35. Mitchell GF, Lacourciere Y, Ouellet JP et al (2003) Determinants of elevated pulse pressure in middle-aged and older subjects with uncomplicated systolic hypertension: the role of proximal aortic diameter and the aortic pressure-flow relationship. Circulation 108(13):1592–1598

36. Boutouyrie P, Tropeano AI, Asmar R et al (2002) Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension 39(1):10–15
37. Laurent S, Katsahian S, Fassot C et al (2003) Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke 34(5):1203–1206
38. Laurent S, Boutouyrie P, Asmar R et al (2001) Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 37(5):1236–1241
39. Cruickshank K, Riste L, Anderson SG et al (2002) Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation 106(16):2085–2090
40. Blacher J, Guerin AP, Pannier B et al (1999) Impact of aortic stiffness on survival in end-stage renal disease. Circulation 99(18):2434–2439
41. Shoji T, Emoto M, Shinohara K et al (2001) Diabetes mellitus, aortic stiffness, and cardiovascular mortality in end-stage renal disease. J Am Soc Nephrol 12(10):2117–2124
42. Meaume S, Benetos A, Henry OF et al (2001) Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. Arterioscler Thromb Vasc Biol 21(12):2046–2050
43. Sutton-Tyrrell K, Najjar SS, Boudreau RM et al (2005) Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation 111(25):3384–3390
44. Mattace-Raso FU, van der Cammen TJ, Hofman A et al (2006) Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 113(5):657–663
45. Shokawa T, Imazu M, Yamamoto H et al (2005) Pulse wave velocity predicts cardiovascular mortality: findings from the Hawaii-Los Angeles-Hiroshima study. Circ J 69(3):259–264
46. Willum-Hansen T, Staessen JA, Torp-Pedersen C et al (2006) Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. Circulation 113(5):664–670
47. Ben-Shlomo Y, Spears M, Boustred C et al (2014) Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol 63(7):636–646
48. Pannier B, Guerin AP, Marchais SJ et al (2005) Stiffness of capacitive and conduit arteries: prognostic significance for end-stage renal disease patients. Hypertension 45(4):592–596
49. Barenbrock M, Kosch M, Joster E et al (2002) Reduced arterial distensibility is a predictor of cardiovascular disease in patients after renal transplantation. J Hypertens 20(1):79–84
50. van Sloten TT, Schram MT, van den Hurk K et al (2014) Local stiffness of the carotid and femoral artery is associated with incident cardiovascular events and all-cause mortality: the Hoorn study. J Am Coll Cardiol 63(17):1739–1747
51. Dijk JM, Algra A, van der Graaf Y et al (2005) Carotid stiffness and the risk of new vascular events in patients with manifest cardiovascular disease. The SMART study. Eur Heart J 26(12):1213–1220
52. Guerin AP, Blacher J, Pannier B et al (2001) Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. Circulation 103(7):987–992
53. Ong KT, Delerme S, Pannier B et al (2011) Aortic stiffness is reduced beyond blood pressure lowering by short-term and long-term antihypertensive treatment: a meta-analysis of individual data in 294 patients. J Hypertens 29(6):1034–1042
54. Ghiadoni L, Bruno RM, Stea F et al (2009) Central blood pressure, arterial stiffness, and wave reflection: new targets of treatment in essential hypertension 19. Curr Hypertens Rep 11(3):190–196
55. Tropeano AI, Boutouyrie P, Pannier B et al (2006) Brachial pressure-independent reduction in carotid stiffness after long-term angiotensin-converting enzyme inhibition in diabetic hypertensives 9. Hypertension 48(1):80–86
56. Asmar RG, London GM, O'Rourke ME et al (2001) Amelioration of arterial properties with a perindopril-indapamide very-low-dose combination. J Hypertens Suppl 19(4):S15–S20

57. Laurent S, Boutouyrie P (2014) Dose-dependent arterial destiffening and inward remodeling after olmesartan in hypertensives with metabolic syndrome. Hypertension 64(4):709–716
58. Bots M, Evans G, Riley W, Grobbee DE (2003) Carotid intima-media thickness measurements in intervention studies design options, progression rates, and sample size considerations: a point of view. Stroke 34:2985–2994
59. Touboul PJ, Hennerici MG, Meairs S et al (2007) Mannheim carotid intima-media thickness consensus (2004–2006). An update on behalf of the advisory board of the 3rd and 4th watching the risk symposium 13th and 15th European stroke conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovasc Dis 23(1):75–80
60. Bots ML, Hoes AW, Koudstaal PJ et al (1997) Common carotid intima-media thickness and risk of stroke and myocardial infarction the Rotterdam Study. Circulation 6(5):1432–1437
61. Salonen JT, Salonen R (1991) Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 11:1245
62. Chambeless LE, Heiss G, Folsom AR et al (1997) Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study. 1987–1993. Am J Epidemiol 146:483–494
63. Hodis HN, Mack WJ, LaBree L et al (1998) The role of arterial intima-media thickness in predicting clinical coronary events. Ann Intern Med 128(4):262–269
64. Lorenz M, Markus H, Bots M et al (2007) Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 115:459–467
65. Den Ruijter HM, Peters SA, Anderson TJ et al (2012) Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA 308:796–803
66. O'Leary DH, Polak JF, Kronmal RA et al (1999) Carotid intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med 340:14–22
67. Moreo A, Gaibazzi N, Faggiano P et al (2015) Multiparametric carotid and cardiac ultrasound compared with clinical risk scores for the prediction of angiographic coronary artery disease: a multicenter prospective study. J Hypertens 33(6):1291–1300
68. Wannarong T, Parraga G, Buchanan D et al (2013) Progression of carotid plaque volume predicts cardiovascular events. Stroke 44(7):1859–1865
69. van Engelen A, Wannarong T, Parraga G et al (2014) Three-dimensional carotid ultrasound plaque texture predicts vascular events. Stroke 45(9):2695–2701
70. Zanchetti A, Bond MG, Hennig M et al (2002) Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: Principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. Circulation 106:2422–2427
71. Wang JG, Staessen JA, Li Y et al (2006) Carotid intima-media thickness and antihypertensive treatment A meta-analysis of randomized controlled trials. Stroke 37:1933–1940
72. Agabiti-Rosei MML, Rizzoni D (2006) Angiotensin II antagonists and protection against subclinical cardiac and vascular damage. In: Mancia G (ed) Angiotensin II receptors antagonists, 2nd edn. CRC Press, Boca Raton, pp 111–126
73. Kang S, Wu Y, Li X (2004) Effects of statin therapy on the progression of carotid atherosclerosis: a systematic review and meta-analysis. Atherosclerosis 177:433–442
74. Huang Y, Li W, Dong L et al (2013) Effect of statin therapy on the progression of common carotid artery intima-media thickness: an updated systematic review and meta-analysis of randomized controlled trials. J Atheroscler Thromb 20(1):108–121
75. Stumpe KO, Agabiti-Rosei E, Zielinski T et al (2007) Carotid intima-media thickness and plaque volume changes following 2-year angiotensin II-receptor blockade. The Multicentre Olmesartan Atherosclerosis Regression Evaluation (MORE) study. Ther Adv Cardiovasc Dis 1(2):97–106
76. Paliotti R, Ciulla M, Hennig M et al (2005) Carotid wall composition in hypertensive patients after 4-year treatment with lacidipine or atenolol: an echoreflectivity study. J Hypertens 23:1203–1209

77. Zanchetti A, Hennig M, Hollweck R et al (2009) Baseline values but not treatment-induced changes in carotid intima-media thickness predict incident cardiovascular events in treated hypertensive patients: findings in the European Lacidipine Study on Atherosclerosis (ELSA). Circulation 120(12):1084–1090
78. Costanzo P, Perrone-Filardi P, Vassallo E et al (2010) Does carotid intima-media thickness regression predict reduction of cardiovascular events? A meta-analysis of 41 randomized trials. J Am Coll Cardiol 56(24):2006–2020
79. Mulvany MJ, Aalkjaer C (1990) Structure and function of small arteries. Physiol Rev 70:921–971
80. Schiffrin EL (2004) Remodeling of resistance arteries in essential hypertension and effects of antihypertensive treatment. Am J Hypertens 17(12Pt1):1192–1200
81. Izzard AS, Rizzoni D, Agabiti-Rosei E, Heagerty AM (2005) Small artery structure and hypertension: adaptive changes and target organ damage. J Hypertens 23:247–250
82. Aalkjaer C, Eiskjaer H, Mulvany MJ et al (1989) Abnormal structure and function of isolated subcutaneous resistance vessels from essential hypertensive patients despite antihypertensive treatment. J Hypertens 7:305–310
83. Endemann DH, Pu Q, De Ciuceis C et al (2004) Persistent remodeling of resistance arteries in type 2 diabetic patients on antihypertensive treatment. Hypertension 43:399–404
84. Rizzoni D, Porteri E, Guelfi D et al (2001) Structural alterations in subcutaneous small arteries of normotensive and hypertensive patients with non-insulin dependent diabetes mellitus. Circulation 103:1238–1244
85. Grassi G, Seravalle G, Scopelliti F et al (2010) Structural and functional alterations of subcutaneous small resistance arteries in severe human obesity. Obesity (Silver Spring) 18:92–98
86. De Ciuceis C, Porteri E, Rizzoni D et al (2011) Effects of weight loss on structural and functional alterations of subcutaneous small arteries in obese patients. Hypertension 58:29–36
87. Rizzoni D, Porteri E, Boari GEM et al (2003) Prognostic significance of small artery structure in hypertension. Circulation 108:2230–2235
88. De Ciuceis C, Porteri E, Rizzoni D et al (2007) Structural alterations of subcutaneous small arteries may predict major cardiovascular events in hypertensive patients. Am J Hypertens 20:846–852
89. Mathiassen ON, Buus NH, Sihm I et al (2007) Small artery structure is an independent predictor of cardiovascular events in essential hypertension. J Hypertens 25:1021–1026
90. Buus NH, Mathiassen ON, Fenger-Grøn M et al (2013) Small artery structure during antihypertensive therapy is an independent predictor of cardiovascular events in essential hypertension. J Hypertens 31:791–797
91. Agabiti-Rosei E, Heagerty AM, Rizzoni D (2009) Effects of antihypertensive treatment on small artery remodelling. J Hypertens 27(6):1107–1114
92. Ritt M, Harazny JM, Ott C et al (2008) Analysis of retinal arteriolar structure in never-treated patients with essential hypertension. J Hypertens 26(7):1427–1434
93. Koch E, Rosenbaum D, Brolly A, Sahel JA, Chaumet-Riffaud P, Girerd X, Rossant F, Paques M (2014) Morphometric analysis of small arteries in the human retina using adaptive optics imaging: relationship with blood pressure and focal vascular changes. J Hypertens 32(4):890–898
94. Sternlicht H, Bakris GL (2017) The kidney in hypertension. Med Clin North Am 101(1):207–217
95. Viazzi F, Pontremoli R (2014) Blood pressure, albuminuria and renal dysfunction: the 'chicken or egg' dilemma. Nephrol Dial Transplant 29:1453–1455
96. Currie G, Delles C (2013) Proteinuria and its relation to cardiovascular disease. Int J Nephrol Renovasc Dis 7:13–24
97. Pascual JM, Rodilla E, González C et al (2005) Long-term impact of systolic blood pressure and glycemia on the development of microalbuminuria in essential hypertension. Hypertension 45:1125–1130
98. Redon J, Martinez F (2012) Microalbuminuria as surrogate endpoint in therapeutic trials. Curr Hypertens Rep 14:345–349

99. Viazzi F, Muiesan ML, Schillaci G, Salvetti M, Pucci G, Bonino B, Signori A, Pontremoli R (2016) Changes in albuminuria and cardiovascular risk under antihypertensive treatment: a systematic review and meta-regression analysis. J Hypertens 34(9):1689–1697
100. Lv J, Ehteshami P, Sarnak MJ et al (2013) Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ 185:949–957
101. Emdin CA, Rahimi K, Neal B et al (2015) Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 313(6):603–615
102. SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK et al (2015) A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 373(22):2103–2116
103. Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, Velazquez EJ, ACCOMPLISH Trial Investigators (2008) Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 359(23):2417–2428