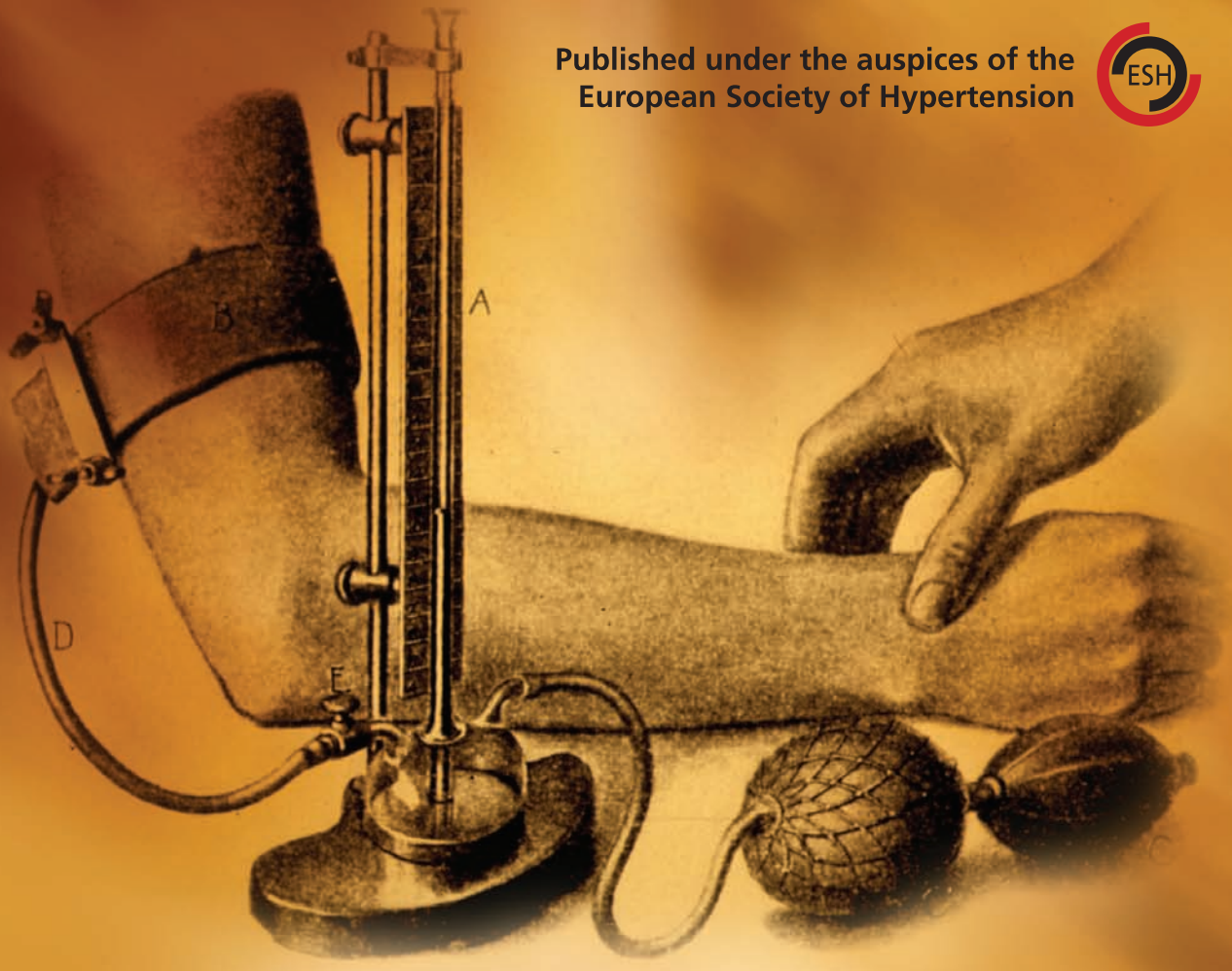
PART 2

Manual of Hypertension

of the European Society of Hypertension

Published under the auspices of the European Society of Hypertension



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First published in the United Kingdom in 2008 by Informa Healthcare, Telephone House, 69-77 Paul Street, London EC2A 4LQ. Informa Healthcare is a trading division of Informa UK Ltd. Registered Office: 37/41 Mortimer Street, London W1T 3JH. Registered in England and Wales number 1072954.

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A CIP record for this book is available from the British Library.
Library of Congress Cataloging-in-Publication Data

Data available on application

ISBN-10: 1 84184 648 1
ISBN-13: 978 1 84184 648 4

Distributed in North and South America by
Taylor & Francis
6000 Broken Sound Parkway, NW, (Suite 300)
Boca Raton, FL 33487, USA

Within Continental USA
Tel: 1 (800) 272 7737; Fax: 1 (800) 374 3401
Outside Continental USA
Tel: (561) 994 0555; Fax: (561) 361 6018
Email: orders@crcpress.com

Book orders in the rest of the world
Paul Abrahams
Tel: +44 (0)20 7017 4036
Email: bookorders@informa.com

Composition by Egerton & Televijay
Printed and bound in India by Replika Press Pvt Ltd

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Preface

In the past few decades, hypertension has been the subject of a large number of books and manuals aimed at providing up-to-date reviews of the large amount of experimental and clinical studies performed in the pathogenesis, diagnosis, and treatment of the disease.

More than one year ago, the European Society of Hypertension thought that would it be helpful for both investigators and clinicians to have a manual that approaches the issue in a different fashion, reflecting the authoritative opinion of the Society. The aim of this book, indeed, is not to offer a full and detailed report on the several pathogenetic and pathophysiological data collected in these years, but rather to focus on emerging new concepts that could affect the diagnostic and therapeutic approach of the disease.

This Manual has been made possible with the endeavouring help of many collegues and friends who are eminent members of the European Society of Hypertension and are recognized world-wide as leading experts in their different areas of hypertension. We hope that the Manual will be regarded as a useful enterprise, continuing the high tradition of the European Society of Hypertension.

Giuseppe Mancia

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Background, history, and epidemiology

SECTION 1

1 HISTORY OF EUROPEAN HYPERTENSION GUIDELINES. DEFINITION AND CLASSIFICATION OF HYPERTENSION AND TOTAL CARDIOVASCULAR RISK

Sverre E Kjeldsen, Giuseppe Mancia, Alberto Zanchetti

HISTORY OF EUROPEAN HYPERTENSION GUIDELINES

The European Society of Hypertension (ESH) was founded in the early 1980s and the society has steadily been growing to become the most influential hypertension society of the world with respect to meetings and membership activities. This textbook—*Manual of Hypertension of the European Society of Hypertension*—is authored by hypertension experts in Europe appointed by the Educational Committee of the ESH. It is largely based on European guidelines on treatment of hypertension that have been developed over the past few years, which are also under revision and are to be updated in 2007.

Until a few years ago, the ESH did not make specific guidelines on hypertension, but chose to endorse guidelines prepared by the World Health Organization (WHO) and the International Society of Hypertension (ISH) (1,2). ESH, in cooperation with the European Society of Cardiology (ESC), incorporated these guidelines, with some modifications, into their joint recommendations for the prevention of coronary heart disease (3,4).

Since 1999, new evidence on some of the important issues left open in the 1999 WHO–ISH guidelines accumulated, requiring updating of the guidelines. In this context, it was considered that the WHO–ISH guidelines were written for a global audience from countries that vary widely in the nature of their health systems and availability of resources. On the other hand, Europe is a much more homogeneous community, with populations enjoying greater longevity, but suffering higher incidences of chronic cardiovascular disease, often with highly developed health systems, devoting consistent resources to health protection. Thus, ESH, in close relationship with ISH, and in collaboration with ESC, intended to respond to the request of the WHO–ISH guidelines that additional recommendations be drawn up by regional experts, specifically designed for the management of patients in their own region (2).

Following the initial brief guidelines update and recommendations issued as a *ESH Newsletter* in 2002 (5), the full 2003 ESH–ESC guidelines (6) were prepared on the basis of the best available evidence on all issues deserving recommendations, and with the consideration that guidelines should have an educational purpose more than a prescriptive one. The 2003 ESH–ESC committee members felt that, although large, randomized, controlled trials and their meta-analyses provide the strongest evidence about several aspects of therapy, scientific evidence depends on multiple sources, and all these sources should be utilized. Consequently, the Committee avoided rigidly classifying its recommendations on the basis of arbitrary classifications and the hierarchy of the strength of the evidence available. This should also help understanding and implementing of the guidelines by the practitioners, to whom they are principally directed. However, for readers preferring a more critical assessment of these guidelines, these recommendations are accompanied by relevant references, and these references are based on large, randomized trials, meta-analyses, or large observational studies, identified by suitable symbols. Furthermore, for practitioners wishing to receive condensed recommendations, the 2003 ESH–ESC guidelines are complemented by a brief set of *Practice Recommendations* (7).

DEFINITION OF HYPERTENSION AND BLOOD PRESSURES AS PREDICTORS

Historically, more emphasis has been placed on diastolic than systolic blood pressure (BP) as a predictor of cerebrovascular and coronary heart disease. This was reflected in the design

of the major randomized controlled trials of hypertension management, which, until the 1990s, almost universally used diastolic BP threshold as inclusion criteria (8). Nevertheless, large compilations of observational data before (9) and since the 1990s (10) confirm that both systolic and diastolic BPs show a continuous, graded, independent relationship to the risk of stroke and coronary events.

In the European setting, the relationship between systolic BP and relative risk of stroke is steeper than that for coronary events, reflecting a closer etiologic relationship with stroke, but the attributable risk—that is, excess deaths due to raised BP—is greater for coronary events than stroke, reflecting the higher incidence of the former in most of Europe. However, with population ageing, the relative incidence of stroke is increasing, as shown in recent randomized controlled trials (11).

The apparently simple and direct relationship between increasing systolic and diastolic BP levels and increasing cardiovascular risk is complicated by the relationship that normally prevails in European populations between BP and age: viz. systolic BP rises throughout the adult age range, whereas diastolic BP peaks at about age 60 years in men and 70 years in women, and falls gradually thereafter (12). While both the continuous rise in systolic BP and the rise and fall in diastolic BP with age are usual in European populations, they represent the results of some of the pathological processes which underlie hypertension and cardiovascular diseases (13), which are variably highly prevalent in Europe.

These observations help explain why, at least in elderly populations, a wide pulse pressure (systolic BP minus diastolic BP) has been shown in some observational studies to be a better predictor of adverse cardiovascular outcomes than either systolic or diastolic pressure individually (14). Perhaps best known among these studies is that from Framingham (15,16), which reported that, for a given level of systolic BP, diastolic BP had an inverse association with cardiovascular risk. However, in the largest compilation of observational data in almost one million patients from 61 studies (70% of which were in Europe), carefully meta-analyzed (10) systolic and diastolic BPs were independently predictive of stroke and coronary mortality, and more so than pulse pressure.

In practice, given that we have randomized, controlled trial data supporting the treatment of isolated systolic hypertension (17,18) and treatment based purely on diastolic entry criteria (9), we should continue to use both systolic BP and diastolic BP as part of guidance for treatment thresholds. As to classification purposes and risk assessment (see below), while it may be argued that, for simplicity, a focus on systolic BP is sufficient, the use of both systolic and diastolic values to categorize BP levels, and thereby overall global risk, remains a simple and pragmatic approach.

CLASSIFICATION OF HYPERTENSION

The continuous relationship between the level of BP and cardiovascular risk makes any numerical definition and classification of hypertension arbitrary. The operational definition offered by Evans and Rose (19) more than 30 years ago, "hypertension should be defined in terms of a BP level above which investigation and treatment do more good than harm," also indicates that any numerical definition must be a flexible one resulting from evidence of risk and availability of effective and well-tolerated drugs.

Because of these considerations, it would perhaps be more correct to use a classification of BP levels without the term hypertension. It has been thought, however, that this may be confusing and detract attention from investigation of the mechanisms raising BP and weaken efforts toward hypertension control (20). Therefore, the 1999 WHO–ISH classification (2) has been retained in Table 1.1, with the reservation that the real threshold of hypertension must be considered a mobile one, being higher or lower on the basis of the global cardiovascular risk profile of each individual. This is made clear in the classification of global cardiovascular risk in the subsequent section. Accordingly, the definition of high normal BP in Table 1.1 includes BP values that may be considered as "high" (i.e., hypertension) in high-risk subjects, or fully normal in low-risk individuals. From the 1999 WHO–ISH guidelines (2), the subgroup "borderline" hypertension has not been retained, because the crossing of the "border" is heavily dependent on several risk of the individual subject, and it was felt the subgroup was not of practical usefulness.

GLOBAL CARDIOVASCULAR RISK

Historically, therapeutic intervention thresholds for the treatment of cardiovascular risk factors, such as BP, blood cholesterol, and blood sugar, have been based on variably arbitrary cutoff points of the individual risk factors. Because of the clustering of risk factors in individuals (21,22) and the graded nature of the association between each risk factor and cardiovascular risk (23), a contemporary approach has been to determine the threshold, at least for cholesterol and BP lowering, on the basis of estimated global coronary (3,4) or cardiovascular (coronary plus stroke) (24) risk over a defined, relatively short-term (e.g., 5 or 10 year) period.

Variably complex and computerized methods have been developed for estimating short-term risk. It should be noted that most risk estimation systems are based on the Framingham study (25). Whilst this database has been shown to be reasonably applicable to some European populations (26), estimates require recalibration in other populations (27) due to important differences in the prevailing incidence of coronary and stroke events. Estimates concerning various European populations or, more specifically,

Table 1.1 Definitions and classification of blood pressure levels (mmHg)

Category	Systolic	Diastolic
Optimal	<120	<80
Normal	120–129	80–84
High normal	130–139	85–89
Grade 1 hypertension (mild)	140–159	90–99
Grade 2 hypertension (moderate)	160–179	100–109
Grade 3 hypertension (severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90

When a patient's systolic and diastolic blood pressures fall into different categories, the higher category should apply. Isolated systolic hypertension can also be graded (grades 1, 2, 3) according to systolic blood pressure values in the ranges indicated, provided diastolic values are <90.

Table 1.2 Stratification of risk to quantify prognosis

	Blood pressure (mmHg)				
Other risk factors and disease history	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 SBP 140–159 or DBP 90–99	Grade 2 SBP 160–179 or DBP 100–109	Grade 3 SBP ≥180 or DBP ≥110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors or TOD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
ACC	High added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

Abbreviations: ACC, associated clinical conditions; DBP, diastolic blood pressure; SBP, systolic blood pressure; TOD, target organ damage.

patients with hypertension are increasingly becoming available (28–34), and, recently, the SCORE project has provided tables to predict the 10-year risk of fatal cardiovascular disease separately for higher-risk countries in Northern Europe and lower-risk countries in Southern Europe (35).

The main disadvantage associated with an intervention threshold based on relatively short-term, absolute risk is that younger adults (particularly women), despite having more than one major risk factor, are unlikely to reach treatment thresholds despite being at a high risk relative to their peers. By contrast, most elderly men (e.g., >70 years) will often reach treatment thresholds while being at very little increased risk relative to their peers. This situation results in most resources being concentrated on the oldest subjects, whose potential lifespans, despite intervention, are relatively limited, and young subjects at high relative risk remain untreated, despite, in the absence of intervention, a predicted significant shortening of their otherwise much longer potential lifespan (36,37). A simple approach to offset this lack of weighting for potential life-years gained for the young at high relative risk, is to determine intervention based on estimated risk levels for the subject projected to the age of 60 (3,4), or to base intervention on relative risk for subjects younger than 60 and on absolute risk level for older patients (28).

The stratification for global risk classification is summarized in Table 1.2 on the basis of these considerations. It is derived from the stratification suggested in the 1999 WHO–ISH guidelines (2), but extended to indicate the added risk of some group of subjects with "normal" or "high normal" BP. The terms *low*, *moderate*, *high*, and *very high added risk* are calibrated to indicate, approximately, an absolute 10-year risk of cardiovascular disease of <15%, 15–20%, 20–30%, and >30%, respectively, according to the Framingham criteria (25), or, approximately, of an absolute risk of fatal cardiovascular disease <4%, 4–5%, 5–8%, and >8% according to the SCORE chart (35). They can also be used as indicators of relative risks, thus leaving physicians free to use one or the other approach without the constraint of arbitrary absolute thresholds probably based on an underestimation of treatment benefits (37,38). The distinction

Table 1.3 Factors influencing prognosis

Risk factors for cardiovascular disease used for stratification	TOD	Diabetes mellitus	ACC
• Levels of systolic and diastolic BP • Men >55 years • Women >65 years • Smoking • Dyslipidemia (Total cholesterol >6.5 mmol/L, >250 mg/dL[a], or LDL-cholesterol >4.0 mmol/L, >155 mg/dL[a], or HDL-cholesterol M <1.0, W <1.2 mmol/L, M <40, W <48 mg/dL) • Family history of premature cardiovascular disease (at age <55 years M, <65 years W) • Abdominal obesity (abdominal circumference M ≥102 cm, W ≥88 cm)	• Left ventricular hypertrophy (electrocardiogram: Sokolow-Lyon >38 mm; Cornell >2440 mm × ms; echocardiogram: LVMI M ≥125, W ≥110 g/m^2) • Ultrasound evidence of arterial wall thickening (carotid IMT ≥0.9 mm) or atherosclerotic plaque • Slight increase in serum creatinine (M 115–133, W 107–124 μmol/L; M 1.3–1.5, W 1.2–1.4 mg/dL) • Microalbuminuria (30–300 mg/24 h; albumin–creatinine ratio M ≥22, W ≥31 mg/g; M ≥2.5, W ≥3.5 mg/mmol)	• Fasting plasma glucose 7.0 mmol/L (126 mg/dL) • Postprandial plasma glucose >11.0 mmol/L (198 mg/dL)	• Cerebrovascular disease: ischemic stroke; cerebral hemorrhage; transient ischemic attack • Heart disease: myocardial infarction; angina; coronary revascularization; congestive heart failure • Renal disease: diabetic nephropathy; renal impairment (serum creatinine M >133, W >124 μmol/L; M >1.5, W >1.4 mg/dL) proteinuria (>300 mg/24 h) • Peripheral vascular disease • Advanced retinopathy: hemorrhages or exudates; papilloedema

[a]Lower levels of total and LDL-cholesterol are known to delineate increased risk, but they were not used in the stratification. *Abbreviations*: ACC, associated clinical conditions; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; LVMI, left ventricular mass index; M, men; TOD, target organ damage; W, women.

between high- and very-high-risk has been maintained, though, admittedly, it does not significantly influence management decisions, mostly in order to preserve a distinctive place for secondary prevention [patients with associated clinical conditions (ACC)].

Table 1.3 indicates the most common risk factors, target organ damage (TOD), diabetes, and ACC to be used to stratify risk. This updates a similar table in 1999 WHO–ISH guidelines (2) in several major respects: (*i*) Obesity is indicated as "abdominal obesity," in order to give specific attention to an important sign of the metabolic syndrome (39). (*ii*) Diabetes is listed as a separate criterion in order to underline its importance as risk, at least twice as large as in the absence of diabetes (35,40). (*iii*) Microalbuminuria is indicated as a sign of TOD, but proteinuria as a sign of renal disease (ACC). (*iv*) Slight elevation of serum creatinine as a sign of TOD is indicated as a serum creatinine concentration of 107–133 μmol/L (1.2–1.5 mg/dL), and concentrations >133 μmol/L (>1.5 mg/dL) as ACC (41,42). (*v*) Generalized or focal narrowing of the retinal arteries is omitted among signs of TOD, as too frequently seen in subjects aged 50 years or older (43), but retinal hemorrhages and exudates as well as papilloedema are retained as ACC. The Committee was aware that the use of categorical tables rather than equations based on continuous variables may have limitations (44), and that cardiovascular risk evaluation is an inexact science (38). Furthermore, the weight of TOD in calculating the overall risk will heavily depend on how carefully it is looked at (45)—an aspect that will be further discussed in Section V on Diagnosis.

In the 2007 ESH–ESC Guidelines (46), the table corresponding to Table 1.2 includes matabolic syndrome at the level of 3 or more risk factors, and the table corresponding to Table 1.3 includes high pulse pressure in the elderly, cholesterol and LDL cholesterol of 5.0 and 3.0 mmol/L, respectively, fasting plasma glucose of 5.6–6.9 mmol/L or abnormal glucose tolerance test, carotid-femoral pulse wave velocity >12 m/s, ankle/brachial BP index <0.9, and GFR < 60 ml/min/1.73 m^2 or creatinine clearance <60 ml/min.

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EPIDEMIOLOGY OF HYPERTENSION 2

Renata Cífková

INTRODUCTION

Blood pressure (BP) is a quantitative trait with a normal, continuous, bell-shaped (Gaussian) distribution pattern, skewed to the upper end in any general population (Figure 2.1), and hypertension represents a clinical definition of the upper part of the distribution curve. Figure 2.1 shows a distribution curve for diastolic BP plotted using BP measurements in 158,906 individuals aged 30–69 years screened for Hypertension Detection and Follow-up Program in the United States (1).

The final BP value is the result of interaction of genetic and environmental factors (Figure 2.2). The dividing line between normotension and hypertension is purely arbitrary and, in fact, artificial.

Hypertension is the most prevalent cardiovascular (CV) disorder, affecting 20–50% of the adult population in developed countries (2). The prevalence of hypertension increases with age, rising steeply after the age of 50, and affecting more than 50% of this population.

BP AS A RISK FACTOR FOR CARDIOVASCULAR DISEASES

Elevated BP has been identified as a risk factor for coronary heart disease (CHD), heart failure, stroke, peripheral arterial disease, and renal failure in both men and women in a large number of epidemiological studies (3–6) (Figure 2.3). Observational evidence is also available that BP levels correlate inversely with cognitive function and that hypertension is associated with an increased incidence of dementia (7). Historically, diastolic BP was long considered a better predictor of cerebrovascular disease and CHD than systolic BP. This was reflected in the design of major randomized controlled trials of hypertension management, which used diastolic BP as an inclusion criterion until the 1990s (8). Individuals with isolated systolic hypertension were excluded from such trials by definition. Nevertheless, a large compilation of observational data before (3) and since the 1990s (9) confirms both systolic and diastolic BP show a continuous graded independent relationship with the risk of stroke and coronary events (Figures 2.4 and 2.5). Data from observational studies involving one million individuals have indicated that death from both CHD and stroke increases progressively and linearly from BP levels as low as 115 mmHg systolic and 75 mmHg diastolic upward (9). The increased risks are present in all age groups ranging from 40 to 89 years old. For every 20 mmHg systolic or 10 mmHg diastolic increase in BP, there is a doubling of mortality from both CHD and stroke.

In addition, longitudinal data obtained from the Framingham Heart Study indicated that BP values in the 130–139/85–89 mmHg range are associated with a more than twofold increase in relative risk from cardiovascular diseases (CVD) compared with those with BP levels below 120/80 mmHg (10) (Figure 2.6).

The apparently simple direct relationship between increasing systolic and diastolic BP and CV risk is confounded by the fact that systolic BP rises throughout the adult age in the vast majority of populations, whereas diastolic BP peaks at about age 60 in men and 70 in women, and falls gradually thereafter (11).

This observation helps to explain why a wide pulse pressure (systolic BP–diastolic BP) has been shown in some observational studies to be a better predictor of adverse CV outcomes than either systolic or diastolic BP individually (12) and to identify patients with systolic hypertension who are at specifically high risk (13). However, the largest meta-analysis of observational data in one million patients in 61 studies (70% of which had been conducted in Europe) (9) showed that both systolic and diastolic BP, more so than pulse pressure, were independently predictive of stroke and CHD mortality. This meta-analysis also confirmed the increasing contribution of pulse pressure after age 55.

It has been shown that, compared to normotensive individuals, those with an elevated BP more commonly have other risk factors for CVD (diabetes, insulin resistance, dyslipidemia) (5,14–16) and various types and degrees of target organ damage (TOD). Because risk factors may interact positively with each other, total CV risk in hypertensive patients is not infrequently high when the BP elevation is also only mild or moderate (5,10,17). In a study by Anderson et al. (18), 686 treated hypertensive men, followed for 20–22 years, had a significantly increased CV mortality, especially from CHD, compared with non-hypertensive men from the same population. These differences were observed during the second

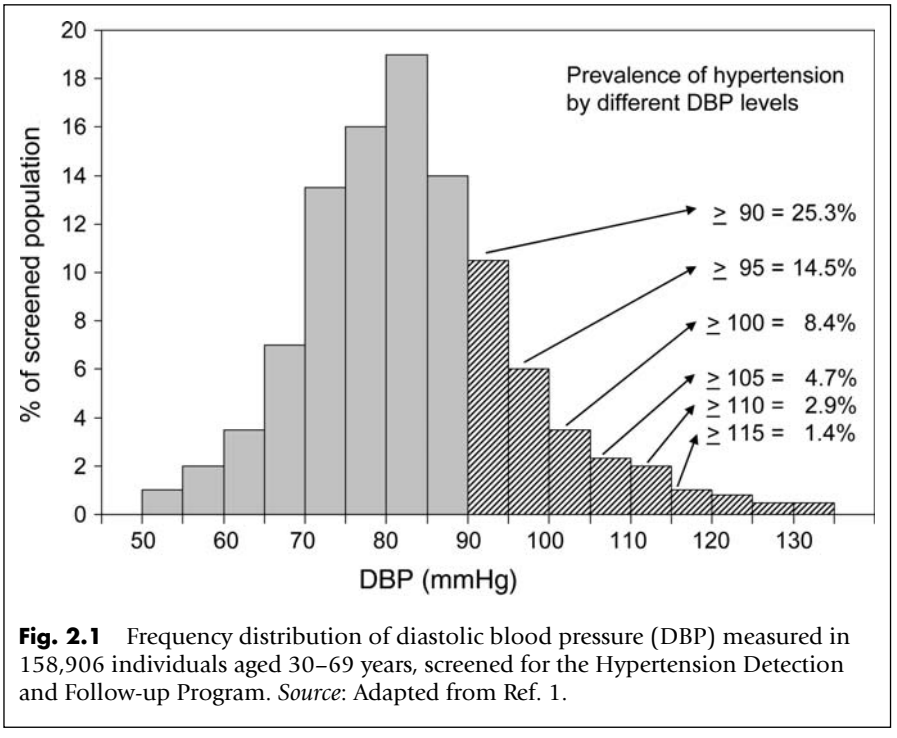


Fig. 2.1 Frequency distribution of diastolic blood pressure (DBP) measured in 158,906 individuals aged 30–69 years, screened for the Hypertension Detection and Follow-up Program. *Source*: Adapted from Ref. 1.

decade of follow-up. The high incidence of myocardial infarction was related to organ damage, smoking, and cholesterol at the time of entry to the study, and to achieved serum cholesterol during follow-up.

POPULATION IMPACT

The impact of hypertension on the incidence of CVD in the general population is best evaluated from the population-attributable risk or, more correctly, the population-attributable burden, which is the proportional reduction in average disease risk over a specified time interval that would be achieved by eliminating the exposure of interest from the population, while the distribution of other risk factors remains unchanged (19). For BP, attributable burden can therefore be defined as the proportion of disease that would not have occurred if BP levels had been at the same alternative distribution (20). The statistics take into account both the prevalence of the risk factor (hypertension) and the strength of its impact (risk ratio) on CVD.

Because of the high prevalence and risk ratio of hypertension in the general population, approximately 35% of atherosclerotic events are attributable to hypertension. The odds ratio, or the relative risk to the individual, increases with the severity of hypertension, but the attributable risk is greatest for mild hypertension because of its greater prevalence in the general population. Therefore, the burden of CVD arising from hypertension in the general population comes from those with relatively mild BP elevation (21). About half of the CV events in the general population occur at BP levels below those recommended for treatment with antihypertensive medications. The burden of non-optimal BP is almost double that of the previous global estimates (22). Globally, approximately two thirds of stroke, one half of CHD, and approximately three quarters of hypertensive disease were

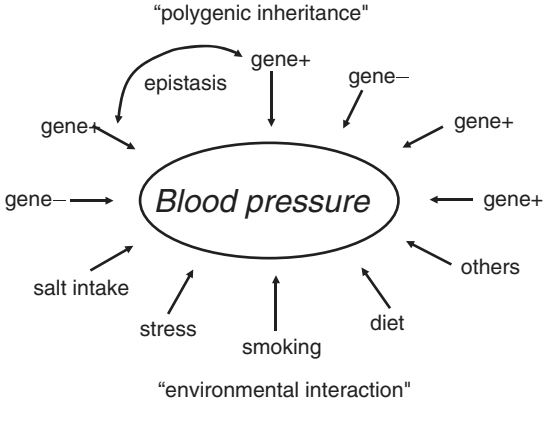


Fig. 2.2 Multifactorial nature of blood pressure. Blood pressure is controlled by both genes and environment, with both epistatic and gene-environment interactions.

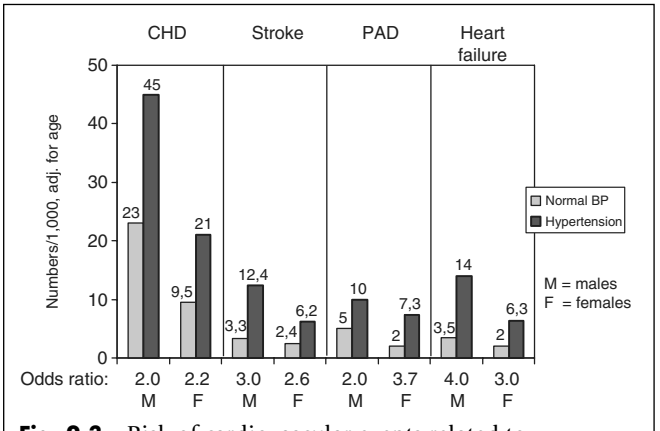


Fig. 2.3 Risk of cardiovascular events related to hypertension and normotension. *Source*: Adapted from Ref. 4.

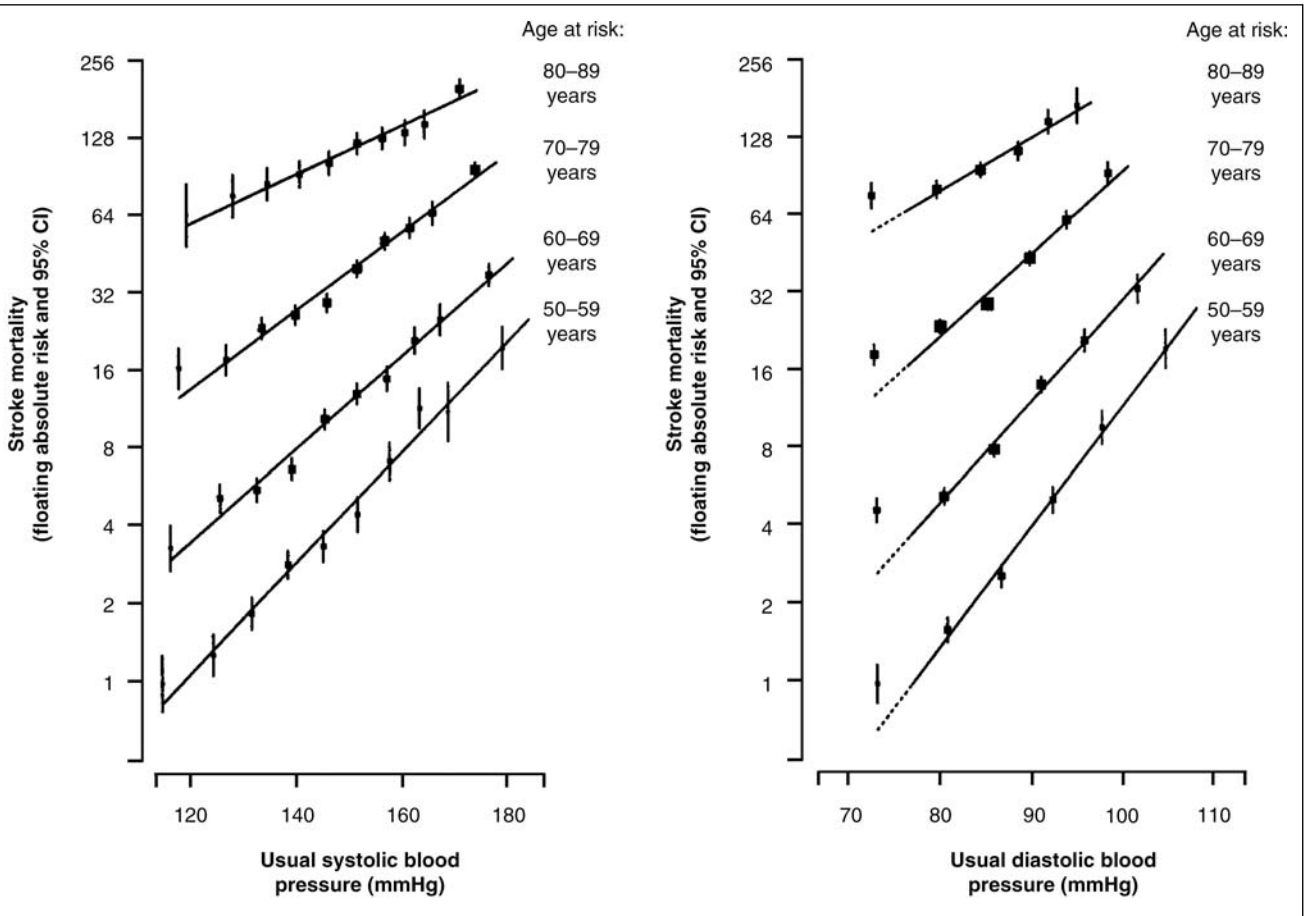


Fig. 2.4 Stroke mortality rate in each decade of age plotted for the usual systolic (*left*) and diastolic (*right*) blood pressure at the start of that decade. Data from one million adults in 61 prospective studies. *Source*: Adapted from Ref. 9.

attributable to non-optimal BP in the year 2000. Worldwide, this equates to approximately 7.1 million deaths (12.8% of the total) and 64.3 million DALYs (1 DALY is one lost year of healthy life; 4.4% of the total). This indicates a need for vigorous non-pharmacological treatment of individuals with high-normal BP and for initiating drug treatment in the vast majority of patients with mild hypertension based on their total CV risk.

POPULATION STRATEGY

In the past, most treatment efforts were aimed at the group with the highest levels of BP. However, this "high-risk" strategy, effective as it may be for those affected, does little to reduce total morbidity and mortality if the "low-risk" patients, who make up the largest share of the population at risk, are ignored (23).

Most people with mild hypertension are now being treated with antihypertensive drugs. However, as emphasized by Rose (24), a more effective strategy would be to lower the BP level of the entire population, which might be accomplished by reduction of sodium intake. Rose estimated that lowering the entire distribution of BP by only 2–3 mmHg would be as effective in reducing the overall risk of hypertension as prescribing current antihypertensive drug therapy for all individuals with definite hypertension. This has been further elaborated by Stamler (25) who made the assumption that a reduction in systolic BP by 2 mmHg may lead to a 6% reduction in stroke mortality, 4% reduction in CHD mortality, and 3% reduction in total mortality (Figure 2.7). The following environmental factors affect BP: diet, physical activity, and psychosocial factors. Dietary factors have a prominent and likely predominant role in BP homeostasis. In non-hypertensive individuals, including those with high-normal BP, dietary changes that lower BP have the potential to prevent hypertension and, more broadly, to reduce BP, thereby lowering the risk of BP-related clinical complications (26). Lifestyle modifications, which may induce more reductions in BP at the population level, include weight reduction in overweight or obese persons, lower sodium intake, consumption of diets rich in fruits and vegetables and rich in low-fat dairy products, and reduced intake of saturated fat and cholesterol [dietary approaches to stop hypertension (DASH)-like diet] (27).

Redon recently published a study showing differences in BP control and stroke mortality across Spain. Poor hypertension control and prevalence of ECG left ventricular hypertrophy were the main factors related to stroke mortality rates (28). Cooper, in an editorial commentary, suggests that we can begin to consider stroke as a surveillance measure that indicates the quality of hypertension control (29). Several

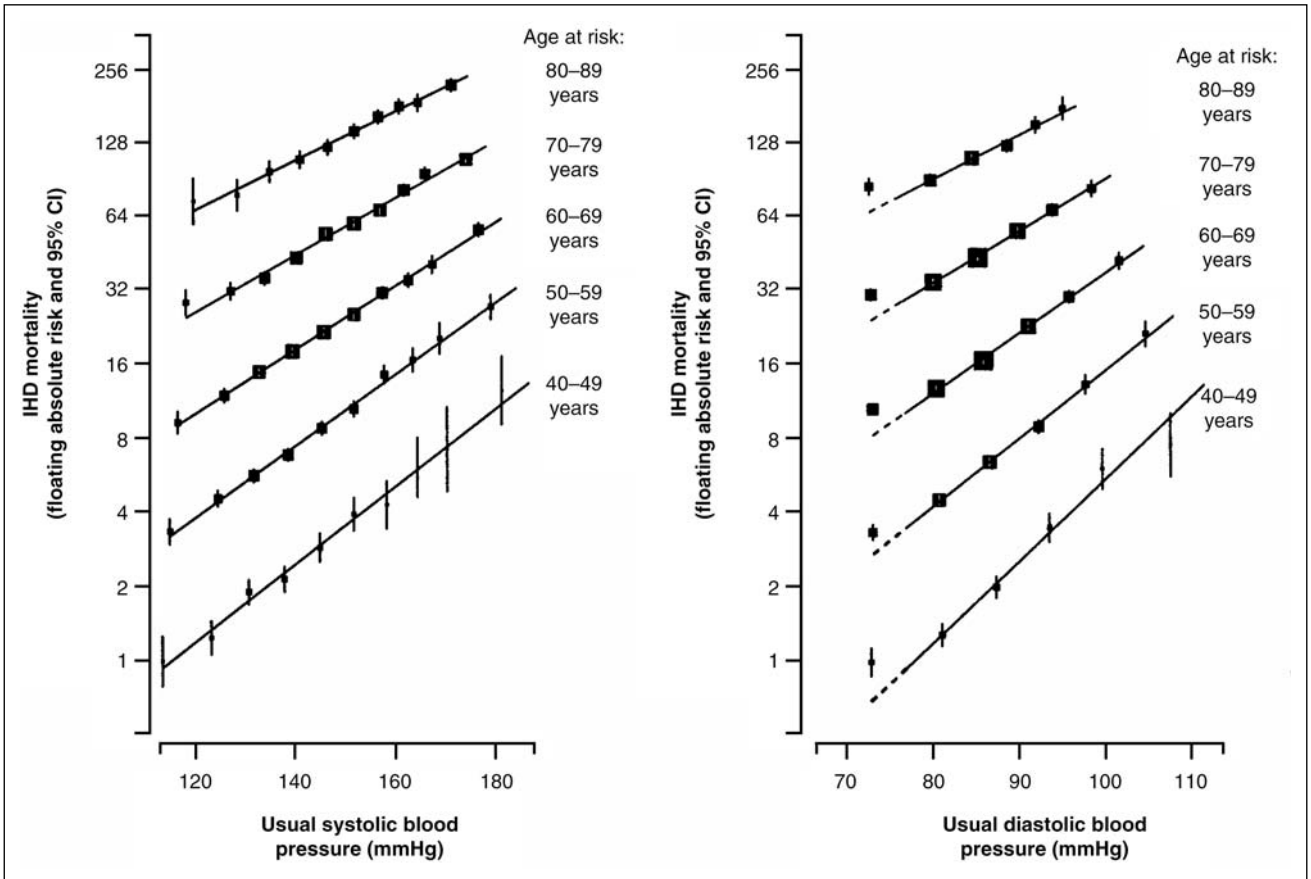


Fig. 2.5 Ischemic heart disease (IHD) mortality rate in each decade of age plotted for the usual systolic (*left*) and diastolic (*right*) blood pressure at the start of that decade. Data from one million adults in 61 prospective studies. *Source*: Adapted from Ref. 9.

decades ago, there was general agreement that medical care did not have a sufficiently widespread effect on population health (e.g., life expectancy or mortality), which was considered to be influenced only by living conditions and nutrition. However, a recent analysis suggests that medical care may have made a significant contribution to extending life expectancy in the US (30). In fact, pill-taking to prevent CV events has become a mass phenomenon, with more than half of the

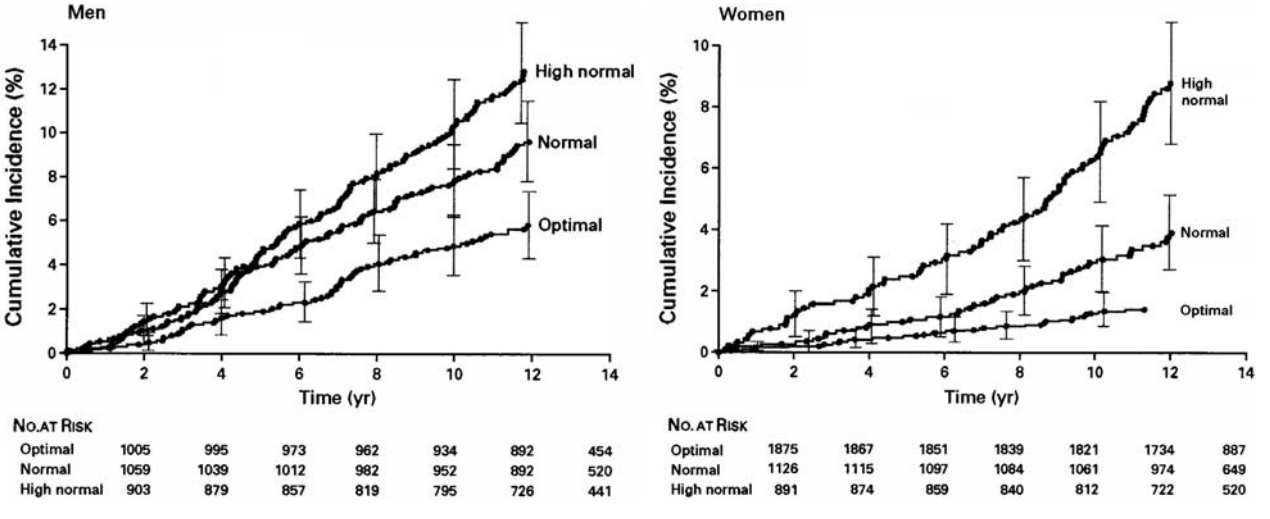
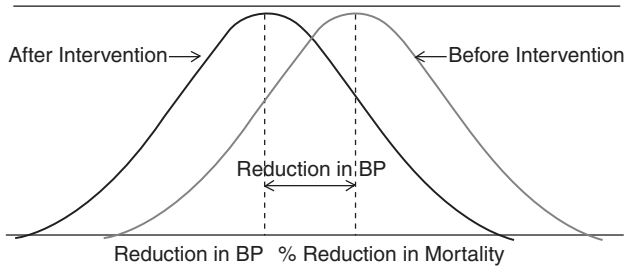


Fig. 2.6 The cumulative incidence of cardiovascular events in men and women enrolled in the Framingham Heart Study with initial blood pressure classified as optimal (<120/80 mmHg), normal (120–129/80–84 mmHg), or high normal (130–139/85–89 mmHg) over a 12-year follow-up. *Source*: Adapted from Ref. 10.



Reduction in BP mmHg	% Reduction in Mortality Stroke	CHD	Total
2	–6	–4	–3
3	–8	–5	–4
5	–14	–9	–7

Fig. 2.7 Estimated effects of population-wide shifts in systolic blood pressure (BP) distribution on mortality. *Source*: Adapted from Ref. 25.

US population over 60 years of age taking antihypertensive medication alone. Long-term therapy has thus become a public health intervention and can be considered a bridge between clinical medicine and traditional population-wide preventive measures.

GLOBAL BURDEN OF HYPERTENSION

Overall, 26.4% (26.6% in men and 26.1% in women) of the world adult population in 2000 had hypertension, and 29.2% (29.0% in men and 29.5% in women) were predicted to have hypertension in 2025 (31). Regions with the highest estimated prevalence of hypertension had roughly twice the rate of regions with the lowest estimated prevalence. In men, the highest estimated prevalence was in the regions of Latin America and the Caribbean, whereas, for women, the highest estimated prevalence was in the former socialist economies, represented in Kearney's paper by Slovak data from 1978–1979. The lowest estimated prevalence of hypertension for both men and women was in the region of Asia represented by Korea, Thailand, and Taiwan. Although hypertension is more common in developed countries (37.3%) than in developing ones (22.9%), the much larger population of the developing countries results in a considerably larger absolute number of individuals affected. The projection of the number of individuals with hypertension for 2025 is probably an underestimate since it does not account for the rapid changes in lifestyle and concurrent increase in the risk of hypertension taking place in these countries.

BP AND AGE

The relationship between age and BP has been demonstrated in a number of cross-sectional studies conducted in populations with different economic status. A remarkable finding is the consistent relationship between BP and age in developed countries.

CHILDHOOD AND ADOLESCENCE

Perhaps the most valuable data for this population are contained in the Second Task Force on Blood Pressure Control in Children (32). Data were obtained by BP measurements in over 70,000 children enrolled into nine cross-sectional studies in the United States and the United Kingdom. BP was determined in the sitting position, using a mercury sphygmomanometer (Doppler ultrasound in infants). In an effort to maintain a uniform methodology that would allow pooling of data, only the first measurement was used for analysis. In children aged 3–12 years, Phase IV Korotkoff sounds were recorded, while, in adolescents aged 13–18 years, both Phase IV and V Korotkoff sounds were recorded. While, at birth, mean BP levels are 70/50 mmHg, systolic BP starts to rise soon after birth reaching a mean value of 94 mmHg by the first year of life. In contrast, the increase in diastolic BP is a mere 2 mmHg. Systolic and diastolic BP levels do not change substantially over the next 2–3 years. After this period, i.e., from four years of age onward, there is a tendency toward a progressive increase with age throughout childhood and adolescence (Figure 2.8). The increase in systolic BP tends to be somewhat more rapid (1–2 mmHg/year) than in diastolic BP (0.5–1 mmHg/year). The rate of BP rise is about the same for both sexes up to 10 years of age, with the curve becoming flatter for girls in the ensuing period. In adolescence, the mean (particularly systolic) BP of boys is higher than that of girls. As a result, systolic BP of boys aged 18 years is 10 mmHg higher than that of girls, with the respective difference between both sexes in diastolic BP being 5 mmHg. No systematic differences have been reported for different ethnicities (blacks, Caucasians, Hispanic Americans) in childhood and adolescence.

The Second Task Force Report on Blood Pressure Control in Children was updated in 1996 (33). The main change was the recommendation to adjust BP not only for the child's sex and age but, also, height, which became the third criterion for BP assessment. This new criterion helps to eliminate bias in assessing BP in children with extreme body height values, i.e., in those small and tall for age. The recommendation for recording of Phase V Korotkoff sounds was extended to include children up to 13 years of age.

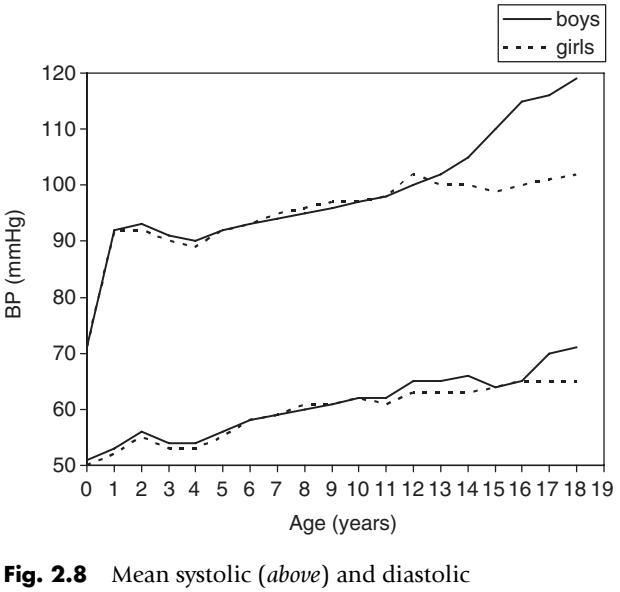


Fig. 2.8 Mean systolic (*above*) and diastolic (*below*) blood pressure (BP) of boys (*bold line*) and girls (*dotted line*) from birth to 18 years. Diastolic BP reflects the use of phase IV Korotkoff sounds. *Source*: Adapted from Ref. 32.

ADULTHOOD AND OLD AGE

In adulthood, systolic and diastolic BP tends to rise with age. The increase is somewhat greater in systolic BP rising up to 80 to 90 years of age whereas diastolic BP remains almost unaltered from age 50 years upward. Ageing results in a progressive increase in pulse pressure (difference between systolic and diastolic pressure). In adults, systolic and diastolic BPs are higher in men than in women (e.g., 120–130/75–80 mmHg in 20-year-old men and 110–120/70–75 mmHg in women of the same age). However, the BP rise in adulthood is steeper in women compared with men (0.6–0.8 mmHg/year in women and 0.33–0.5 mmHg/year in men between ages 20 and 70 years). As a result, systolic BP of women aged 70 and over is equal to or higher than that of men. Data regarding BP in the elderly are limited. However, several studies of questionable reliability have suggested that systolic BP of women in their late 80s or 90s is 10–20 mmHg higher compared with their male counterparts. The gender difference may be partly explained by different survival rates. Male hypertensives are more likely to die from CVD.

As mentioned above, both blacks and whites show similar BP levels in childhood and adolescence. Among the 20- to 30-year olds, mean BP is higher in blacks compared with whites, and the difference continues to grow in the ensuing 10-year periods. The National Health and Nutrition Examination Survey I reported mean differences of 4.1–10.6/3.5–7.0 and 5.3–17.7/3.4–10.9 mmHg between 30- and 70-year-old males and females, respectively (Figure 2.9) (34).

The age-related rise in systolic BP is primarily responsible for an increase in both the incidence and prevalence of hypertension with increasing age (35). The impressive increase in BP to hypertensive levels with age is also illustrated by Framingham data, indicating that the four-year rates of progression to hypertension are 50% for those aged 65 and older with BP in the 130–139/85–89 mmHg range, and 26% for those with BP in the 120–129/80–84 mmHg range (36).

BP TRACKING

Several longitudinal studies have shown that essential hypertension in adults is associated with high BP levels in childhood. The concept that BP rank is established early in childhood has received increasing attention since early detection and prevention of high BP levels in childhood may reduce the incidence of adult hypertension. The tendency for individuals to stay roughly in the same rank of the BP distribution as they age is known as "tracking". It means that individuals from the lower part of the distribution curve tend to have the smallest BP increases with age (i.e., they continue to remain in the lower part of the distribution curve).

While BP tracking is generally believed to exist within populations, long-term prediction for a specific individual is fairly unreliable (37).

BP tracking is most relevant in childhood, as it allows identification of individuals likely to develop hypertension during their lifetime.

POPULATIONS WITH A LOW BP

A constant finding in all populations who do not develop hypertension and whose mean BP does not tend to rise with age is a low salt intake. The relationship seems to be a causal one. A case in point are some African tribes retaining their original lifestyle without exposure to excessive salt intake. Changes in lifestyle and eating habits are usually associated with a higher prevalence of all risk factors for hypertension [increase in body mass index (BMI), increased salt intake, and decreased potassium intake].

It is generally believed that BP levels and hypertension prevalence are lower in the rural population, as compared with the urban one forced to quit its hitherto traditional, simple lifestyle. A substantially greater rise in BP occurs during migration to another continent (Japanese to Hawaii and further onto the USA, blacks migrating to Europe) (38).

AGE AND GENDER DIFFERENCES

Global estimates of BP by age, sex, and subregion show considerable variation in estimated levels (analyses based on data from about 230 surveys including 660,000 participants) (39). Age-specific mean systolic BP values ranged from

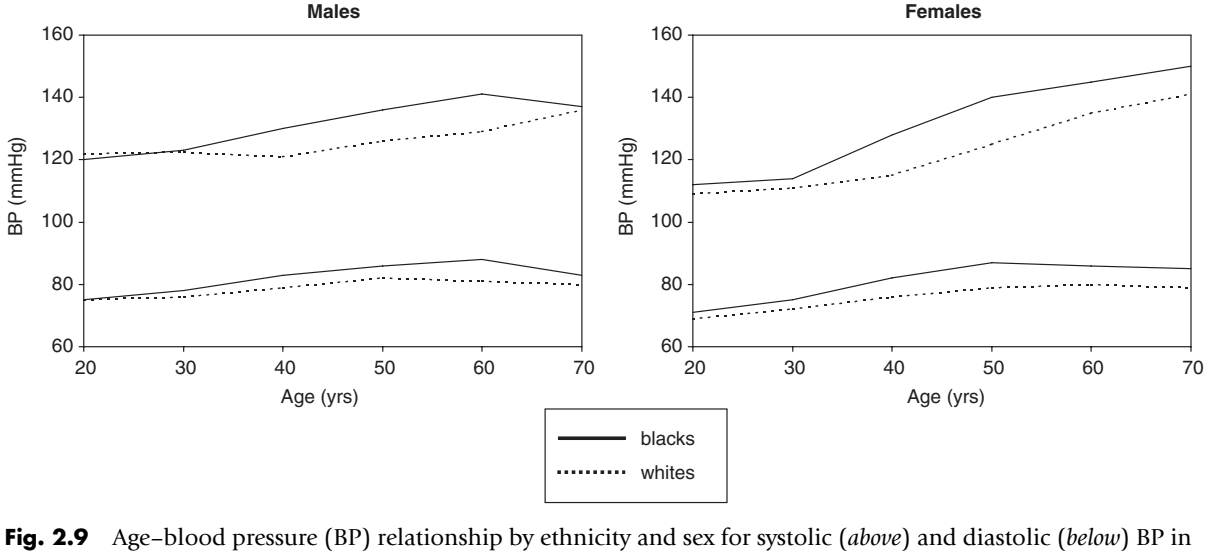


Fig. 2.9 Age–blood pressure (BP) relationship by ethnicity and sex for systolic (*above*) and diastolic (*below*) BP in the general population of the United States, 1976–1980. *Source*: Adapted from Ref. 34.

114 to 164 mmHg for females, and from 117 to 153 mmHg for males. Females typically had lower systolic BP levels than males in the 30- to 44-year-old groups, but, in all subregions, systolic BP levels rose more steeply with age for females than males. Therefore, systolic BP levels in those aged ≥60 years tended to be higher in females.

PREVALENCE OF HYPERTENSION

Whenever comparing the prevalence of hypertension, one should be aware this is heavily dependent on the definition of hypertension, population examined, number of BP readings taken on each occasion, and, finally, on the number of visits.

The prevalence of hypertension reported by Kearney et al. (2) varies widely, with rates as low as 3.4% in rural Indian men and as high as 72.5% in Polish women. In developed countries, the prevalence of hypertension ranges between 20 and 50%.

REGIONAL DIFFERENCES

INTER-CONTINENTAL AND WITHIN-EUROPE DIFFERENCES

Subregions with consistently high mean systolic BP levels include parts of Eastern Europe and Africa. Mean systolic BP levels are the lowest in south-east Asia and parts of the western Pacific.

A comparative analysis of hypertension prevalence and BP levels in six European countries, the United States, and Canada, based on the second BP reading, showed a 60% higher prevalence of hypertension in Europe compared with the US and Canada in population samples aged 35–64 years (40). There were also differences in the prevalence of hypertension among European countries, with the highest rates in Germany (55%), followed by Finland (49%), Spain (47%), England (42%), Sweden (38%), and Italy (38%). Prevalences in the United States and Canada were half the rates in Germany (28% and 27%, respectively). The differences in prevalence cannot be explained by differences in mean BMI (North America, 27.1 kg/m^2; Europe, 26.9 kg/m^2).

Findings from the World Health Organization MONItoring trends and determinants in CArdiovascular diseases (MONICA) Project showed a remarkably higher prevalence of hypertension in Eastern Europe, and virtually no difference in the rates of controlled hypertension among Eastern and Western populations (41).

REGIONAL DIFFERENCES WITHIN A COUNTRY

Regional differences in BP levels have been observed in a number of developed countries. Differences were reported between urban and rural populations, with a tendency towards higher BP levels in urban areas. In a number of areas, regional variations in BP levels are closely related to cardiovascular mortality. This is the case, e.g., of Japan where mean BP levels are the highest in the north-east part of the largest island (Tohoku), also known for high stroke-related mortality rates.

Minor differences in mean BP levels have been reported in the US, being the highest in the south, and the lowest in the west. This is consistent with regional differences in stroke-related mortality (42).

Marked geographic differences in CV mortality have also been noted in the United Kingdom. The lowest rates of death from CVD and stroke have been reported in south-east and eastern England. Cardiovascular mortality tends to rise west- and northward, reaching the highest rates in the valleys of southern Wales, northern England, and Scotland. Results of the British Regional Heart Study (43) and the Nine Towns Study documented geographic variation related to different CV mortality rates. While some of the variations could be attributed to factors such as body weight and alcohol and sodium-potassium intake, most of the variations remain unexplained (44).

ETHNIC DIFFERENCES

Prevalence of hypertension varies among different racial groups within the population. An excellent database is provided by National Health and Nutrition Examination Survey (NHANES), which used stratified multistage probability samples of the civilian non-institutionalized US population. The age-adjusted prevalence of hypertension is the highest in non-Hispanic blacks, followed by non-Hispanic whites, and Mexican Americans (45).

TRENDS IN THE PREVALENCE OF HYPERTENSION

The prevalence of hypertension in the United States declined uniformly across all population groups between NHANES I and NHANES II, with an additional and greater decline between NHANES I and the first two phases of NHANES III. However, the NHANES survey of 1999–2000 reported an increase in the prevalence of hypertension (46). No significant increase in the overall prevalence of hypertension was detected at the last survey performed in 2003–2004 (45).

A significant decrease in the prevalence of hypertension was reported in Australia, with three surveys performed as part of the National Heart Foundation's Risk Factor Prevalence Study in 1980, 1983, and 1989 (47).

Two Health Surveys for England conducted in 1994 and 1998 reported a similar prevalence of hypertension (38% and 37%, respectively) (48), which was also the case in Greece, where surveys were performed between 1979 and 1983, and in 1997 (49,50).

A significant decline in the prevalence of hypertension was found in the Belgian (51), Finnish (52), and Czech (53) populations, whereas a slight increase was observed in the MONICA Augsburg Project in Germany (54).

An increase in the prevalence of hypertension was reported in China (55), Singapore (56), and India (57–61).

In conclusion, over the past one to two decades, the prevalence has remained stable or decreased in developed countries, and has increased in developing countries.

AWARENESS AND TREATMENT OF HYPERTENSION

Awareness and treatment of hypertension varies considerably between countries and regions (2). In developed countries, there are approximately one half to two thirds of hypertensives in the general population aware of their diagnosis, and one third to one half receiving treatment. The levels of awareness and treatment in most developing countries tend to be lower than those reported in developed countries.

TRENDS IN AWARENESS AND TREATMENT OF HYPERTENSION

There are only few countries having data on longitudinal trends reported. During the 12-year interval between NHANES II and III, the proportion of hypertensive patients aware of their condition increased from 51% to 73% (46). Increases in awareness were higher for women than for men, among both blacks and whites. The Health Survey for England reported increased hypertension awareness and treatment from 46.0% and 31.6% in 1994 to 52.2% and 38.0% in 1998 (48). In Germany, from 1984/85 to 1994/95, awareness remained at 50% in men and 60% in women. The proportion of hypertensives receiving drug treatment increased by 7.9% in men, and 4.1% in women (62).

An enormous increase in awareness of hypertension was reported in Finland (from 54.5% to 75.9% in men and from 72.8% to 84.3% in women) between 1982 and 1997 (52). In the Czech Republic, there was an increase in the awareness (from 49.5% to 67.2%) and treatment (from 29.3% to 49.3%) of hypertension from 1985 to 2000/01 (53).

HYPERTENSION CONTROL

Hypertension is poorly controlled worldwide, with less than 25% controlled in developed countries, and less than 10% in developing countries (2). Hypertension control rates also vary within countries by age, gender, ethnicity, socioeconomic status, education, and quality of health care (63). While awareness of hypertension has improved in the United States and other Western countries over the past decade, hypertension control remains inadequate, as only a portion of those who are aware of their diagnosis are treated, and an even smaller number of those receiving treatment are treated adequately. Sadly, however, the most important parameter likely to have an impact on public health is neither the number of those who are aware of their hypertension nor the number taking steps to improve it but, rather, the percentage of those whose BP is under control (64).

ENVIRONMENTAL FACTORS

AIR TEMPERATURE AND SEASONAL VARIATION IN BP

A number of reports have pointed out that a lower air temperature is associated with a higher mean BP. As air temperature in Scotland and northern England is lower compared with southern England, the differences in air temperature may be theoretically responsible for some regional differences in BP across the United Kingdom.

A seasonal effect on BP was first described by Rose (65), analyzing measurements in 56 men observed for 1–3 years at a clinic for ischemic heart disease. The Medical Research Council's trial of mild hypertension found systolic and diastolic BP levels were higher in winter than in summer. The seasonal variation in BP was greater in older than in younger individuals and was significantly related to maximum and minimum daily air temperature measurements, but not to rainfall (66).

SOCIAL STATUS

The British Regional Heart Study and the Nine Towns Study reported a lower systolic BP in white-collar workers compared with blue-collar workers (44,67). Individuals with a lower level of education also show a higher prevalence of other risk factors, in particular obesity and lower physical activity. An inverse relationship between education and BP has been shown in many adult populations (68). In the less educated, BMI levels and more adverse intake patterns of multiple macro- and micronutrients account substantially for their higher BP levels (69).

BODY WEIGHT AND PHYSICAL ACTIVITY

BP and BMI are closely inter-related. The relative risk (odds ratio) for the development of hypertension rises markedly with increasing BMI (70). The importance of this relationship is reinforced by the high and increasing prevalence of overweight and obesity worldwide (71–73).

A variety of epidemiological studies have documented an inverse correlation between the level of physical activity and BP levels. Prospective cohort studies have reported a higher incidence of hypertension in individuals with lower levels of physical activity and lower cardiorespiratory fitness (74). Randomized controlled studies have furnished evidence of a beneficial effect of physical activity on BP. A meta-analysis of controlled interventional studies concluded that adequate dynamic physical training contributes significantly to BP control. The training-induced decrease in BP averaged 2.6/1.8 mmHg in normotensives and 7.4/5.8 mmHg in hypertensives (75,76).

SODIUM AND POTASSIUM INTAKE

There is a correlation in most populations between normal dietary sodium intake (usually expressed as 24-hour urinary sodium excretion) and mean BP (77). However, 24-hour urinary sodium output is biased by large intra-individual variability. In most populations, the age-related rise in BP is significantly associated with sodium intake (78).

There are major differences in the individual response of BP to salt intake. Afro-Americans, the middle-aged, the elderly, those with diabetes, and people with hypertension respond more sensitively to changes in salt intake compared with the general population. These groups tend to have a less responsive renin–angiotensin–aldosterone system (79). The recommended adequate sodium intake has been recently reduced from 2.4 to 1.5 g/d (65 mmol/d) (80) corresponding to 3.8 g/d sodium chloride, which may be difficult to achieve.

Individuals on a predominantly vegetarian diet show lower BP levels and their BP rises less with increasing age compared with those on diets of animal origin (81). Vegetarians have lower BP levels compared with the non-vegetarian population, even in developed countries (82). The lowest levels of BP in industrialized nations were reported in strict vegetarians not consuming virtually any products of animal origin. Their diet includes whole-grain products, lots of green-leaved vegetables, pumpkins, and root vegetables. A diet rich in potassium and polyunsaturated fat and containing little starch, saturated fat, and cholesterol correlates inversely with BP levels in a large population of United States males (83). Over the past decade, increased potassium intake and dietary patterns based on the DASH trial (a diet rich in fruit, vegetables and low-fat dairy products, with a reduced content of dietary cholesterol, as well as saturated and total fat) (84) have emerged as effective strategies that also lower BP.

Table 2.1 Rates of progression to hypertension in Framingham Heart Study

Blood pressure (BP) category	Percentage of 4-year progression to hypertension			
	Men, age 35–64 years	Men, age 65–74 years	Women, age 35–64 years	Women, age 65–74 years
Optimal BP	5	15	5	16
Normal BP	18	25	12	26
High normal BP	37	47	37	49

Source: Adapted from Ref. 36.

ALCOHOL CONSUMPTION

Observational studies and clinical trials have documented a direct, dose-dependent relationship between alcohol intake and BP, particularly as the intake of alcohol increases above approximately two drinks per day (85,86). Importantly, this relationship has been shown to be independent of potential confounders such as age, obesity, and salt intake (87). Although some studies have shown that the alcohol-hypertension relationship also extends into the light drinking range (≤2 drinks per day), this is the range in which alcohol may reduce CHD risk.

A meta-analysis of 15 randomized controlled trials reported that decreased consumption of alcohol (median reduction in self-reported alcohol consumption, 76%; range, 16–100%) reduced systolic and diastolic BP by 3.3 and 2.0 mmHg, respectively. The BP reductions were similar in normotensive and hypertensive individuals; there was a dose-dependent relationship between reduction in alcohol consumption and decline in BP (86).

A reduction in alcohol consumption is associated with a decrease in BP (a decrease in alcohol consumption by one alcoholic drink will result in decreases in both systolic and diastolic BP by about 1 mmHg).

Women and lean individuals absorb larger amounts of ethanol than men (88), consequently, their daily consumption should not exceed 20 ml of ethanol.

Excessive alcohol intake is a major risk factor for the development of hypertension and may be responsible for resistance to antihypertensive therapy (89).

DIETARY FACTORS WITH LIMITED OR UNCERTAIN EFFECT ON BP

Several predominantly small clinical trials and meta-analyses of these trials (90–92) have documented that high-dose omega-3 polyunsaturated fatty acid (commonly called fish oil) supplements can lower BP in hypertensive individuals with BP reductions occurring at relatively high doses (≥3 g/day). In hypertensive individuals, average systolic and diastolic BP reductions were 4.0 and 2.5 mmHg, respectively (92).

Overall, data are insufficient to recommend an increased intake of fiber alone (93,94), supplemental calcium, or magnesium (95,96) as means to lower BP. Additional research is warranted before specific recommendations can be made about how the amount and type of carbohydrates (97,98) affect BP.

INCIDENCE OF HYPERTENSION

There are much less data about the incidence, i.e., newly developed cases, of hypertension than about its prevalence. The incidence of hypertension in the Framingham cohort over four years was directly related to the prior level of BP and to age, with similar rates in men and women (37). Obesity and weight gain also contributed to progression of hypertension. A 5% weight gain after 4 years was associated with 20% increased odds of hypertension (Table 2.1). Another longitudinal database is provided by the NHANES study, which found minimal differences in the incidence of hypertension between men and women for all age groups. Incidence rates for blacks were at least twice the rates of whites for almost every age–sex group (99).

Short-term incidence rates of hypertension are available for middle-aged adults in Korea, confirming again only minor differences in the crude two-year incidence of hypertension between males and females. Incidence rates were markedly increased (two or five times higher) in individuals with higher BP at baseline. Older age and overweight were also major predictors for hypertension (100).

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PULSE PRESSURE AS A CARDIOVASCULAR RISK FACTOR

3

Athanase Benetos

INTRODUCTION

With the aging of the population, the incidence of systolic hypertension is increasing among the elderly. The primary reason for this evolution is the age-related development of arterial stiffness, which leads to an increase in systolic blood pressure (SBP) and pulse pressure (PP), and a decrease in diastolic blood pressure (DBP). The role of PP in cardiovascular (CV) morbidity and mortality has been well established over the last 10 years for various populations. Study results indicate that the evaluation of central and peripheral PP, as well as direct measurements of arterial stiffness, are of clinical interest for identifying high-risk patients.

PP AND CV MORBIDITY AND MORTALITY IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

In the past, many epidemiological investigations did not include patients with high SBP and normal or low DBP (1–3). However, since the 1970s, several studies (4,5) have emphasized the greater risks of an elevated SBP compared to that of an elevated DBP, especially in older patients. PP, however, was rarely mentioned until the end of the 1980s (1). In 1989, a study from France (6) described an association between PP and left ventricular hypertrophy (LVH) in both sexes and found a positive correlation with death from coronary artery disease in women. In 1994, Madhavan et al. (7) reported that hypertensive subjecs in the upper tertile of pretreatment PP ($>$63 mmHg) had a greater mortality than those in the lower tertiles, and that PP, but not SBP or DBP, was an independent predictor of myocardial infarction. In a later study (8) from the same group, an extensive number of treated and untreated hypertensive patients were examined. After adjustment for other CV risk factors, PP was the only measure of blood pressure (BP) significantly and independently related to the intreatment incidence of myocardial infarction.

In 1997, we reported results from a study in a large French cohort that showed that a wide PP was an independent and significant predictor of all-cause mortality, total CV mortality, and especially coronary mortality (9). This study was realized in 19,000 men, aged 40–69 years, with no CV diseases, who had a routine health examination, and who were followed up for a mean period of about 20 years. Subjects were divided into groups according to age (40–54 and 55–69 years) and the level of mean arterial pressure (MAP $<$107 and $>$107 mmHg). A wide PP was an independent and significant predictor of all-cause, total CV and especially coronary mortality in all subgroups of subjects. In this study the association between PP and cerebrovascular mortality was weaker than for coronary mortality.

In a subsequent report in 1998, we showed that the evaluation of PP is of interest even in individuals presenting normal values of SBP ($<$140 mmHg) and DBP ($<$90 mmHg) (10). Thus, normotensive men with PP $>$55 mmHg have an increased relative CV risk of 40% compared to normotensives of the same age who belonged to the lower PP group ($<$45 mmHg).

We also investigated, in two independent French male cohorts, the risk of CV mortality according to the long-term evolution of BP by testing the association between spontaneous (non-treatment related) changes in SBP and DBP over a period of approximately 5 years and subsequent CV mortality over a 20-year follow-up period (11). In both cohorts, after adjustment for age and major risk factors, the group with increased SBP and decreased DBP, i.e., those patients with the most pronounced increase in PP, had the highest CV risk. These results indicate that the development of arterial stiffness (the cause for the increase in PP) is a strong determinant of CV mortality, independently of absolute BP values. Thus, in the case of normal or slightly increased BP levels, when treatment is not necessary, long-term follow-up of BP levels may help estimate an individual's CV risk and contribute to therapeutic decision-making. In addition, in subjects with high BP, to whom physicians should propose a first treatment, comparison with older BP readings when available could contribute to a better estimation of CV risk.

In the last 10 years, a large number of clinical studies have shown that increased PP is a strong predictor of CV morbidity and mortality, especially coronary mortality, and incidence of heart failure, independently of mean BP levels (12–14). These observations have been made in different populations but are apparently more pronounced in diabetics and elderly subjects.

ROLE OF PP IN DIABETIC PATIENTS

Diabetic patients show a more marked increase in PP with age compared to non-diabetic patients due to a more pronounced increase in arterial stiffness (15–17). In accordance with this concept, increase in PP with age is more pronounced in diabetics with initial micro-, macro-albuminuria, and retinopathy, suggesting that the progression in arterial aging is more pronounced in the presence of target organ damage (17).

Several clinical studies have shown that large artery stiffness and its main clinical expression, such as high PP, develop prematurely in the presence of diabetes and are key factors of CV complications and mortality in diabetics. It has been shown that in type II diabetics, PP was associated with both micro- and macrovascular complications (18). Cockcroft et al. (19), in a study with a 4-year follow-up among type II diabetic subjects, have shown that both PP and SBP, but not DBP, were positively associated with CV events. The authors concluded that PP was a better predictor of CHD events than SBP in persons with type 2 diabetes, but that SBP remained a better predictor for CV disease.

Schram et al. (20) studied the association between PP and CVD disease in young type I diabetics. They found that PP, in addition to MAP, was a significant determinant of CV complications. This is contrary to what has previously been reported in a general population, which is that DBP better reflects cardiovascular disease (CVD) risk in younger subjects, whereas SBP and PP better reflect the risk in older subjects (21). The fact that in young type 1 diabetics PP is a strong determinant of CV complications suggests that these patients have a more advanced arterial age than their chronological age. This could explain why what is found only for older subjects in the general population is observed even in much younger subjects with type 1 diabetes. Actually, diabetes induces several functional and structural changes of the arterial wall which could explain the development of arterial stiffness. The endothelial dysfunction has been described in several studies. One of the major mechanisms of accelerated stiffening in diabetics appears to be the reaction between glucose and the proteins of the extracellular matrix called non-enzymatic glycation (22,23). This leads to the formation of advanced glycation end products, responsible for the increase in collagen cross-links.

These reactions observed during aging are greatly accelerated in the presence of diabetes, accounting for arterial stiffness and increase in SBP and PP in diabetics. These structural alterations may also explain the failure of antihypertensive drugs to control SBP in diabetics (24). The predominant role of SBP and PP in the evolution of diabetes and its related complications has also been suggested by the results of several large clinical trials that show that SBP control is by far the most important therapeutic goal for protecting type 2 diabetics.

WHY DOES PP INCREASE WITH AGE?

Until the ages of 50–60 years, both SBP and DBP increase with age. Thereafter, in the majority of cases, SBP increases with age disproportionally to DBP. The most common cause for the disruption of the correlation between SBP and DBP (leading to an excessive increase in SBP and PP) is the progressive stiffening of the arterial wall (25,26). Actually, arterial stiffness develops as a consequence of several structural and functional changes of the large arteries. Wall hypertrophy, calcium deposits, and changes in the extracellular matrix, such as an increase in collagen and in fibronectin, fragmentation and disorganization of the elastin network, enzymatic and non-enzymatic cross-links, and cell–matrix interactions, are the main structural determinants of the decrease in the elastic properties and development of large artery stiffness (22). Loss of vascular endothelium function (decrease in the release of vasodilators and increased synthesis of vasoconstrictors) and modification of smooth muscle reactivity may be the main functional changes leading to decreased elasticity and increased stiffness.

It is important here to point out that SBP depends on left ventricular performance and on the stiffness of the aorta and the other large arteries (25,27). Thus, peak SBP will be greater if the arterial wall is more rigid. On the other hand, after the closure of the aortic valves, arterial pressure gradually falls as blood is drained to peripheral vascular networks. The minimum DBP is determined by the duration of the diastolic interval and the rate at which the pressure falls. The rate of fall in pressure is influenced by the rate of outflow, i.e., the peripheral resistance, and by the visco-elastic arterial properties. At a given vascular resistance, the fall in DBP will be greater if the rigidity of large arteries is augmented. The visco-elastic properties of arterial walls are also a determinant of the speed of propagation of the arterial pressure wave (pulse wave velocity, PWV) and of the timing of wave reflections. Thus, stiffening of the arteries increases PWV and may be responsible for an earlier return of the reflected waves, which superimposes the incident pressure wave, thus further contributing to the increase in SBP and PP (27). Therefore, arterial stiffness is the major cause of elevated SBP and PP in the elderly, which is one of the most powerful determinants not only of mortality but also of morbidity, hospitalization, loss of autonomy, and handicaps.

CHANGING ROLES OF SBP, DBP, AND PP WITH AGING

These considerations can also explain why SBP and PP better reflect the risk in older subjects whereas DBP better reflects the CVD risk in younger subjects (21,28). These age-dependent changes in the prognostic value of BP levels are due to several factors. DBP in young patients is mainly dependent on peripheral resistance and therefore low DBP reflects low peripheral resistance. Moreover, in younger subjects with hyperkinetic circulation, DBP is less variable than SBP, thus better reflecting CV risk. In older subjects, a low DBP may reflect high arterial stiffness, which is a major manifestation of arterial aging, rather than low peripheral resistance (25–27). In this case, low DBP is associated with high SBP and high PP and increased CV risk. The clinical application of these considerations is that—as clearly stated during the latest guidelines of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC)—"in persons older than 50 years SBP is a much more important CV risk factor than DBP" (29).

IS PP A STRONG DETERMINANT OF CV MORTALITY RISK IN VERY OLD SUBJECTS?

Although it has been shown that PP is the most powerful BP index in predicting CV end points in elderly persons (21,28,30), the results of studies carried out in subjects over 80 years of age challenge this view. In a study involving elderly institutionalized patients (mean age 87 years), we found that BP, in particular SBP and PP, did not predict CV mortality. Actually, in that population only aortic PWV, a direct indicator of arterial stiffness, was a major independent predictor of CV mortality and was an extremely powerful marker (31).

In a community-based study among subjects 85 years of age or older, survival was lower in subjects with low SBP and DBP (32). This paradox seems to be related to the presence of co-morbidities since it disappears after adjusting for confounding parameters. However, after these statistical adjustments, no positive relationship was found between BP and CV morbidity and mortality, indicating that BP may not be a risk indicator in this group of patients. Other studies in elderly patients have shown that a decrease in BP over a long period of time predicts high morbidity and mortality (33). In a recent study from the United States, realized among institutionalized subjects, no relationship was observed between BP levels and CV risk (34). The abolishment of the association between BP and CVD risk in the very elderly is related to several age-related changes which are summarized below.

- The presence of frequent co-morbidities in the very elderly, mainly denutrition, heart failure, and several neurological disorders, reduces BP levels and thus masks the association between high BP and CVD risk (35).
- Exaggeration of BP variability, mainly SBP and PP variability, due to the alterations of homeostatic mechanisms. Arterial stiffness, baroreceptor failure, and neurological diseases are responsible for such variability and for the presence of orthostatic or post-prandial hypotension (36). Therefore, SBP and PP recorded during casual measurements may not reflect real SBP and PP levels. Several international guidelines propose the systematic realization of multiple BP measurements (home measurements, 24-h BP recordings) in order to obtain more valuable BP levels, especially before treating very elderly patients.
- Finally, we should mention the relatively frequent overestimation of BP levels in the presence of severe mediacalcosis (pseudo-hypertension) (37) due to the lack of compressibility of peripheral arteries.

Thus, in very elderly people with multiple co-morbidities, the BP-related risk could be better evaluated by combining home measurements and direct evaluation of arterial stiffness, which are not as influenced by the above mentioned disease and alterations. However, extensive studies are needed to confirm the interest of these measurements for the evaluation of treatment efficacy in high-risk elderly patients.

CENTRAL VERSUS PERIPHERAL PP LEVELS

In younger subjects without accelerated arterial aging, SBP and PP increase significantly from the central to the peripheral arteries, due primarily to lower stiffness and lower velocity in the propagation of reflection waves in central arteries (27,38). Central and peripheral DBP values however are not significantly different. The clinical consequence is that SBP and PP measured at the peripheral arteries overestimate the central aortic values. After the age of 55–60 years, central SBP and PP increase more than peripheral pressures as a consequence of arterial aging, which is more pronounced at the site of the central arteries. In these subjects, central SBP and PP levels are often equal or even higher than the values recorded at the peripheral arteries. Actually, central aortic pressure, an important determinant of left ventricular load, is influenced more than peripheral pressure by the stiffness of large arteries and the timing and magnitude of pressure wave reflections (25,39–41). In 280 patients undergoing a diagnostic coronary angiography, central PP was recorded in the aortic root before angiography (42). Aortic PP was strongly correlated with the presence and extent of coronary artery disease. By contrast, peripheral brachial PP did not differ in the different groups of patients according to the severity of coronary artery disease. These results indicate that central BP recordings can evaluate the severity of atherosclerosis and detect high-risk patients better than peripheral BP.

Several clinical studies have shown that various classes of BP-lowering drugs may have profoundly different effects on central pressure waveforms despite similar effects on brachial artery pressures (43–45). Although these results have been observed primarily in short-term studies, two recent long-term trials have also shown significant differences between antihypertensive drugs. The REASON study (46,47) showed that, despite similar effects on peripheral SBP and PP, the angiotensin-converting enzyme inhibitor perindopril had more pronounced effects on central BP than the beta-blocker atenolol. More recently, an analysis from the ASCOTT-CAFE study (48) showed that even though brachial SBP and brachial PP were not significantly different between treatment groups, central aortic SBP and central aortic PP were significantly lower with amlodipine–perindopril therapy as compared to the beta-blocker–diuretics treatment. Moreover, this study found that central aortic PP was identified as a significant determinant of CV and renal outcomes.

Taken together these results indicate that central aortic SBP and PP measurements are more appropriate for assessing CV risk than brachial BP measurements. The recent development of several noninvasive devices enables the measurement of central aortic hemodynamics in large populations (42–44).

WHY IS PP ASSOCIATED WITH CV RISK?

If the association between PP and CV risk has been demonstrated in a very large number of clinical studies, the pathophysiological mechanisms of this association still remains unclear. Schematically, we can advance at least three hypotheses.

1. PP and increased cyclic stress. Experimental studies indicate that fatigue and fracture of elastic fibers within the arterial wall are related to both steady-state and pulsatile stress (39,49). In vivo, the former is primarily dependent MAP, whereas the latter is related to amplitude of PP and also to heart rate. Therefore, the first hypothesis is that increased PP by itself could be responsible for cardiac and arterial fatigue and subsequent complications, such as LVH, arterial hypertrophy and

dilatation, endothelial damage, and extracellular matrix changes.
2. Altered ventricle-aortic coupling influences myocardial perfusion by elevating the proportion of coronary flow during the systolic time period (50). Thus increased PP and low DBP lead to decreased coronary perfusion, which mainly occurs during the diastolic phase of the cardiac cycle.
3. PP as an indicator of stiffness. PP is associated with CVD risk since it is an indicator of arterial stiffness, and, therefore, PP is just an epiphenomenon and not responsible for CV alterations.

We believe that these three hypotheses are complementary rather than contradictory. Some studies have shown that increased PP in the absence of arterial stiffness (Marfan disease, hyperdynamic circulation) could be responsible for arterial hypertrophy and dilation. Excessive decrease in DBP can lead to coronary insufficiency, especially since an increase in stiffness is responsible for increased LVH and, therefore, increased needs of the myocardium. It is therefore possible that the combination of the direct and indirect effects of increased PP are all responsible for the increase in CVD risk (Figure 3.1).

CONCLUDING REMARKS

One of the problems when treating for hypertension is that a very large number of subjects have to be treated in order to prevent a small number of CV complications (51). This suggests that the standard criteria, mainly DBP, even if they are generally correlated with CV risk, may not be specific or sensitive enough to identify groups of subjects who are at high risk due to BP values. An increase in PP, especially when both a high SBP and a low DBP are present, is due to an excessive arterial stiffness, which is one of the major signs of arterial aging, and is associated with elevated CV risk. An increasing number of experts propose to shift our risk evaluation from DBP to SBP or PP (29,52,53). Although it is not possible at this moment to define normal PP levels, most of the studies have shown that a PP higher than 65 mmHg is associated with a clinically important increase in CV risk. Noninvasive assessment of central PP by applanation tonometry and of arterial stiffness using the PWV approach, can provide supplementary information for the evaluation of CV risk and the estimation of treatment efficacy.

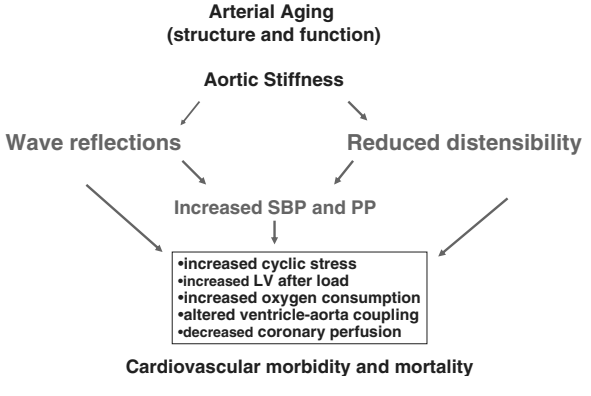

Fig. 3.1 Schematic representation of the relationships between arterial stiffness, pulse pressure (PP), and cardiovascular (CV) events. An increase in PP, especially when this is due to both a high systolic blood pressure (SBP) and a low diastolic blood pressure, is due to excessive arterial stiffness and is associated with elevated CV risk.

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Associated risk factors

SECTION 2

OBESITY AND OBSTRUCTIVE SLEEP APNEA

4

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INTRODUCTION

Obesity is becoming recognized as one of the most important risk factors for the development of hypertension. The epidemic of obesity and obesity-related hypertension is paralleled by an alarming increase in the incidence of diabetes mellitus, chronic kidney disease, and obstructive sleep apnea (OSA). For many years, OSA was linked primarily to impaired cognitive function and daytime somnolence. However, there is increasing evidence that OSA may also be implicated in the pathogenesis of hypertension and cardiovascular disease (CVD). This chapter examines the relationship between obesity, hypertension, and OSA, and reviews major mechanisms underlying this link.

EPIDEMIOLOGY OF OBESITY

The World Health Organization accepts a body mass index (BMI) of 25.0 kg/m^2 or higher as abnormal; the overweight category is classified as obese when the BMI is 30.0 kg/m^2 or more (Table 4.1) (1). The International Obesity Task Force estimates that at least 1.1 billion adults are overweight, including 312 million obese individuals (2). Figure 4.1 presents the prevalence of obesity by age and gender in the subregions of the world. Obesity is common in both Western and Eastern Europe. At all ages, women are generally found to have higher rates of obesity than men.

The risks of hypertension, diabetes, and dyslipidemia increase from a BMI of about 21.0 kg/m^2, reducing life expectancy and increasing the health and societal burden (2). Excess bodyweight is the sixth most important risk factor contributing to the overall burden of disease worldwide (2). In the United States, obesity is set to overtake smoking in 2005 as the main preventable cause of illness and premature death (3).

Central obesity is much more closely related to cardiovascular and metabolic risk factors than peripheral obesity. Co-morbidities of central obesity are reflected in the metabolic syndrome, and are discussed in Chapter 5. The International Diabetes Federation defines central obesity as waist circumference >94 cm for Europid men and >80 cm for Europid women, with ethnicity-specific values for other groups (4). This waist circumference cutoff is lower than the main Adult Treatment Panel III recommendations (>102 cm for males and >84 cm for females) (5). In clinical practice, it is simpler to use the waist measurement than the waist/hip ratio. However, recent findings from The INTERHEART study (6) provides evidence for the predictive importance of the waist/hip ratio independent of waist or BMI measures alone. Waist-to-hip ratio shows a graded and highly significant association with myocardial infarction risk worldwide (Figure 4.2). Therefore, it was suggested (2) that the early emphasis on waist/hip ratios might have to be reapplied.

Table 4.1 Classification of adults according to body mass index (BMI)

Classification	BMI (kg/m^2)
Underweight	<18.5
Normal range	18.5–24.9
Overweight	≥25.0
Preobese	25.0–29.9
Obese class I	30.0–34.9
Obese class II	35.0–39.9
Obese class III	≥40.0

Source: From Ref. 1.

Given the close link between obesity and CVD, it has been suggested that current trends in obesity might lead to a decline in life expectancy in the United States in the 21st century (7). Similar trends are likely to occur in other countries.

EVIDENCE LINKING OBESITY AND HYPERTENSION

Obesity and, in particular, central obesity have been consistently associated with hypertension and increased cardiovascular risk. Based on population studies, risk estimates indicate that at least two-thirds of the prevalence of hypertension can be directly attributed to obesity (8).

Several epidemiological studies show that the age-adjusted prevalence of hypertension increases progressively with higher levels of BMI in men and women (Figure 4.3) (9). The risk of developing hypertension is strongly linked to both waist

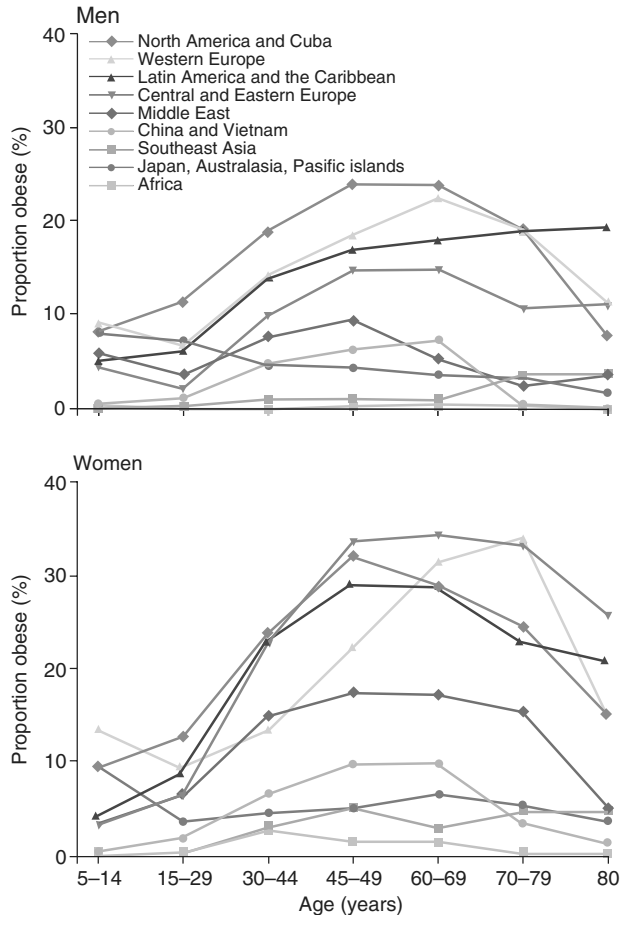

Fig. 4.1 Prevalence of obesity worldwide by age and gender. *Source*: Reproduced from Ref. 2.

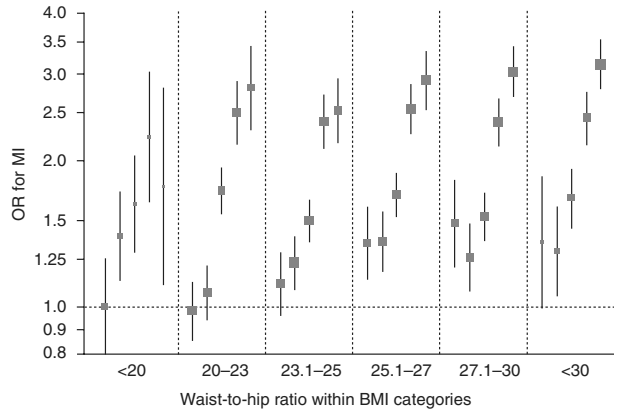

Fig. 4.2 Association of waist-to-hip ratio (expressed as quintiles) within BMI categories with MI risk in the INTERHEART study. Increasing waist-to-hip ratio was a predictor of MI, even in those regarded as very lean and in those regarded as being of ideal weight, overweight, or obese. *Abbreviations*: BMI, body mass index; MI, myocardial infarction; OR, odds ratio. *Source*: Reproduced from Ref. 6.

circumference and waist/hip ratio. Blood pressure (BP) appears highest among those with high waist and small hip circumference measures (10). In men, the attributable risk of hypertension induced by abdominal obesity ranges from 21% to 27% and in women ranges from 37% to 57% (11).

Most hypertensive patients are either overweight or obese. Figure 4.4 shows data from a cross-sectional population survey conducted in Finland, which suggests that more than 85% of hypertension occurs in subjects with a BMI $>25\,kg/m^2$ (12).

Both obesity and hypertension contribute to the development of left ventricular hypertrophy (13). Obesity and hypertension appear to have an additive effect in men but a synergistic effect in women. Therefore, obese hypertensive women are at particular risk of developing left ventricular hypertrophy.

Further understanding of the relationship between weight and BP has come from observational studies of weight change. The Nurses' Health Study showed that women who lost at least 5 kg had a significantly lower relative risk of developing hypertension than women who did not change their weight (14). Compared with women whose weight remained stable over 14 years of follow-up after the age of 18 years, women who gained more than 25 kg in weight had a five-fold increase in the risk of hypertension.

Apart from hypertension, abdominal adiposity has also been implicated in the pathogenesis of coronary artery disease, stroke, and congestive heart failure (2). Recent evidence from France suggests that, in overweight and obese subjects, cardiovascular risk is not significantly increased unless hypertension is present (15). This observation underscores the role of hypertension as a mediator through which obesity may cause CVD.

While obese subjects are prone to hypertension, hypertensive subjects also appear to be prone to weight gain. Both the Framingham and Tecumseh studies have shown that future weight gain is significantly greater in hypertensive patients than in normotensive subjects, suggesting that even normal-weight hypertensives are at high risk for development of obesity (16). Therefore, the relationship between obesity and hypertension might be described as a "two-way street" (17), implying an individual susceptibility to both conditions or common environmental features.

MECHANISMS LINKING OBESITY TO HYPERTENSION

There is growing evidence that adipose tissue may be directly involved in the pathogenesis of hypertension (18).

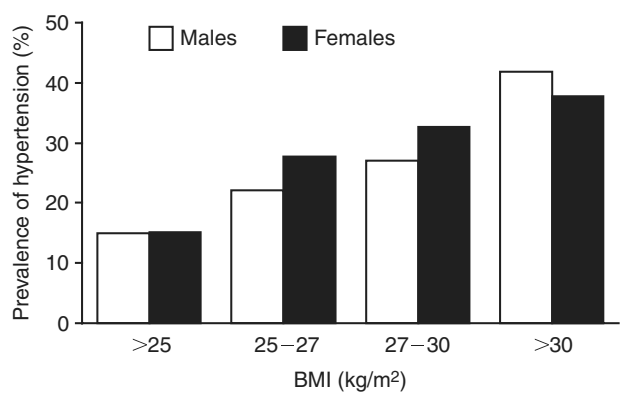

Fig. 4.3 Prevalence of hypertension (%) according to body mass index (BMI) in NHANES III. *Source*: From Ref. 9.

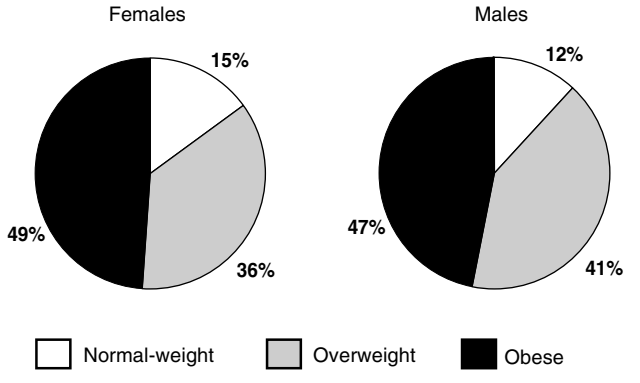

Fig. 4.4 Cross-sectional data from Finland show that only a minority of patients being treated with antihypertensive drugs are of normal weight; around half are obese (body mass index ≥30 kg/m^2). *Source*: From Ref. 12.

Understanding the pathophysiology of obesity-related hypertension has important implications in terms of clinical management. Several mechanisms appear to be implicated in the development of hypertension associated with obesity (19) (Figure 4.5). These include alterations in the renin–angiotensin–aldosterone system (RAAS), increased sympathetic nervous system activity (20), insulin resistance, leptin resistance (21), altered coagulation factors, inflammation, and endothelial dysfunction (22).

Obesity might lead to hypertension by increasing renal sodium reabsorption, impairing pressure natriuresis and volume expansion (23). Furthermore, obesity may also cause marked structural changes in the kidneys that eventually lead to chronic renal failure and further increases in BP (24,25). Obesity may cause glomerular hyperfiltration, increased urinary albumin loss, and progressive loss of renal function caused by focal segmental glomerulosclerosis (26,27). Tubular injury, as the first sign of renal damage in hypertension, is closely linked to metabolic disturbances (28). Kincaid-Smith (29) recently proposed that obesity and the insulin resistance syndrome play a major role in the genesis of renal failure in hypertensive patients by what conventionally had been labeled "hypertensive nephrosclerosis." In patients with established renal disease, obesity accelerates disease progression (30,31). The importance of obesity in causing renal damage has recently been emphasized by population-based studies in apparently healthy subjects. First, multivariate analysis of the data of the PREVEND study showed that the BMI is independently associated with urinary albumin excretion, and that this relationship is closer in males than in females (25) (Figure 4.6). The relationship between BMI and impairment of renal function is evident even in subjects without overt obesity (32). Second, in the general population, obesity is associated with an increased incidence of chronic kidney disease (33) and end-stage renal failure (34).

Central obesity is characterized by a sympathetic activation greater for magnitude than that detectable in peripheral obesity (35). The mechanisms of sympathetic activation in obesity are not completely understood but participation of the hypothalamus–hypophysis axis (36), stimulation of the hypothalamic pro-opiomelanocortin pathway by hyperleptinemia (37), and frequently co-existing OSA (38,39) might be implicated (see below). Insulin resistance has been linked to volume expansion, sodium retention, and enhanced sympathetic nervous system activity. Furthermore, insulin resistance, especially if associated with obesity, may increase cardiovascular risk through increased activity of the systemic RAAS (40) and subclinical inflammation, as estimated by C-reactive protein (41). Obesity-related hypertension has been recently associated with the accumulation of "dysfunctional" adipose tissue, characterized by the presence of "large" adipocytes, which may be directly involved in the production of angiotensinogen, pro-inflammatory cytokines, and reactive oxygen species (42).

Obesity is associated with distinctive hemodynamic alterations (43–45). While both cardiac output and plasma volume are increased, peripheral resistance is significantly decreased in obese subjects compared to normal-weight individuals. Increased blood volume might have direct deleterious effects on left ventricular dimension and function. Finally, obesity has recently been associated with increased stiffness of muscular arteries (46).

It is clear that obesity-related hypertension is a multifactorial disorder. At this time it is not possible to identify one single mechanism as the dominant etiologic factor. Genesis and evolution of obesity-related co-morbidity presumably depends on several genetic and environmental

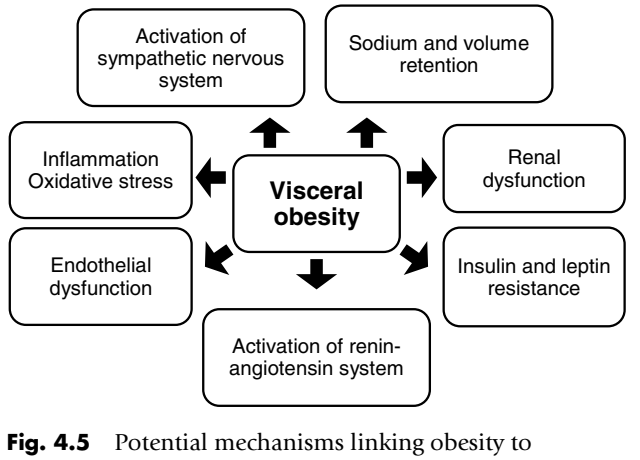

Fig. 4.5 Potential mechanisms linking obesity to hypertension. *Source*: From Ref. 19.

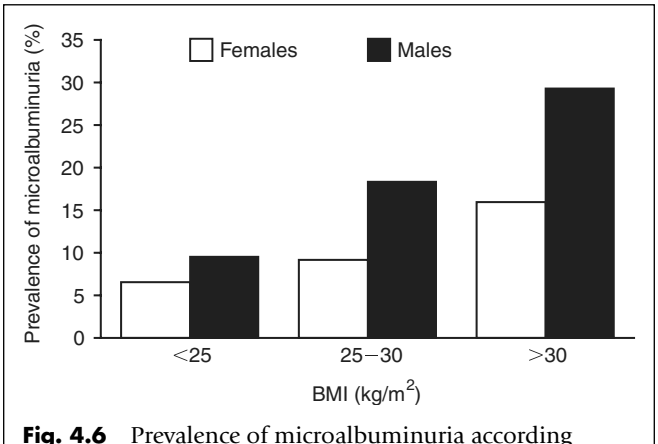

Fig. 4.6 Prevalence of microalbuminuria according to body mass index (BMI) in the PREVEND study. *Source*: From Ref. 25.

factors. It is likely that obesity, hypertension, metabolic abnormalities, and renal factors interact and potentiate their individual impact on cardiovascular risk (Figure 4.7) (47). The number of nephrons is reduced in patients with primary hypertension (48). In these patients, obesity may confer an increased risk of chronic kidney disease, especially when additional factors, such as diabetes or lipid abnormalities, are superimposed.

Obesity-related metabolic abnormalities and impairment of cardiovascular function may be present even at young age and progress asymptomatically for decades before clinical manifestations set in. It is conceivable that these early abnormalities found in young obese subjects might facilitate the future development of hypertension and atherosclerosis independent of other traditional risk factors. This hypothesis is supported by recent findings that link obesity to accelerated progression of coronary artery calcification as a marker of atherosclerosis in apparently healthy individuals with an otherwise favorable cardiovascular risk profile (49).

MANAGEMENT OF OBESITY-RELATED HYPERTENSION

DIAGNOSIS

Use of the correct size of cuff is essential for precise BP measurements. Measuring BP in obese patients can be difficult. Too small of a cuff size will result in an overestimation of BP, while too large of a cuff size will lead to an underestimation. A standard size cuff is not appropriate in the majority of obese patients. The British Hypertension Society (50) recommends a large cuff with a bladder measuring 12×40 cm for obese arms, whereas the American Heart Association (51) recommends a large adult cuff with a bladder measuring 16×38 cm for arm circumferences of 35–44 cm, and an adult thigh cuff with a bladder measuring 20×42 cm for thigh circumferences of 45–52 cm.

The Sokolow-Lyon voltage criteria are significantly less sensitive in obese subjects than in normal-weight subjects, underestimating the presence of anatomic left ventricular hypertrophy (52). Although echocardiography is the preferred method of assessing left ventricular hypertrophy in an obese hypertensive subject, its quality is poor in a substantial proportion of patients.

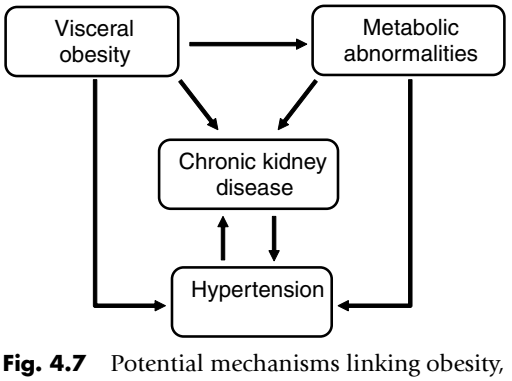

Fig. 4.7 Potential mechanisms linking obesity, hypertension, and chronic kidney disease. *Source*: Reproduced from Ref. 47.

EFFECTS OF WEIGHT LOSS

Obesity, as a major contributor to global cardiovascular risk, requires coherent management (2). Effective long-term weight loss necessitates persistent changes in dietary quality, energy intake, and physical activity (2). Weight loss is associated with significant reduction in BP and has beneficial effects on associated risk factors. The relationship between change in BP and weight loss is relatively weak. However, BP decrease is closely related to a reduction in abdominal fat mass (53). The BP lowering effect of weight reduction may be enhanced by simultaneous reduction in sodium intake (54). Even a modest reduction in body weight can cause a meaningful reduction in the activity of the RAAS in the circulation and in adipose tissue, which makes a major contribution to the BP decrease. Weight loss of 5% is associated with the reduction of angiotensinogen levels by −27%, renin by −43%, aldosterone by −31%, angiotensin-converting enzyme activity by −12%, and angiotensinogen expression by −20% in adipose tissue (55). Furthermore, weight loss has been shown to improve endothelial function (56), decrease sympathetic nerve activity (57), and improve baroreflex function (57). Animal studies indicate that weight loss decreases proteinuria and might even reverse morphological signs of renal damage (58). This repair of renal injury is independent of BP control. Whether weight loss, induced by either lifestyle changes or pharmacotherapy, is also associated with reduced numbers of cardiovascular events remains to be determined.

USE OF ANTI-OBESITY DRUGS

Treatment with orlistat results in both weight loss and weight loss maintenance. Meta-analysis of the placebo-controlled studies evaluating the effects of orlistat on BP shows that greater weight loss in patients treated with orlistat is associated with significantly greater decrease in BP (59).

Treatment of obese patients with sibutramine can produce dose-dependent increases in BP and heart rate, especially during initial treatment. However, a recent meta-analysis (60) indicates that sibutramine treatment is unlikely to elicit a critical increase in BP even in hypertensive patients. The cardiovascular effects of the drug appear to be related to the weight loss achieved: patients who lose 5% or more of initial body weight have a reduction in BP (61). Sibutramine is not contraindicated in patients with well-controlled hypertension. In a study that evaluated the effects of sibutramine 10 mg in obese hypertensive patients, there was a similar decrease in BP in patients taking placebo and patients taking sibutramine (62). The role of sibutramine in the management of high-risk patients is currently being tested in the SCOUT trial.

A recent study by Despres et al. (63) has shown that 1 year treatment with 20 mg of rimonabant leads to significant decreases in systolic and diastolic BP in overweight patients with dyslipidemia. BP decrease was more pronounced in patients with hypertension than in normotensive subjects.

THE SURGICAL INTERVENTION STUDIES

The Swedish Obese Subjects Study Scientific Group (64) assessed the long-term benefits of bariatric surgery and conventional treatment in 4,047 patients who were followed up for at least 2 years; 1,703 of those subjects were followed up for 10 years. Two- and ten-year rates of recovery from diabetes, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, hypertension, and hyperuricemia were more favorable in the surgery group than in the control group. However, the recovery rate from hypertension (34% after 2 years and only 19% after 10 years) was much lower than the recovery rates from other metabolic and risk factors. The surgery group had lower 2- and 10-year incidence rates of diabetes, hypertriglyceridemia, and hyperuricemia than the control group. However, the difference between the groups in the incidence of hypertension was undetectable. Thus, while bariatric surgery might provide benefit to morbidly obese patients in terms of several risk factors, the impact of the procedure on BP is relatively modest.

ANTIHYPERTENSIVE DRUG TREATMENT

Despite overwhelming evidence linking obesity to hypertension, current guidelines do not provide specific recommendations for pharmacological management of the hypertensive patients with obesity (65,66) due to limited data from prospective trials. Indeed, earlier clinical studies performed in the 1980s and 1990s included primarily normal-weight hypertensives. In contrast to earlier studies, several recent trials included overweight and obese patients. Consequently, mean BMI in these trials ranged between 27 and 30 kg/m^2 (Figure 4.8) (67). Furthermore, in some of the trials, *post hoc* analyses were performed, looking for possible differential effects of antihypertensive treatments in obese versus non-obese participants.

Antihypertensive treatment based on diuretics and beta-blockers may aggravate metabolic abnormalities. Furthermore, treatment with beta-blockers may promote weight gain (68).

There is growing evidence of the potential benefits of angiotensin blockade in the management of obesity hypertension. Both angiotensin-converting enzyme inhibitors (ACEI) and angiotensin type-1 receptor blockers (ARB) have been associated with favorable metabolic properties and end-organ protection in addition to their antihypertensive effects (69). The Treatment in Obese Patients with Hypertension (TROPHY) study (70) has shown that the number of BP responders was greater with the ACEI than with the diuretic hydrochlorothiazide. Treatment with ARB may result in a significant improvement in insulin sensitivity and decreased sympathetic nerve traffic compared with diuretic treatment, despite similar decrease in BP (71). A sub-analysis of the LIFE study (72) demonstrated greater benefit of losartan-based treatment in obese subjects with left ventricular hypertrophy as opposed to atenolol-based treatment. Certain ARBs may induce PPARγ activity, thereby promoting PPARγ-dependent adipocyte differentiation (73). These findings provide a potential mechanism for their insulin-sensitizing/antidiabetic effects. Finally, several clinical trials have shown that blockade of the RAAS reduces the incidence of new-onset diabetes (74). Based on these considerations, drugs blocking the RAAS might be considered as first-line therapy of obesity-related hypertension.

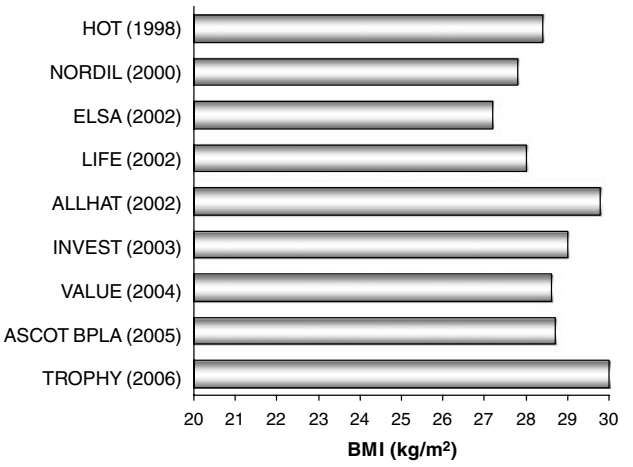

Fig. 4.8 Mean body mass index (BMI) in selected hypertension clinical trials completed between 1998 and 2006. *Abbreviations*: ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-BPLA, The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm; ELSA, European Lacidipine Study on Atherosclerosis; HOT, Hypertension Optimal Treatment trial; INVEST, International Verapamil-Trandolapril Study; LIFE, Losartan Intervention For Endpoint reduction in hypertension study; NORDIL, Nordic Diltiazem study; TROPHY, Trial of Preventing Hypertension; VALUE, the Valsartan Antihypertensive Long-term Use Evaluation trial. *Source*: Reproduced from Ref. 67.

Hypertension management in obese individuals is complicated by poorer response to treatment, and the increased need for multiple medications. A recent study of 45,125 unselected consecutive primary care attendees has shown that BP control rates are significantly lower in obese hypertensive than in normal-weight hypertensives (75). The odds ratio for good BP control (<140/90 mmHg) in diagnosed and treated patients was 0.8 (95% confidence interval [CI] 0.7–0.9) in overweight patients, 0.6 (95% CI 0.6–0.7) in grade 1, 0.5 (95% CI 0.4–0.6) in grade 2, and 0.7 (95% CI 0.5–0.9) in grade 3 obese patients.

The majority of patients would require two or more drugs to achieve target BP. If BP goal is not achieved with first-line therapy (ARB or ACEI), adding a long-term calcium channel blocker or low-dose thiazide diuretic might be considered. The next step should include a combination of the three drugs. Adding a low dose of either β-blocker, α-blocker, or spironolactone might be of benefit in patients with resistant hypertension. Recently, spironolactone in doses of 25–50 mg/day was shown to provide additional antihypertensive benefit in resistant, obese hypertensives despite concurrent treatment with an ACEI or ARB, calcium channel blocker, and thiazide diuretic (76,77). In selected patients, treatment with I_1-imidazoline agonists might be considered, as these drugs, in addition to improvement in insulin sensitivity, were shown to decrease sympathetic traffic (78).

OBSTRUCTIVE SLEEP APNEA—DIAGNOSIS AND EPIDEMIOLOGY

There is growing recognition of the widespread incidence and health consequences of OSA (79,80). OSA is characterized by recurrent episodes of cessation of respiratory airflow caused by upper airway inspiratory collapse during sleep, with a consequent decrease in oxygen saturation (81).

Signs and symptoms suggestive of OSA include daytime somnolence, impaired concentration, unrefreshing and restless sleep, choking episodes during sleep, witnessed apneas, nocturia, irritability/personality change, decreased libido, and increased motor vehicle accidents. This should trigger application one of a validated questionnaire: the Epworth Sleepiness Scale or the Berlin Questionnaire (82). The Epworth Sleepiness Scale (83) asks subjects to rate, from 0 to 3, their chance of dozing off while performing eight different activities such as watching TV, sitting quietly in a public place, or lying down in the middle of the afternoon. A total score of 6 or more on the Epworth suggests the patient suffers from daytime sleepiness. A score of 10 or more suggests excessive daytime sleepiness, while 16 or more suggests dangerously excessive daytime sleepiness. The Berlin questionnaire (84) includes one introductory and four follow-up questions about snoring, three questions about daytime somnolence (including one concerning sleepiness while driving), and one question about history of hypertension. It also collects information about age, gender, ethnicity, height, weight, and neck circumference. The presence of OSA is determined by positive responses to at least two of the following three criteria: (*i*) persistent symptoms (>3 times per week) for at least two snoring questions; (*ii*) persistent (>3 times per week) somnolence during daytime and/or while driving; and (*iii*) history of hypertension or a BMI >30 kg/m^2. The questionnaire has high internal validity and performs accurately in a primary care setting.

Polysomnography remains the "gold standard" diagnostic tool for assessing sleep-disordered breathing. The severity of OSA is measured as the apnea-hypopnea index (AHI). An apnea, defined as cessation of airflow for at least 10 s, is classified as obstructive or central on the basis of presence or absence of respiratory effort. Definition of hypopnea includes one of three features:

- Substantial reduction in airflow (>50%);
- Moderate reduction in airflow (<50%) with desaturation (>3%); or
- Moderate reduction in airflow (<50%) with electroencephalographic evidence of arousal.

The AHI (i.e., the number of apneic and hypopneic events per hour) is used as one index of the presence and severity of sleep apnea. For OSA, an AHI of 5–15 indicates mild apnea; of 15–30, moderate apnea; and of greater than 30, severe apnea.

Data from the Wisconsin Sleep Cohort Study (85), a longitudinal study of the natural history of cardiopulmonary disorders of sleep in which a random sample of 602 employed men and women 30–60 years old were studied by overnight polysomnography, suggest that 24% of the middle-age men and 9% of the middle-age women had sleep-disordered breathing (AHI > 5/h), with 4% of men and 2% of women also having hypersomnolence.

THE RELATIONSHIP BETWEEN OBESITY AND OSA

Obesity is probably the most important risk factor for OSA. Several cross-sectional studies have consistently found an association between increased body weight and the risk of OSA. Up to 40% of morbidly obese subjects have significant OSA, and the vast majority of these patients remain undiagnosed (86). A prospective population-based study of 690 randomly selected subjects has shown that a 10% weight gain was associated with a six-fold increase in the risk of developing sleep apnea (87). In the same study, a 10% weight loss predicted a 26% decrease in the AHI.

Whereas obesity increases the risk for OSA, sleep apnea may predispose to weight gain and obesity. Indeed, patients with newly diagnosed OSA have a history of excessive recent weight gain in the period preceding the diagnosis (88).

EVIDENCE LINKING OSA TO HYPERTENSION

Obstructive sleep apnea has been linked to hypertension in several experimental, epidemiological, and clinical studies. Animal models of sleep apnea have provided strong evidence for a causal relationship with hypertension (89). Studies in humans have demonstrated that patients with sleep apnea have an increased BP and a higher incidence of hypertension (90–92). The most compelling evidence linking OSA and hypertension was provided by data from the Wisconsin Sleep Cohort Study. This study has demonstrated a dose–responses association between sleep-disordered breathing at baseline and the presense of de novo hypertension 4 years later (93). The odds ratios for the presence of hypertension at the 4-year follow-up study according to the AHI at base line were estimated after adjustment for baseline hypertension status, BMI, neck and waist circumference, age, sex, and weekly use of alcohol and cigarettes. Relative to the reference category of an AHI of 0 events per hour at baseline, the odds ratios for the presence of hypertension at follow-up were 1.42 (95% CI 1.13–1.78) with an AHI of 0.1–4.9 events per hour at base line as compared with none, 2.03 (95% CI 1.29–3.17) with an AHI of 5.0–14.9 events per hour, and 2.89 (95% CI 1.46–5.64) with an AHI of 15.0 or more events per hour (Figure 4.9). These findings suggest two important concepts. First, sleep-disordered breathing is a risk factor for hypertension in the general population. Second, even sleep apnea that is considered mild may also contribute significantly to overall BP levels.

While the prevalence of sleep apnea increases with age, the link between sleep-disordered breathing and hypertension may be attenuated by aging (94). A recent analysis of the Sleep Heart Health Study (95) has shown that OSA is independely associated with hypertension in middle-aged subjects but not in elderly subjects. Interestingly, isolated systolic BP was not associated with sleep-disordered breathing. In those aged <60 years, AHI was significantly associated with higher odds of systolic/diastolic hypertension [OR = 2.38 (95% CI 1.30–4.38) for AHI 15–29; OR = 2.24 (95% CI 1.10–4.54) for AHI ≥ 30]. Thus, taking into account age and distinguishing between hypertensive subtypes reveals a stronger association between sleep-disordered breathing and

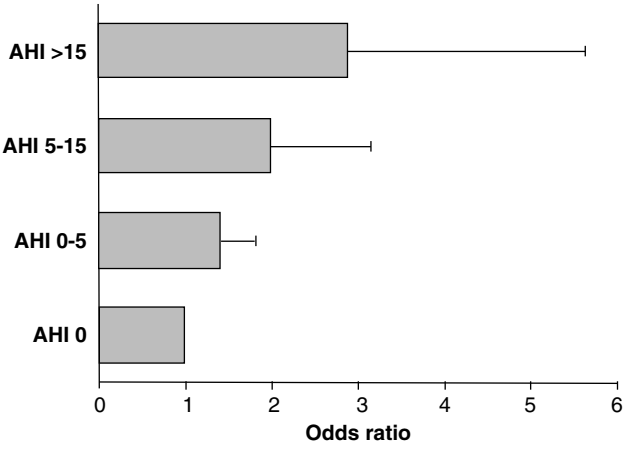

Fig. 4.9 Adjusted odds ratios for the presence of incident hypertension at 4-year follow-up according to the apnea-hypopnea index (AHI) at baseline. Data are shown as odds ratio (line bars indicate lower and upper 95% confidence intervals). *P* for trend = 0.002. *Source*: Reproduced from Ref. 103, based on data from Ref. 93.

hypertension for young and middle-aged subjects than previously reported.

The prevalence of hypertension is underdiagnosed in OSA patients if BP is assessed by office readings only. Baguet et al. (96) have shown that ambulatory BP monitoring might be of particular significance in the hypertension diagnosis of OSA patients. While 42% of their OSA patients demonstrated office hypertension, 58% had daytime hypertension, and 76% had nighttime hypertension. Thus, OSA is characterized by a "non-dipping" pattern of hypertension, which itself has been associated with an adverse cardiovascular prognosis (97).

Obstructive sleep apnea increases the prevalence of target organ damage in patients with hypertension, and is an independent risk factor for the development of left ventricular hypertrophy (98). Furthermore, OSA affects functional and structural properties of large arteries contributing to hypertension and atherosclerosis progression. Middle-aged patients with OSA free of overt CVD were shown to have increased pulse-wave velocity and increased intima-media thickness (99). Marked increases in transmural pressure of the aorta wall during obstructive events may contribute to the increased risk of thoracic aorta dissection in hypertensive patients. Indeed Sampol et al. (100) have recently demonstrated a high prevalence of previously undiagnosed and frequently severe OSA in patients with thoracic aorta dissection.

The risk of developing CVD is increased in middle-aged OSA subjects independently of other risk factors (101). Patients with OSA have a peak in sudden death from cardiac causes during the sleeping hours, which contrasts strikingly with the nadir of sudden death from cardiac causes during this period in the general population (102).

INTERACTIONS BETWEEN OBESITY AND OSA

Obstructive sleep apnea, hypertension, and obesity often coexist and interact, sharing multiple pathophysiological mechanisms and consequences (Figure 4.10) (103). OSA may contribute to some of the pathological processes traditionally ascribed to hypertension or obesity alone.

SYMPATHETIC ACTIVATION

Normal sleep is associated with distinct alterations in BP and heart rate (104). The changes in autonomic circulatory control are dependent upon sleep stage. By contrast, these sleep stage-dependent changes are disrupted in OSA. The sympathetic and hemodynamic profile during sleep in patients with OSA is dictated primarily by the duration and severity of apnea rather than by sleep stage itself. Patients with OSA undergo repetitive obstructions to normal breathing during sleep. As a consequence of obstructed breathing, these patients undergo recurrent and often prolonged periods of cessation of airflow, with consequent decreases in arterial oxygen content and increased arterial carbon dioxide levels. BP increases gradually during apnea because of the vasoconstrictor effect of the sympathetic response to hypoxia and hypercapnia (105). On resumption of breathing, there is a consequent increase in venous return, and cardiac output increases. This increased cardiac output enters a vasoconstricted peripheral vasculature, which results in abrupt and sometimes marked increases in arterial pressure.

Remarkably, the high sympathetic drive is present even during daytime wakefulness when subjects are breathing normally and both arterial oxygen saturation and carbon dioxide levels are also normal (Figure 4.11). This is true whether these patients are newly diagnosed, never-treated sleep apneic patients on no medications, or whether they are on antihypertensive therapy (106,107).

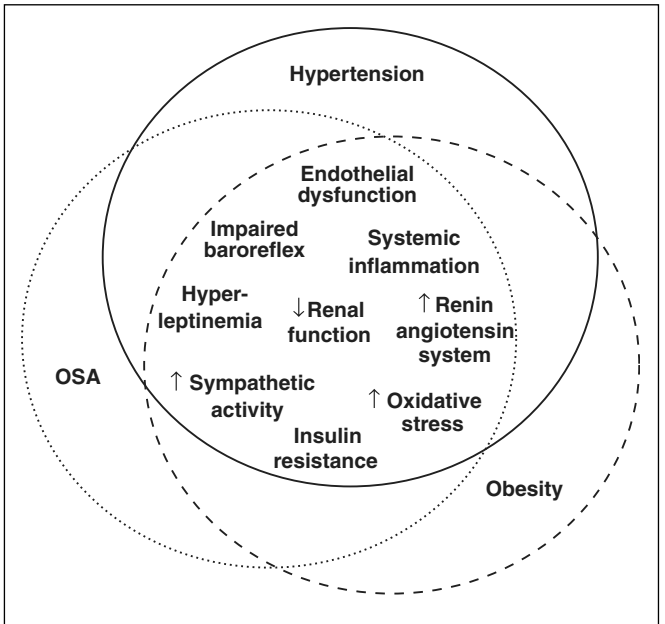

Fig. 4.10 Putative pathophysiological mechanisms involved in the interactions between obstructive sleep apnea (OSA), obesity, and hypertension. *Source*: Reproduced from Ref. 103.

ALTERATIONS IN CARDIOVASCULAR VARIABILITY

In addition to high levels of sympathetic activity, OSA patients have clear-cut abnormalities in cardiovascular variability during wakefulness. BP variability is markedly increased, heart rate is faster, and RR interval variability is decreased in patients with OSA (108). This alteration occurs even in the absence of hypertension, heart failure, or other disease states. The degree of derangement in cardiovascular variability is linked to the severity of OSA.

Possible mechanisms underlying the derangement in neural control in sleep apnea include abnormalities in chemoreflex function. 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 muscle sympathetic nerve activity (MSNA) (109). Other mechanisms include baroreflex dysfunction (110–112).

The increased sympathetic activity and abnormal cardiovascular variability in sleep apnea patients may contribute to the long-term pathogenesis of CVD. Decreased heart rate variability and increased BP variability might increase the risk of future hypertension (113) and hypertensive end organ damage (114).

ACTIVATION OF RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

It has been suggested that OSA patients may have significantly higher levels of angiotensin II and aldosterone compared with healthy control subjects matched by body mass (115). Furthermore, there is a significant positive correlation between angiotensin II and daytime BP in OSA patients. In patients with resistant hypertension, hyperaldosteronism is more likely to be present in patients with confirmed OSA than in those at low-risk for OSA based on the absence of symptoms (116). There are several possible mechanisms whereby the RAAS may be activated in OSA, including activation of the sympathetic nervous system, release of adipocyte-derived mediators, increased sodium reabsorption in the kidney, hyperinsulinemia, or hyperleptinemia.

INSULIN AND LEPTIN RESISTANCE

There is evidence of an independent association between OSA and insulin resistance. Although increased insulin resistance was also related to obesity, in multiple regression the association between OSA and insulin resistance was independent of obesity (including central obesity, assessed as waist/hip ratio) and was seen in both obese and non-obese subjects (117,118). Plasma leptin levels are elevated in patients with OSA beyond the levels seen in similarly obese healthy control subjects, suggesting that leptin resistance may be further increased in OSA (119).

INFLAMMATION

Obstructive sleep apnea has been linked to activation of systemic inflammation, as evidenced by increased levels of CRP in healthy subjects with OSA compared with matched control subjects (120). Elevated CRP may contribute to atherosclerotic risk as well as endothelial dysfunction, and may play an important role as a risk factor for hypertension.

OXIDATIVE STRESS

Intermittent hypoxia and recurrent reoxygenation during episodes of OSA can lead to the generation of highly reactive free oxygen radicals (121). The severity of OSA is

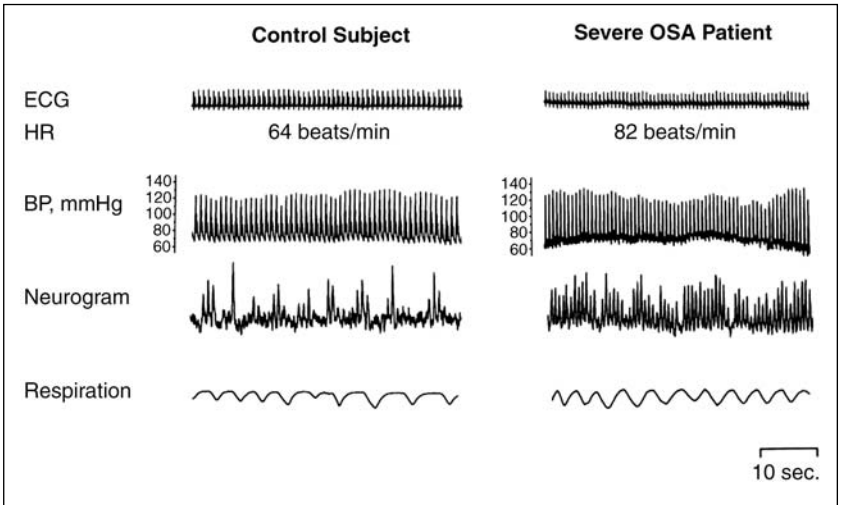

Fig. 4.11 Electrocardiogram (ECG), blood pressure (BP), sympathetic neurograms, and respiration in a control subject (*left*) and in a patient with severe obstructive sleep apnea (OSA) (*right*), showing faster heart rate (HR), increased BP variability, and markedly elevated muscle sympathetic nerve activity in the patient with OSA. *Source*: Reproduced from Ref. 108.

independently associated with oxidative stress (122). Among various sleep-disordered breathing parameters, the oxygen desaturation index appears to be most closely related to oxidative stress.

ENDOTHELIAL DYSFUNCTION

Hypoxia and hypercapnia accompanying apneic events may play a role in eliciting inflammation, oxidative stress, metabolic dysregulation, and release of vasoactive substances, such as endothelin (123), all of which can contribute to endothelial damage. It has been shown that OSA patients exhibit decreased vasodilatation in response to acetylcholine in comparison with matched controls, whereas responses to sodium nitroprusside (a direct donor of NO) and verapamil did not vary between groups (124). Furthermore, experimental studies have shown that vascular sensitivity to endothelin-1 is increased in intermittent hypoxia-induced hypertension (125). Endothelial dysfunction, together with attenuated nitric oxide production and increased endothelin-1 vascular sensitivity in OSA patients, could thus potentially play a role in OSA-related hypertension.

GENETIC FACTORS

While the genetic contribution to essential hypertension is widely recognized, there is surprisingly little information on the role of genetic factors in the pathogenesis of OSA. Hypertensives with a positive family history of hypertension are characterized by a greater oxygen desaturation and higher AHI than those with a negative family history (126). Lin et al. (127) have recently assessed the association of the insertion/deletion polymorphism of the ACE gene with sleep-disordered breathing and hypertension in 1,100 subjects of the Wisconsin Sleep Cohort. Sleep-disordered breathing and the insertion/deletion polymorphism had an interactive effect on BP independently of age, sex, ethnicity, and BMI. An association of the deletion allele with hypertension was found in patients with mild-to-moderate OSA but not in subjects without sleep-disordered breathing.

CONTRIBUTION OF OSA TO RESISTANT HYPERTENSION

It is important to consider OSA in the differential diagnosis of hypertensive patients who are obese. Furthermore, undiagnosed OSA is extremely prevalent (up to 83%) in patients with hypertension resistant to conventional drug therapy (128). Thus, OSA should also be considered in those hypertensive patients who respond poorly to combination therapy with antihypertensive medications. In particular, there is growing evidence that hypertensive patients, who are classified as "non-dippers" on ambulatory pressure measurements, should be investigated for OSA (129). The 6th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure had recommended that OSA be considered in patients with resistant hypertension. The more recent 7th report from this Committee cites OSA as first on the list of identifiable causes of hypertension.

EFFECTS OF TREATMENT OF OSA

Therapeutic strategies for OSA include sleep postural changes, avoidance of sleeping on the back, weight loss, avoidance of alcohol and sedative hypnotics, and upper airway surgical procedures. The most widely used treatment consists of continuous positive airway pressure (CPAP) administered during the night. CPAP treatment prevents airway collapse during inspiratory efforts. Treatment with CPAP results in acute and marked reduction in nocturnal sympathetic nerve traffic and blunts BP surges during sleep.

Effective long-term treatment of OSA by CPAP treatment of OSA has been shown to improve BP control in hypertensive patients, particularly when BP is measured over 24 h (130,131). This benefit is seen in both systolic and diastolic BP, and during both sleep and wakefulness. The benefit is larger in patients with more severe sleep apnea, is independent of the baseline BP (132), and is especially evident in patients taking drug treatment for BP. Interestingly, faster heart rate also predicts a greater CPAP effect on BP (133).

Becker et al. (134) randomly assigned 60 consecutive patients with moderate to severe OSA to either effective or subtherapeutic CPAP treatment for 9 weeks on average. Apneas and hypopneas were reduced by approximately 95% and 50% in the therapeutic and subtherapeutic groups, respectively. Mean arterial BP decreased by 9.9 ± 11.4 mmHg with effective CPAP treatment, whereas no relevant BP change occurred with subtherapeutic CPAP. Lack of BP decrease, despite a 50% reduction in the AHI, underscores the importance of effective treatment.

CPAP may provide beneficial effects beyond better BP control. Long-term CPAP treatment decreases MSNA in otherwise healthy OSA patients (135), and improves glycemic control in type 2 diabetics (136). Interestingly, the effect of CPAP on insulin sensitivity is greater in non-obese than in obese OSA patients (137).

Surgical treatments of obesity may have striking effects on OSA. A recent systematic review and meta-analysis of articles on bariatric surgery has shown that up to 85% of OSA patients experience complete resolution of sleep-disordered breathing (138). This may conceivably serve as a potential option in markedly obese patients with OSA who cannot tolerate CPAP therapy.

CONCLUSIONS

Obesity appears to be the most important risk factor for the development of hypertension. There is growing evidence that adipose tissue may be directly involved in the pathogenesis of hypertension. Obesity is an independent risk factor for the development and progression of target organ damage and CVD in patients with hypertension. Current guidelines do not provide specific recommendations for the pharmacological management of hypertensive patients with obesity. However, several lines of evidence suggest that antihypertensive agents that block the RAAS may be especially beneficial in treating obese hypertensive patients. Hypertension management in obese individuals is complicated by poorer response to treatment, and the increased need for multiple medications. The clustering of obesity and other features of the metabolic syndrome might have important implications for prevention, particularly with regard to

whether interventions targeted at visceral obesity would have beneficial effects on cardiovascular morbidity.

There is growing evidence of a causal relationship between OSA, obesity, and hypertension. Untreated OSA may have direct and deleterious effects on cardiovascular function and structure through several mechanisms, including sympathetic activation, oxidative stress, inflammation, and endothelial dysfunction. OSA may contribute to or augment elevated levels of BP in a large proportion of the hypertensive patient population. It is important to consider OSA in the differential diagnosis of hypertensive patients who are obese. OSA should be especially considered in those obese hypertensive patients who respond poorly to combination therapy with antihypertensive medications.

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DIABETES, HYPERTENSION, AND INSULIN RESISTANCE

5

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INTRODUCTION

Diabetes is a morbid condition characterized by metabolic abnormalities and by long-term complications involving the eyes, kidneys, nerves, and blood vessels. The prevalence of diabetes, especially type 2 diabetes, is rapidly increasing throughout the world, and it is becoming the leading cause of new blindness, end-stage renal disease (ESRD), and non-traumatic amputations. Nevertheless, cardiovascular disease is the major cause of premature mortality in patients with type 2 diabetes, and hypertension is a major contributor to the development of cardiovascular and renal disease in these patients (1).

An association between high blood pressure (BP) and reduced glucose tolerance, both diabetes mellitus and impaired glucose tolerance, has been recognized beyond the confounding influence of common factors like age and obesity. Besides the fact that both conditions are strongly associated, their simultaneous impact in the vascular tree and in the organs prone to develop lesions sharply increases the cardiovascular and renal risk (2). Moreover, both are increasing conditions given the epidemic dimensions driven by the progressive increase of the overweight and obese in Westernized cultures. Consequently, the impact of a diagnosis of reduced glucose tolerance or overt diabetes is of interest in terms of risk stratification and management in a hypertensive subject.

ASSOCIATION BETWEEN HYPERTENSION AND DIABETES

Evidence of a high prevalence of hypertension in diabetes and the higher risk of diabetes in hypertensive subjects indicates that these two common chronic diseases frequently coexist. Moreover, each pathophysiological disease entity, although independent in its own natural history, serves to exacerbate the other.

PREVALENCE OF HYPERTENSION IN DIABETES

The diabetic population is not homogeneous, and several distinct diabetes syndromes have been delineated. Type 1 or insulin-dependent diabetes results from a rapid destruction of the pancreatic β-cells, while type 2 or non–insulin-dependent diabetes takes a long time to develop through a previous state of impaired fasting glucose. While in type 1 diabetes there is an absolute deficiency of insulin, in type 2 diabetes insulin resistance is the main mechanism underlying the disease.

In terms of association with hypertension, among type 1 diabetics, the prevalence of hypertension rises from 5% at 10 years, to 33% at 20 years and to 70% at 30 years (3). Type 1 diabetics typically develop renal disease before developing clinically recognized hypertension. Using ambulatory BP monitoring, however, has recently challenged this concept. Even in normotensive subjects an elevation in sleep systolic BP antedates the development of microalbuminuria, an early marker of renal damage (4). The early pressure overload may have a causative role in the development of diabetic nephropathy (DN) in susceptible individuals. This is keeping with the idea that a predisposition to essential hypertension increases the risk of DN, a concept proposed by Viberti et al. (5) and Krolewski et al. (6), based on the findings of a higher prevalence of hypertension in parents of type 1 diabetics with proteinuria. The development of hypertension, however, accelerates the course of microvascular and macrovascular disease.

In contrast, the prevalence of hypertension in patients with type 2 diabetes is up to three times greater than in age- and sex-matched populations (7), and, in newly diagnosed diabetics, around 40% of subjects are hypertensives. Increasing age, obesity, and the onset of renal disease are all factors increasing the likelihood of hypertension.

The relationship between urinary albumin excretion (UAE) and the prevalence of hypertension was nicely demonstrated by Tarnow et al. (8). Defining hypertension, a 3-year average BP equal to or higher than 140/90, prevalent in type 1 diabetes, was 42%, 52%, and 79% in the normoalbuminuric, microalbuminuric, and macroalbuminuric groups, respectively. In type 2 diabetes, the corresponding figures were 71%, 90%, and 93%, respectively. Considering that, according to the last recommendations, BP above 130/80 mmHg indicates hypertension in diabetics, hypertension is present in the majority of type 2 diabetics and in a large proportion of those with type 1.

Hypertension, however, can also be the consequence of secondary causes linked to diabetes, such as those outlined in Table 5.1.

Table 5.1 Hypertension in diabetes

Essential hypertension
Diabetic nephropathy
Secondary causes of diabetes-induced hypertension
Renal artery stenosis
Pyelonephritis
Renal insufficiency
Secondary causes of high glucose and hypertension
Acromegaly
Primary aldosteronism
Pheocromocytoma
Cushing's syndrome

RISK OF DIABETES IN HYPERTENSION

Patients with hypertension have a high prevalence of insulin resistance and have a substantially increased risk of developing type 2 diabetes mellitus. Epidemiological evidence supports a link between hypertension and insulin resistance. Hypertension is associated with insulin resistance independently of other confounding factors (9). Likewise, fasting insulin levels correlate with systolic and diastolic BP independent of age, weight, and serum glucose values.

The impact of antihypertensive medication on the risk of developing diabetes has been a matter of debate. In a prospective cohort study that included 12,550 adults, ages 45–60 years old, the development of type 2 diabetes was almost 2.5 times more likely in people with hypertension as it was in their normotensive counterparts (10). After considering potential confounding variables, subjects with hypertension who were taking thiazide diuretics were not at greater risk for the subsequent development of diabetes than subjects with hypertension who were not receiving any antihypertensive therapy. Likewise, subjects who were taking angiotensin-converting enzyme inhibitors (ACEI) and calcium-channel antagonists were not at greater risk than those not taking any medication. In contrast, subjects with hypertension who were taking beta-blockers had a 28% higher risk of subsequent diabetes. A beneficial impact of decreasing the risk for the development of diabetes with ACEI- or angiotensin receptor blocker-based treatments has been described. Detailed systematic reviews of the potential beneficial effects have been published recently. In general, treatment with these classes of drugs reduces the rate of new-onset diabetes as compared with the use of diuretic and/or β-blockers. Inhibiting the renin–angiotensin–aldosterone system (RAAS) may improve blood flow to muscles, decrease the activity of the sympathetic nervous system, enhance insulin signaling, lower FFA levels, increase plasma adiponectin levels, and improve glucose disposal. Another putative mechanism by which the inhibition of the RAAS may improve insulin sensitivity is through effects on PPAR -γ, which is inhibited by angiotensin II (11).

BP CHARACTERISTICS IN DIABETES

BP elevation in diabetic subjects has several characteristics that strongly influence the rate and velocity of developing target organ damage. Predominance of the systolic component and frequent abnormal circadian variability are the two most important characteristics. At least one-third of the hypertensive diabetics have isolated systolic hypertension (8), and around half of the diabetics show a non-dipping BP pattern. These depend on the interaction between the mechanisms that contribute to BP elevation (insulin resistance and hyperinsulinemia, sympathetic and renin-angiotensin overactivity, and abnormal Na^+ handling) and the impact of abnormal glucose metabolism in vascular and renal structures.

HIGH SYSTOLIC BP

The predominance of a disproportionate systolic BP elevation is a consequence of the early and fast development of arterial stiffness in diabetics. The increased pulse wave velocity (PWV), reflecting arterial stiffness in hypertensive diabetics, is likely to reflect both structural and functional abnormalities of the arterial wall. Using aortic PWV measurements, Tedesco et al. (12) found significantly higher PWV in hypertensive diabetics compared to patients with diabetes or high BP alone, and, in turn, PWV in these patients was higher than in healthy controls. Thus, the additive nature of hypertension and diabetes to cardiovascular risk is reflected by abnormalities in PWV measurements.

Several mechanisms can participate in this early alteration in vascular elasticity. Arterial stiffness is determined by its viscoelastic properties, which is in turn dependent on the structure and function of the vessel wall. Alterations in the extracellular matrix of the media and adventitia have long been implicated in the pathogenesis of age- and BP-related increases in arterial stiffness (13,14). Non-enzymatic glycation as a result of elevated blood glucose and consequent collagen cross linkage may also lead to alterations in the mechanical properties of the arteries in diabetics (15). Hence, it is perhaps not surprising that concomitant hypertension and hyperglycemia result in an even more pronounced increase in arterial stiffness when compared with either abnormality in isolation.

The endothelium may also affect the elastic properties of the artery by directly affecting vascular tone (16). There is a balance between vasoconstrictors (such as angiotensin II and endothelin) and nitric oxide (NO), the key endothelium-derived vasodilator. Certainly, reduced NO bioavailability is closely linked to structural and functional endothelial abnormalities, and endothelial perturbations are well described in diabetes and hypertension (17).

The reduced arterial distensibility results in high PWV and wide pulse pressure due to the early return of the reflecting waves. The consequences are an increase in the left ventricle workload and a decrease in the coronary perfusion, enhancing the risk for left ventricular hypertrophy and dysfunction.

ABNORMAL BP CIRCADIAN VARIABILITY

The frequent presence of abnormal circadian variability, such as absence of a normal nocturnal dip, implies the existence of abnormalities in the BP regulatory mechanisms. Although the reduction in BP at night is mainly dependent on the

reduction in sympathetic driving, there are other factors that can contribute to the blunted decline in the physiological nocturnal fall and, as a consequence, the persistence of higher BP values during night. Among these factors, reduced sensibility of baroreceptors and volume overload are the most important. Central sympathetic overdriving is observed as a consequence of baroreceptor dysfunction. An increase in intravascular volume after recumbence, as a result of reabsorption from peripheral tissues, may also contribute to the maintenance of elevated BP values. The impact of each of the components in an individual subject differs, with predominance of one or another mechanism, according to the clinical condition.

Continuous elevated BP values overload the vascular tree and have an impact on the susceptible organs, mainly the kidneys. The impact of BP on renal structures depends not only on BP values, but also on the persistence of the BP values over time, mainly during the hours when the patient is resting or sleeping. In the recumbent position, activity of the mediators controlling preglomerular tone and sympathetic and renin-angiotensin activities is reduced (18), allowing the persistent transmission of high pressure into the glomerulus and tubule pericapillaries. Concurrent renal damage produced by diabetes works in addition to the former mechanisms, contributing to accelerate the rate of renal function decline.

Some evidence supports the potential role of systemic BP transmission as a mechanism of inducing renal damage, whereas other evidence supports the non-dipping pattern as a consequence of the renal damage itself. Neither the cause nor the consequence, interpretations of these data are mutually exclusive. In some cases, higher BP values during nighttime may contribute to the progression toward renal insufficiency, while in other cases the values are but a consequence of the altered renal function itself. In the latter, higher BP may also participate in accelerating the renal function decline.

HYPERTENSION, DIABETES, AND CARDIOVASCULAR RISK

In several observational studies, an increased risk for cardiovascular events due to macrovascular disease has been documented for hypertension in patients with established type-2 diabetes, most notably from the Multiple Risk Factor Intervention Trial (MRFIT) (19) (Figure 5.1), the U.K. Prospective Diabetes Study (UKPDS) (20), and the Diabetes Epidemiology: Collaborative Analysis Of Diagnostic Criteria in Europe DECODE (21) studies. In fact, there seems to exist a linear relationship between mean in-study systolic BP and the prospective risk of coronary heart disease (CHD) in the UKPDS (22), so far the largest intervention study in type 2 diabetes worldwide, which also contains an observational part. All macrovascular disease end-points in diabetes are increased by uncontrolled hypertension, such as CHD, stroke, and peripheral arterial disease.

This increased risk could be due to both the hemodynamic burden and shear stress of high BP itself, and the fact that an increased systolic BP, or pulse pressure, is a marker of increased arterial stiffness. This phenomenon could be regarded as a sign of early vascular aging (EVA) in patients with diabetes, especially in the context of long diabetes duration and poor metabolic control. Other risk factors will add to the vascular risk, such as smoking, hyperlipidemia, and chronic inflammation. New markers of vascular aging relate to endothelial dysfunction or biological aging in general, for example telomere length (23). Telomeres are genetic structures capping the end of the DNA-helix and of importance for the capacity of cell division ("mitotic clock"). With every cell division the telomere length is shortened until it has reached a critically short length, which indicates that no further cell division is possible. Telomere attrition has been associated with atherosclerosis, CHD, diabetes, insulin resistance, and cardiovascular risk factors, such as smoking and obesity (24,25). In one study, an association was described between pulse pressure and shorter telomeres (26), the association being more pronounced in males than in females. In conclusion, the new understanding of the increased risk of hypertension in diabetes relates to a process of EVA with more or less pronounced arterial stiffening, chronic inflammation, insulin resistance, endothelial dysfunction, and shorter telomere length. An intriguing question is whether all these abnormalities can be improved by BP lowering per se, or if additional interventions are needed to halt or even reverse the process of the EVA syndrome.

FETAL FACTORS LEADING TO HYPERTENSION AND TYPE-2 DIABETES

Poor fetal growth resulting in intrauterine growth retardation (IUGR) and low birth weight has been described in several epidemiological studies to be of great importance for the development of disturbances of BP regulation and metabolic disturbances, as outlined by many researchers (27). This is even more pronounced if the IUGR is later followed by a rapid catch-up growth in early post-natal life and early childhood, according to the so-called "mismatch" hypothesis as outlined by Gluckman and Hanson (28). The mechanisms connecting IUGR with BP elevation and development of hypertension include, for example, a reduced number of nephrons in the kidney and, therefore, less effective handling of sodium and water; capillary rarefication and endothelial dysfunction; and, finally, abnormalities in neuroendocrine regulation and the activity of the hypothalamic-pituitary-adrenal axis (29).

The corresponding mechanisms of importance for the impairment of glucose metabolism and the development of type 2 diabetes include impaired muscle tissue development linked to increased insulin resistance, as well as impaired β-cell secretion of insulin due to a low number of pancreatic β cells or a suboptimal cell regeneration capacity (30). When a subject with IUGR and later catch-up growth experiences poor dietary habits, smoking, and sedentary lifestyle in adult life, the organs are programmed for the development of diabetes and increased cardiovascular risk.

The cause of IUGR is still a matter of debate, as poor maternal nutrition is not the only causative factor, inspite of the fact that numerous animal experiments have shown that restriction of maternal energy intake and protein restriction could harm fetal development in many ways. Additional factors causing IUGR could be related to smoking, stress exposure, infections, or other environmental factors. However, as the cardiovascular risk of mothers with IUGR offspring is also increased, this points to the influence of some common genetic factors behind both IUGR and the increased cardiovascular risk in mother and offspring alike (31).

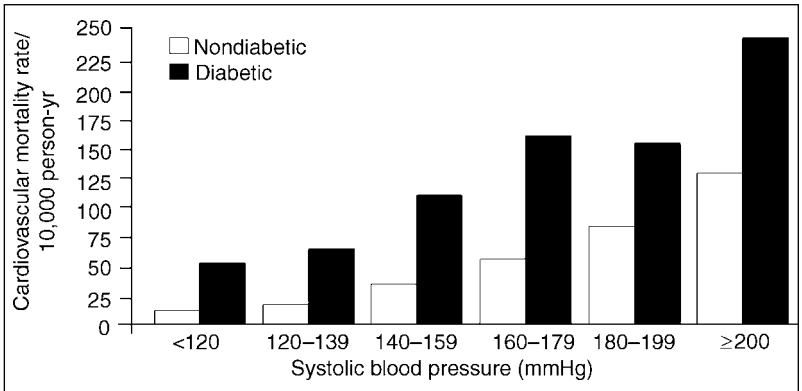

Fig. 5.1 Cardiovascular mortality in diabetic and non-diabetic subjects according to systolic blood presure in the Multiple Risk Factor Intervention Trial (MRFIT). *Source*: From Ref. 19.

HYPERTENSION, DIABETES, AND RENAL RISK

The two most frequent expressions of chronic kidney disease, increases in UAE and reduction in the glomerular filtration rate (GFR), frequently run parallel. Both are strongly influenced by the interaction of BP and glucose levels, and, while BP is the main determinant of microalbuminuria, glucose level is the most important determinant of renal insufficiency. Diabetes and hypertension together account for about 60% of the new cases of ESRD reported not only in the United States, where there is an African-American population prone to developing renal failure, but also in Europe where the population makeup differs significantly.

The interaction between hypertension and diabetes is a two-way street. The importance of renal disease in the prevalence of hypertension has been discussed above, and high BP plays a key role in the development and progression of renal disease and DN. This is a microvascular lesion that can progress to ESRD, and it is associated with premature death from cardiovascular disease. Seventy to ninety percent of the cases correspond to type 2 diabetes, while type 1 accounts for 10% of the cases. In addition, the incidence of ESRD within the type 2 diabetes population has increased dramatically in the past few years. This is thought to partly be a consequence of improved treatments for hypertension and CHD, allowing more patients with type 2 diabetes to live long enough for nephropathy and ESRD to develop (32). Another, perhaps more important, factor may be that patients are not being treated correctly and, therefore, the BP target ($\geq$130/80 mmHg) is not being achieved, resulting in increased genesis of renal failure. High BP, however, is the most important factor for the rate of GFR decline (33).

A large amount of information exists on the higher prevalence of renal damage in diabetics as compared to age- and sex-matched non-diabetic subjects in terms of both UAE and GFR. At the same age, diabetics have at least twice the prevalence of microalbuminuria as compared to normoglycemics, and at least a three to five times greater prevalence of renal insufficiency. Subjects with mild abnormalities of the carbohydrate metabolism, such as impaired fasting glucose or glucose intolerance, have figures in between those for the diabetic and the normoglycemic subjects. Recently, an analysis of the relationship between UAE and GFR in a large cohort of hypertensives from Primary Care showed that the proportion of patients with abnormal UAE was 54.5%, and 21.8% had a GFR $\leq$ 60 mL/min/1.73 m^2 (34). This study shows a clear association between UAE and the frequency of renal insufficiency, with a higher prevalence among those with higher UAE. The association between abnormal UAE and renal insufficiency was more evident in diabetic subjects as compared to those with normoglycemia or impaired fasting glucose.

Even more relevant on clinical grounds is the information coming from intervention studies. Evidence of a causative role for hypertension in DN was provided by Mogensen (35) and Ruggenenti et al. (36). They showed that by reducing BP, filtrate loss in DN could be delayed. By lowering BP, the occurrence of early nephropathy was reduced in several studies (37). In hypertensive, normoalbuminuric patients with type 2 diabetes, it seems that both BP reduction and ACEI therapy appear to act independently. ACEI therapy is particularly effective when BP is poorly controlled. In the more advanced stages of the disease, a linear relationship is observed between the BP values achieved during antihypertensive treatment and the rate of GFR decline (38). Analyses of long-term clinical trials have shown that the lower the BP is over a range of values, the greater is the preservation of renal function. Currently, however, it is believed that lowering BP is not enough. It is becoming increasingly important to reduce proteinuria. Antihypertensive drugs that attenuate increases in proteinuria or reduce proteinuria from baseline levels by at least 30% provide greater slowing of renal disease progression when compared with agents that do not have this effect (39,40). This is the main reason for recommending a BP goal of $<$125/75 mmHg (Figure 5.2) and a blockade of the RAAS in subjects with DN (38).

CONCLUDING REMARKS

In conclusion, hypertension, diabetes, renal function, and cardiovascular risk are all interrelated phenomena, shaped by the interaction between genes and the environment. New knowledge based on whole genome scans of diabetes (41) has shed light on the genetic background for the development of type 2 diabetes and related traits, leading to hypertension and lipid disorders. A similar whole genome

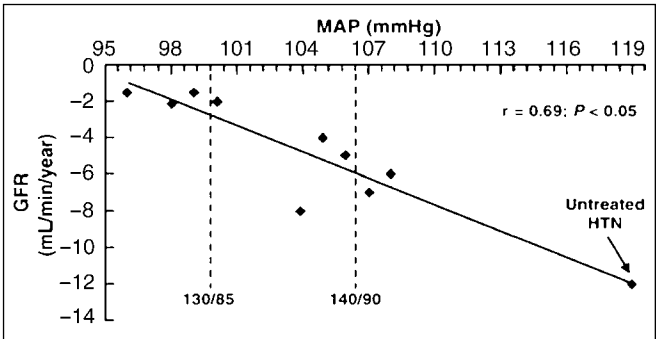

Fig. 5.2 Relationship between achieved mean arterial blood pressure (MAP) and glomerular filtration rate (GFR) decline in several hypertension (HTN) trials. *Source*: From Ref. 38.

scan approach is also underway to characterize essential hypertension. It is hoped that this new knowledge could transform into the emerging role of pharmacogenomics when drug therapy is tailored to the need and tolerability of the individual patient. As insulin resistance seems to be a major factor linking hypertension and type 2 diabetes, new ways of treating insulin resistance hold hopes for counteracting both consequences and the concomitant cardiovascular risk. Some support for this approach has been given in trials using glitazones, a class of drugs that might increase insulin sensitivity and, at the same time, improve glucose metabolism and lower BP to a small but significant extent (42). Glitazones are currently being tested for cardiovascular protection in end-point studies, such as the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial (43), as is also another insulin sensitizing drug, rimonabant, in the Comprehensive Rimonabant Evaluation Study of Cardiovascular ENDpoints and Outcomes (CRESCENDO) trial (44).

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CLASSICAL AND NEW RISK FACTORS 6

Athanasios J Manolis, Genovefa Kolovou

INTRODUCTION

Cardiovascular disease is the leading cause of death in industrialized Western countries, and is rapidly increasing in the developing countries. By 2020, it is expected to be the leading cause of death worldwide. The risk of cardiovascular disease increases with the presence of certain modifiable and non-modifiable classical and new risk factors, including hypertension, cigarette smoking, dyslipidemia, abdominal obesity, diabetes mellitus, age, physical inactivity, family history of premature coronary heart disease, neurohormonal activation, C-reactive protein (CRP), elevated heart rate, hyperuricemia, hyperhomocysteinemia, and abnormalities in several coagulation factors. Ongoing research on these various factors promises to provide new insights into the pathogenesis of coronary heart disease. Among the different risk factors for cardiovascular disease, hypertension is one of the most important. Frequently, hypertension co-exists with other risk factors. Only one in five hypertensive patients are free of additional risk factors, while the majority have at least one or more than one. It was reported that dyslipidemia is present in 65%, overweight or obese in 45%, and type 2 diabetes mellitus in 16% of hypertensive patients. This clustering of risk factors with hypertension increases the cardiovascular risk and exaggerates blood pressure (BP). In the INTERHEART study, the investigators reported that hypertensive patients with more than three risk factors had a >20-fold increase in cardiovascular risk. Therefore, risk assessment is essential for making decisions on the type and intensity of therapy for hypertension.

For many years, treatment guidelines have viewed cardiovascular risk factors as distinct and separate entities. The guidelines of the European Society of Hypertension–European Society of Cardiology (ESH–ESC) recognize the importance of global cardiovascular risk and stratifies hypertensive patients based on the presence of risk factors, like target organ damage, diabetes, and associated clinical conditions, to low, moderate, high, and very high added risk, and treat them accordingly (Figure 6.1).

HYPERTENSION AND DYSLIPIDEMIA

Arterial hypertension is known as a long-lasting chronic disease that affects many life-supporting organs and is estimated as an independent risk factor for cardiovascular disease. Further, hypercholesterolemia is an independent risk factor for developing cardiovascular disease. It has been shown that the presence of dyslipidemia is more frequent in hypertensive than in normotensive subjects (1). According to data from the Framingham Heart Study, 80% of patients with hypertension have other risk factors for cardiovascular disease. In the National Health and Nutrition Examination Survey, the prevalence of combined hypertension and hypercholesterolemia was 18% (2). Furthermore, the prevalence of combined hypertension and hypercholesterolemia was higher in those with metabolic syndrome (37%), diabetes mellitus (41%), or self-reported cardiovascular disease (44%), compared to only 8.9% of those without metabolic syndrome, diabetes mellitus, or cardiovascular disease. Moreover, in the National Health and Nutrition Examination Survey, the prevalence of combined hypertension and hypercholesterolemia markedly increased with age from 1.9% in those aged 20–29 years to 56% in those aged ≥80 years. In the same survey, women had slightly higher percentage of combined hypertension and hypercholesterolemia than men (20% versus 16%, $P < 0.05$). Thomas et al. (3) reported on the large cohort of French subjects (108,879 men and 84,931 women) aged 18–55 years that the prevalence of combined hypertension and hypercholesterolemia for men was 13% and for women was 5%. Moreover, Thomas et al. (3) suggested that, in men, a borderline elevation of both systolic BP (130–139 mmHg) and serum cholesterol (200–239 mg/dL) leads to a three- to four-fold increase in cardiovascular disease and coronary heart disease risk. Neaton et al. (4) in the large America population (men screened in the Multiple Risk Factor Intervention Trial) found that, for men who were nonsmokers and who had systolic BP and serum cholesterol in the highest quintile (systolic BP >142 mmHg and cholesterol >245 mg/dL), the age-adjusted coronary mortality was approximately 10 times greater than for nonsmokers with systolic BP and serum cholesterol in the lowest quintile (systolic BP >118 mmHg and cholesterol >182 mg/dL). These results are similar to the European population (3). Houterman et al. (5) reported data from a Dutch cohort of 50,000 men and women 30–54 years of age. They found that among persons with high cholesterol, the combination of high BP and smoking was associated with relative risks of

Other risk factors and disease history	Blood Pressure (mmHg) Normal SBP 120–129 or DBP 80–84	High Normal SBP 130–139 or DBP 85–89	Grade 1 SBP 140–159 or DBP 90–99	Grade 2 SBP 160–179 or DBP 100–109	Grade 3 SBP 180 or DBP 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very High added risk
3 or more risk factors, TOD, or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very High added risk
ACC	High added risk	Very High added risk	Very High added risk	Very High added risk	Very High added risk

Fig. 6.1 ESH–ESC stratification for cardiovascular risk. *Abbreviations*: ACC, associated clinical conditions; ESH–ESC, European Society of Hypertension–European Society of Cardiology; DBP, diastolic blood pressure; SBP, systolic blood pressure; TOD, target organ damage.

9.7 for coronary heart disease, 13.9 for cardiovascular disease, and 5.7 for all-cause mortality in men, and 15.9, 9.3, and 4.3, respectively, in women. It has been reported that hypertensive patients have higher baseline blood lipid concentration than normotensive individuals. In the Oslo study (6), it was shown that middle-aged men with diastolic BP above 110 mmHg had average plasma cholesterol concentration greater by 27 mm/dL compared to those with diastolic BP below 70 mmHg. In the Goteborg primary prevention study (7), even when BP was reduced, the hypertensive patients who developed myocardial infarction had higher average plasma cholesterol compared to those who remained event free. Our group (8) found that hypertensive patients have abnormal triglyceride responses to fatty meals (the relationship between postprandial hyperlipidemia and coronary heart disease was described by many research groups), even when the fasting blood lipid and lipoprotein concentration is normal. It seems that hypertension and hypercholesterolemia tend to occur in combination. This association may reflect the common cause or aggravating factors for both high BP and high cholesterol. The underling mechanisms may be many. First, both hypertension and hypercholesterolemia result in endothelial dysfunction. Endothelial dysfunction is a pathological event characteristic of aging, and essential hypertension simply causes earlier onset and worsening of this age-related alteration. Both essential hypertension and hypercholesterolemia is characterized by a defect of endothelial nitric oxide synthesis (9,10). Nitric oxide is a major mediator of endothelium-dependent vasodilation, and is also an effective inhibitor of platelet aggregation, smooth muscle cell migration and proliferation, monocyte adhesion, and adhesion molecule expression. A dysfunctional endothelium (caused by hypertension or hypercholesterolemia) loses its capacity to protect the vessel wall against the development of atherosclerosis. This leads to increased penetration of lipoproteins, oxidation of LDL particles, and formation of foam cells. Secondly, current evidence points to the interplay between hypercholesterolemia and hypertension acting through the rennin-angiotensin system. Increased levels of angiotensin II are correlated with hypertension, which is a major trigger for endothelial dysfunction. Angiotensin II (Figure 6.2) increases lipid uptake in cells and lipid accumulation in the vessel wall. In addition, LDL upregulates expression of the type I (AT_1) receptor (angiotensin II binds to this receptor). The AT_1 receptor mediates most of the cardiovascular effects of angiotensin II, including oxidative stress, vasoconstriction, aldosterone secretion, renal sodium resorption, sympathetic stimulation, vasopressin release, cardiac and vascular cell hypertrophy, and cell proliferation. The upregulation of the AT_1 receptor has been reported in hypercholesterolemic men. This may also explain why hypercholesterolemia is frequently associated with hypertension. Thirdly, the expression and activity of angiotensin-converting enzymes have been demonstrated to increase during hyperlipidemia. The deleterious effects of the angiotensin-converting enzyme (11) on the cardiovascular system were initially thought to be a consequence of the formation of angiotensin II, which initiates a cascade of events involving increased free radical production and vascular smooth muscle cell p oliferation. However, as bradykinin (poweful endothelium-dependent vasodilator) is much more readily hydrolyzed by the angiotensin-converting enzyme than angiotensin I, the hydrolysis of bradykinin may also contribute to this event. Furthermore, angiotensin-converting enzyme angiotensin II and its receptors were found in areas of inflammation in human atherosclerotic lesions. Moreover, a marked accumulation of tissue angiotensin-converting enzyme and angiotensin II in the inflamed shoulder regions of vulnerable plaques that are prone to rupture was also found.

In summary, both high BP and hyperlipidemia lead to endothelium dysfunction and atherogenesis. Thus, the treatment of both conditions with drugs that minimize excessive oxidative stress is significant to the maintenance of normal endothelial cell function and a reduction in cardiovascular morbidity and mortality.

HEART RATE

In recent years, evidence has accumulated that an elevated heart rate is also an important risk factor for cardiovascular and non-cardiovascular death in middle-aged persons. However, even though its prognostic importance has been

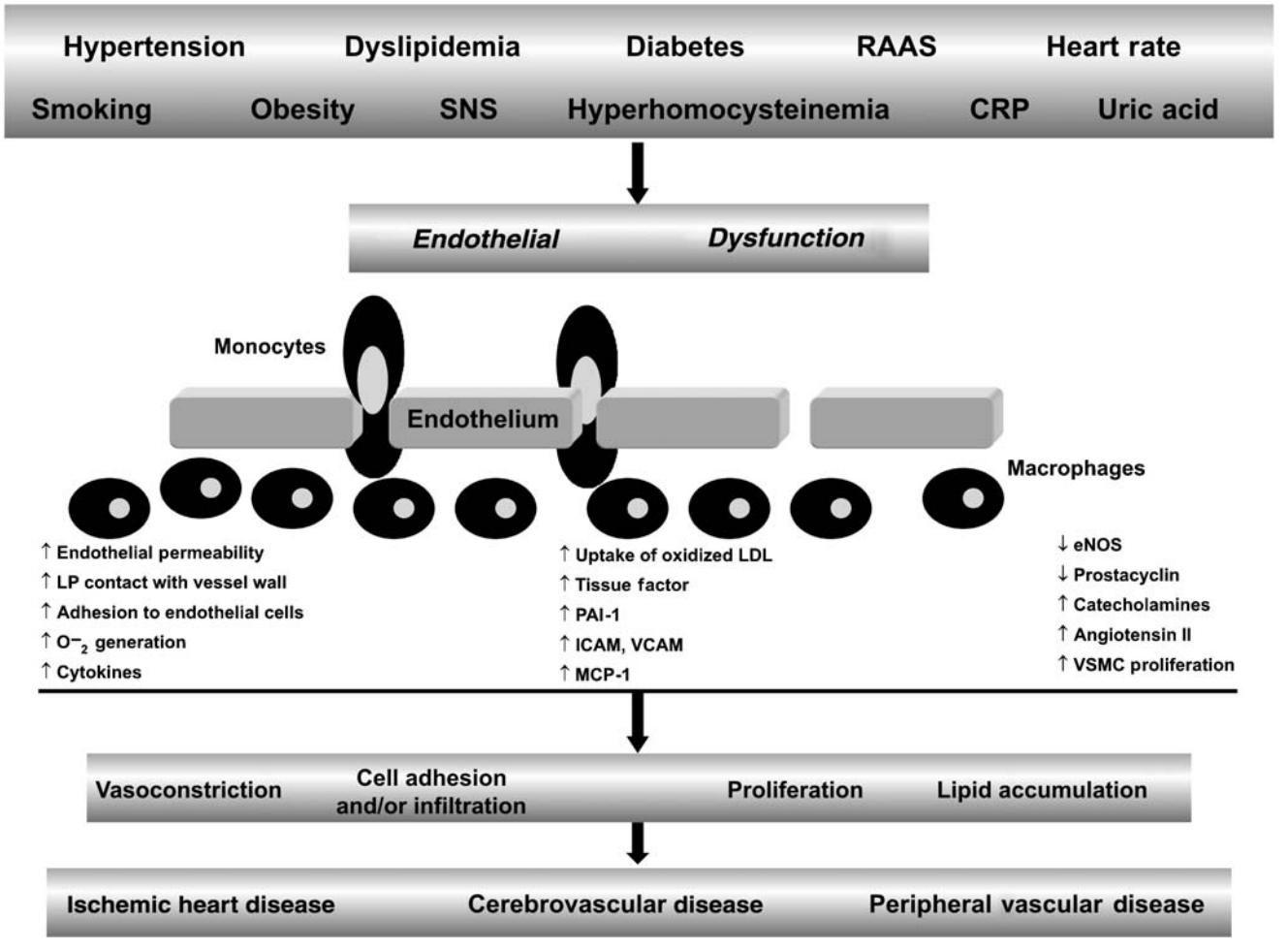

Fig. 6.2 Link between risk factors, endothelial dysfunction, and atherosclerosis. *Abbreviations*: CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase; ICAM, intercellular adhesion molecule; LDL, low-density lipoprotein; LP, lipoprotein; MCP-1, monocyte chemotactic protein-1; PAI-1, plasminogen activator inhibitor-1; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system; VCAM, vascular cell adhesion molecule; VSMC, vascular smooth muscle cell.

overlooked by scientists, it is still ignored by physicians. The HARVEST study (12) showed that clinical heart rate and heart rate changes during the first 6 months of follow-up were independent predictors of subsequent systolic and diastolic BP changes, regardless of the initial BP levels and other confounders. In the same study, the ambulatory heart rate was not an independent predictor of BP change after 6 years of follow-up. In the PAMELA study, neither in- nor out-of-office heart rate predicted cardiovascular or all-cause mortality, and thus no heart rate value was considered for the final multivariate regression model. Studies on the clinical significance of heart rate in hypertensive subjects have shown that the relationship between heart rate, morbidity, and mortality exists (13). Furthermore, elevated heart rate may be a strong predictor of cardiovascular death not only in middle-aged men but also in elderly men. According to the Syst-Eur trial (14), an elevated heart rate higher than 80/min had a 1.89 risk of all-cause death and 1.60 risk of cardiovascular mortality in elderly subjects. One of the possible mechanisms can be due to the connection between heart rate, obesity, hypertension, activation of the sympathetic nervous system, and atherosclerosis. The heart rate may be an index of sympathetic activation. The close association between sympathetic activity and hypertension, as well as target organ damage, such as left ventricular hypertrophy, coronary heart disease, and other diseases, is well established. High heart rate may increase the risk of hypertension in patients with acute coronary syndrome, heart failure, and predispositions to lethal ventricular arrhythmias (15). Moreover, there is a significant correlation between the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system.

Heart rate is a highly variable physiologic phenomenon and can be influenced by a large variety of environmental and other stimuli, such as stress, medical visits, position, method of measurement, etc. Thus, to provide reliable and comparable results, heart rate assessment should be strictly standardized to minimize methodological bias. How should heart rate be measured? According to a recent statement of the ESH, the following information should be provided in studies reporting heart rate data: (*i*) resting period before measurement; (*ii*) environmental conditions; (*iii*) method of measurement; (*iv*) number of measurements; (*v*) duration of measurement; (*vi*) body position; and (*vii*) the nature of the observer (16). There is no general agreement

on the body position for heart measurement, hence the sitting or the supine position can be used. A period of 30 s appears to be sufficient to obtain a reliable estimate of heart rate. Regarding gender, in most studies the predictive value of elevated heart rate for all-cause mortality has been found to be weaker in women than in men. Furthermore, in some studies, no association between heart rate and cardiovascular mortality was found (17). Previous studies have shown beneficial effects from the reduction in heart rate with beta-blockers and non-dihydropyridine calcium antagonists, mainly in myocardial infarction and heart failure, but all studies were retrospective and included normotensive patients. It is expected, that a 10–12% reduction in heart rate will lead to a 20–40% decline in cardiovascular morbidity and mortality, although more studies should to be performed to prove it. Meanwhile, according to the statement of the ESH, the practicing physician may use heart rate for cardiovascular risk stratification and patient management, keeping in mind that achieving good BP control remains the over-reaching goal in the treatment of hypertension.

HYPERHOMOCYSTEINEMIA

Homocysteine is formed during demethylation of methionine. Several studies have indicated that hyperhomocysteinemia is associated with high BP (18) and smoking (19). This correlation was not found in nonsmokers (20). Elevated plasma homocysteine levels have been implicated as a risk factor for cardiovascular and peripheral disease. However, its unclear whether a casual relationship exists between homocysteine and cardiovascular risk, or if homocysteine is related to other confounding cardiovascular risk factors or is a marker of existing disease burden. The causes of hyperhomocysteinemia include genetic causes, vitamin deficiency (folic acid, B_{12}, B_6), smoking, the use of certain medications, and impaired renal function. In the Framingham Heart Study (21), in Tromso, Norway (22), and in women from the Atherosclerosis Risk in Communities (ARIC) study (23), homocysteine levels were higher in subjects with coronary heart disease. In the British Regional Heart Study (24), homocysteine levels were higher in patients with stroke.

The mechanisms by which elevated homocysteine impairs vascular function are not completely understood. The potential mechanisms could be: impaired endothelium function and more precise worsen the disruption of nitric acid by acting on its synthesis and action; oxidation of LDL particles; increased lipid uptake and penetration; increased monocyte adhesion to the vessel wall; stimulatory effects on smooth muscle proliferation; and activation of coagulation factors and platelet function (25). Routine screening for elevated homocysteine is not yet recommended. However, screening may be needed in subjects with multiple risk factors, such as high BP and high levels of blood cholesterol.

C-REACTIVE PROTEIN

Numerous inflammatory markers have been shown to predict cardiovascular events. These include cell adhesion molecules, cytokines, chemokines, fibrinogen, serum amyloid A, and CRP. Elevated high sensitive (hs) CRP is a marker for subclinical atherosclerosis, and is involved in the progression of atherosclerosis. Recent large-scale prospective epidemiological studies have shown that plasma levels of hsCRP are strong and independent predictors of the future risk of atherosclerotic events in otherwise apparently healthy men and women (26). This prompted the addition of CRP to the list of factors for cardiovascular disease in the recent published ESH–ESC guidelines. The production of CRP is under the control of interleukin (IL)-6; however, IL-1 and tumor necrosis factor may also contribute to hepatic synthesis and secretion of CRP. According to the American Association and Centers for Disease Control and Prevention (27), CRP levels can be used as a risk marker for cardiovascular disease in individuals with a Framingham risk score between 10% and 20%. CRP levels <1 mg/L are considered as low risk, 1–3 mg/L as average risk, and <3 mg/L as high risk; however, CRP levels <10 mg/l cannot be used to assess cardiovascular risk. For assessing the cardiovascular risk, the person should be free from acute inflammation for at least 2 weeks, and the measurement of hsCRP is recommended. Chronic low grade inflammation seems to be an early feature of many chronic degenerative disorders, such as abdominal obesity, diabetes mellitus, etc., and these disorders are also commonly associated with hypertension. Furthermore, CRP may upregulate AT_1 receptors, leading to proliferation of vascular smooth muscle cells and, subsequently, to hypertension. In a population survey, the prevalence of hypertension was 1.36 and 1.56 times higher in subjects in the third and fourth quartiles of CRP, respectively, compared to subjects in the first quartiles. Also, hsCRP was positively correlated with pulse wave velocity, augmentation index, central pressure, and central systolic BP (28). In a substudy of the LIFE trial, it was found that hcCRP is a strong cardiovascular risk marker, even after adjustment for traditional risk factors, but did not predict cardiovascular events independently of urine albumin/creatinine ratio. In the Womenís Health study, CRP improved coronary heart disease risk prediction, particularly in the intermediate risk group (29), while in the ARIC study (30), which assessed the association of 19 novel risk markers with the incidence of coronary heart disease in 15,792 adults, CRP was significantly associated with coronary heart disease, but it did not add significantly as the other novel risk factors. Lloyd-Jones et al. (31) reviewed the literature published before January 2006 and found that CRP may add to risk estimation in a limited subset of individuals who are at intermediate predicted risk according to the Framingham risk score. In the Val-MARC trial, where valsartan alone was compared to valsartan plus hydrochlorothiazide, the valsartan alone lowered hsCRP levels independently of the degree of BP reduction (32). In another study, the treatment with irbesartan lowered inflammatory biomarkers. We still do not know whether the decrease in CRP also lowers high BP.

Others dispute the role of CRP in cardiovascular disease, and its role in cardiovascular disease risk remains controversial. Furthermore, CRP levels are influenced by lifestyle changes and certain pharmacological interventions, including statin therapy. This further underscores the importance of establishing the role of CRP in atherothrombosis. Perhaps the role of hsCRP as a cardiovascular risk factor is more clear in primary than in secondary prevention.

SERUM URIC ACID

An association between serum uric acid concentration and cardiovascular risk has been recognized for many years. The NHANES I and III, the PIUMA study, the MONICA project, the Gothenburg prospective study, the OSAKA health survey, the SHEP trial, the INDANA database, the LIFE study, the Bogalusa heart study, and others have shown an association between serum uric acid, cardiovascular risk, and/or the development of hypertension (33,34). These findings are difficult to interpret, because high serum uric acid levels are associated with other conditions that increase cardiovascular morbidity and mortality, such as hyperlipidemia, diabetes mellitus, obesity, and hypertension. Serum uric acid is commonly elevated in essential hypertension. About 25–35% of hypertensive subjects exhibit hyperuricemia. Uric acid is the main product of purine metabolism and is formed from xanthine by the action of xanthine oxidase. Serum uric acid levels vary with height, body weight, BP, renal function, alcohol intake, menopause, etc. Indeed, studies performed on the general population have failed to show an association between serum uric acid levels and cardiovascular risk (35). The pathogenetic mechanism of uric acid involvement in cardiovascular risk is not well understood. However, uric acid may contribute to endothelial dysfunction, but the accurate mechanism is not known. Hyperuricemia is also associated with the activation of circulating platelets, stimulates vascular smooth muscle proliferation, and has a proinflammatory effect. Renal injury also occurs in hyperuricemic rats, consisting of afferent arteriopathy, fibrosis, glomerular hypertrophy, and albuminuria (36).

IS THERE EVIDENCE THAT SERUM URIC ACID CAUSES HYPERTENSION IN HUMANS?

Epidemiological studies have shown a continuous relation of serum uric acid with BP that is stronger in younger subjects. Iwashima et al. (37) found that serum uric acid is independently associated with left ventricular hypertrophy and the combination with hyperuricemia is an independent and powerful predictor for cardiovascular disease, while Viazzi et al. (38) found that serum uric acid levels increase the risk of having left ventricular hypertrophy and carotid abnormalities. Hyperuricemia is also an independent risk factor for predicting the development of hypertension. In the SHEP trial, those patients with a serum uric acid increase of >0.06 mmol/L had a similar risk for coronary heart disease with the placebo group, suggesting that monitoring serum uric acid levels during diuretic treatment may help identify patients who will most benefit from treatment. In the LIFE trial they found that an increase of serum uric acid over 4.8 years was attenuated by losartan compared with atenolol treatment, appearing to explain 29% of the treatment effects on the primary composite end-point, and showing that the association between serum uric acid and events was stronger in women than in men. We and other investigators found a difference in the response of treatment with losartan in comparison with other angiotensin receptor antagonists in serum uric acid levels (39). Serum uric acid seems to have a pathogenetic role in the development of hypertension and renal and cardiovascular disease. However, there are no studies that have examined whether lowering uric acid will reduce BP in hypertensive patients. It is time to design human studies for the role of uric acid in the field of hypertension and cardiovascular disease.

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7 ASSESSMENT OF THE CIRCADIAN CARDIOVASCULAR RISK WITH AMBULATORY BLOOD PRESSURE MEASUREMENT

Eoin O'Brien

INTRODUCTION

In this chapter, I review the evidence that ambulatory blood pressure measurement (ABPM) can provide a means of assessing circadian cardiovascular risk. I will not attempt to review the circadian risk from the biochemical, hormonal, and thrombotic viewpoints other than to acknowledge that there is considerable harmony in the physiological, hemodynamic adjustments that occur during each 24-h cycle, and to indicate at the outset that what may be measurable with ABPM may well be the effect of changes in other hemorheological mechanisms that are orchestrated to cope with the vast variation in activity and circumstance that characterizes human behavior during a 24-h period.

THE CIRCADIAN RHYTHM OF THE CARDIOVASCULAR SYSTEM

While this review is confined to assessing the role of ABPM in circadian risk, it is important to acknowledge the complex associated perturbations that characterize the 24-h period. The subject has been well reviewed by Giles (1,2). The occurrence of several life-threatening acute cardiovascular events tend to peak at certain times of the day. For example, acute myocardial infarction, ischemic events, sudden cardiac death, and stroke are more likely to occur in the morning hours, soon after waking, than at other times of the day (3). An excess of cardiovascular events associated with circadian changes in blood pressure (BP), for example the morning surge, non-dipping, or excessive dipping, may be explained, or are at least associated with, circadian variations of various biochemical and physiological parameters. In other words, circadian variations in BP serve as sensitive indicators of a cascade of physiological events that include increased sympathetic and plasma rennin activity (4,5), leading to increased levels of angiotensin II (6), catecholamines, and cortisol (7), all of which may forecast acute cardiovascular catastrophes. Increased myocardial oxygen demand in response to physical activity, and simultaneous increases in platelet aggregability and blood viscosity leading to an early morning hypercoaguable state further facilitate thromboembolism (8). As Giles has pointed out, it is not difficult to envisage these changes together with a morning surge in BP and enhanced platelet aggregation, thrombosis, and occlusion, culminating in shear stress and the fissure of unstable atherosclerotic plaques, leading to acute myocardial infarction, ischemic stroke, and sudden cardiac death (1) (Figure 7.1). Another example of BP being the reflecting mirror of complex biochemical circadian variation is the association of a nocturnal non-dipping pattern in hypertensive subjects prone to retaining sodium (9). The nocturnal consequences of altered BP patterns have been largely ignored in clinical practice because the methodology for assessing nocturnal profiles of BP—24-h ABPM—has been accepted only slowly in clinical practice, or used only sparingly for recording BP at night.

MEASUREMENT OF BP AND RISK

The most commonly used method of BP measurement in clinical practice is the auscultation method with a mercury sphygmomanometer and stethoscope. This conventional technique undoubtedly provides information on cardiovascular risk. A meta-analysis of clinic BP measurement in 1 million adults participating in 61 prospective studies showed that a 10 mmHg higher usual systolic BP or 5 mmHg higher usual diastolic BP would be associated with approximately 40% higher risk of stroke death and around 30% higher risk of death from ischemic heart disease and other vascular causes (10). The technique, however, has many limitations, which include the presence of a white coat reaction, interobserver and intraobserver variability, and terminal digit preferences, all of which may bias the accuracy of measurement (11,12). Moreover, conventional sphygmomanometry as employed in clinical

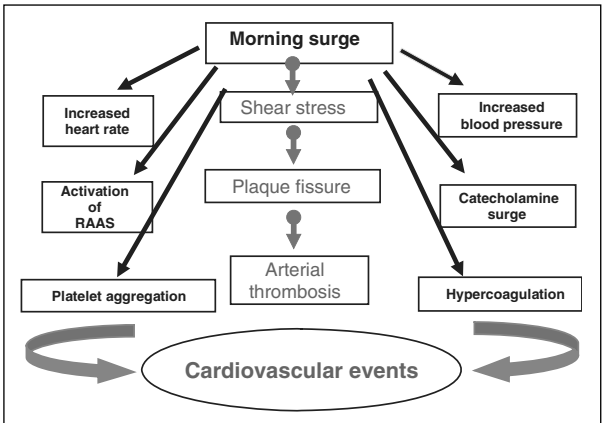

Fig. 7.1 Mechanisms triggering cardiovascular events during the early morning blood pressure surge. *Abbreviation*: RAAS, renin–angiotensin–aldosterone system. *Source*: From Ref. 1.

practice fails to give any information on circadian risk. Interestingly though, efforts to improve the prognostic value of the technique and to gain insight into circadian effects were made in the first half of the 20th century. In 1922, Addis, recognizing the extreme variability of BP, endeavored to minimize this by obtaining BP measurements in the morning after awakening but before rising, and he termed this basal BP (13). Sir Horace Smirk developed this concept further in a series of experiments in which he measured BP under very standardized conditions in sedated hypertensive patients and normotensive controls. The lowest BP obtained by this technique was called the "basal BP" in contrast to conventionally measured BP in the hospital, which he termed "casual BP," with the difference between the two being called "supplemental BP." In health, the basal BP was found to be practically a physiological constant, but in hypertensive patients the basal BP, while more variable than in normotensive subjects, was much less variable than the casual BP. He showed that basal BP was a much better guide to prognosis than casual pressures, and he likened basal BP to sleeping BP (14,15). Smirk's remarkable contribution, which has largely been overlooked in recent years, has been restored to historical probity by Pickering (16) and contributes to further reasoning in this review.

Self BP measurement also provides information on risk, but again is limited in the information it can provide on circadian risk, mainly because nocturnal BP measurements are not available (17)., Recently, however, Imai and colleagues have modified a device for self-measurement of BP to provide nocturnal BP measurements (18). As technology develops and the cost of automated devices reduces, the day cannot be too far distant when BP measuring devices will provide the user with the facility to measure casual BPs, pressures at home or at work, and to perform intermittent measurements over a 24-h or longer period of time—effectively, a "device for all seasons."

At present, however, ABPM is the only technique that permits close examination of the circadian profile and identification of patterns that may be associated with risk. There is now general agreement that ABPM is indispensable to good clinical practice (12) and there is indisputable evidence showing that ambulatory BP is superior to office values in predicting cardiovascular risk (19–25). Moreover, recent evidence suggests that nighttime BP may be the most sensitive predictor of all measurements (26–29) (Figure 7.2).

INDICES OF RISK IN THE CIRCADIAN PROFILE

SYSTOLIC VERSUS DIASTOLIC BP

In Western countries, systolic BP is a stronger predictor of cardiovascular risk than diastolic BP in the majority of the adult population. This greater risk is attributable, at least in part, to systolic BP levels being more directly related to cardiovascular complications, a greater prevalence of systolic hypertension in older patients, and systolic hypertension being more resistant to treatment (30). However, the relative

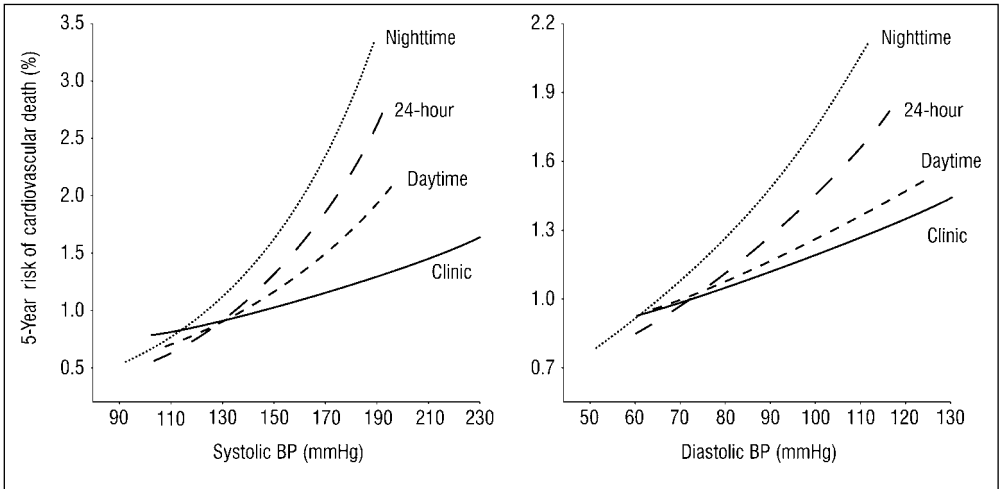

Fig. 7.2 Adjusted 5-year risk of cardiovascular death in the study cohort of 5,292 patients for clinic and ambulatory blood pressure (BP) monitoring. Using multiple Cox regression, the relative risk was calculated with adjustment for baseline characteristics, including gender, age, presence of diabetes mellitus, history of cardiovascular events, and smoking status. The 5-year risks are expressed as number of deaths per 100 subjects. *Source*: From Ref. 26.

risk of systolic versus diastolic BP is age related. In the Framingham Heart Study, diastolic BP was a better predictor of coronary heart disease for participants aged less than 50 years of age: between the ages of 50 and 59 years, diastolic and systolic BP assume comparable risk; and after the age of 60 years, the risk of coronary heart disease remains positively correlated with systolic BP, but is inversely related to diastolic BP (31). Similar findings have been reported in a Japanese population (32). In the Dublin Outcome Study, systolic 24-h ABPMs predicted outcome more sensitively than diastolic BP in a population whose average age was 60 years, with nighttime systolic BP being the strongest predictor of outcome—for each 10 mmHg increase in mean nighttime systolic BP, the mortality risk increased by 21% (26).

PULSE PRESSURE AND MEAN PRESSURE

Pulse pressure is an established cardiovascular risk factor (33,34). It has been shown that in a large sample of subjects with predominantly systolic and diastolic hypertension whose age spanned eight decades, the risk of cardiac complications of elevated BP showed a strong, positive, and independent association with its pulsatile component (pulse pressure) but not with its steady component (mean BP), whereas the risk of cerebrovascular complications showed a similarly strong, positive, and independent association with its steady component but not with its pulsatile component. Moreover, these associations persisted after adjustment for the significant influence of numerous risk factors (33). These findings suggest that elevated peripheral vascular resistance appears to be more damaging to the brain, and that increased large artery stiffness appears to be more damaging to the heart in middle-aged individuals with hypertension. In the Ohasama Study, the predictive power of four indices of ABPM—systolic, diastolic, mean, and pulse pressure—were assessed; ambulatory pulse pressure was the weakest predictor of stroke, but exclusion of age from covariates increased its predictive power, suggesting that the stroke risk of pulse pressure was a reflection of aging per se (35).

AMBULATORY ARTERIAL STIFFNESS INDEX

Recently, a new index has been derived from ABPM. The ambulatory arterial stiffness index (AASI), defined as 1 minus the regression slope, a measure of the dynamic relationship between diastolic and systolic BP throughout the whole day, has been shown to predict cardiovascular mortality in a large cohort of hypertensive individuals (34). To date, one cross-sectional analysis (36) and three prospective cohort studies (34,37,38) have demonstrated an association of AASI either with signs of target organ damage in never-treated hypertensive patients or with the incidence of cardiovascular mortality and morbidity (36).

The AASI is particularly predictive of stroke (34,37,38), even at levels of BP within the normotensive range (34,38). Moreover, when adjusted for pulse pressure, AASI retains its predictive value (34,37,38). Currently ongoing analyses of a Copenhagen cohort have shown that AASI predicts stroke over and beyond aortic pulse wave velocity (39). AASI may therefore prove to be a readily applicable index that can be derived from a routine ABPM to predict outcome. The practical importance of such an index is that it may permit early categorization of hypertensive patients into those at risk from cardiovascular events and, thus, indicate those in need of aggressive BP lowering.

BP VARIABILITY

Many indices of BP variability can be derived from 24-h ABPM (40–42). BP variability is undoubtedly an important determinant of target-organ damage and of higher cardiovascular risk in hypertension, and smooth 24-h control of BP with antihypertensive drugs should be given consideration as a means of improving prognosis (40,41). However, in patients with uncomplicated mild hypertension, BP variability assessed by noninvasive ABPM was not an independent predictor of cardiovascular outcome (42).

HEART RATE

As heart rate is readily obtainable from ABPM, it has the potential to add another dimension to the assessment of risk. Several epidemiological studies have shown an association between heart rate and both cardiovascular and non-cardiovascular mortality. Heart rate is inversely proportional to life expectancy, and an elevated heart rate is a risk factor for hypertension, atherosclerosis, and cardiovascular morbidity and mortality (43). The relationship between resting heart rate and mortality has been observed in the general population and in patients with hypertension, coronary artery disease, and after acute myocardial infarction (43). In most of these studies, clinic measurements of heart rate have been used to investigate the association with cardiovascular risk. A consensus meeting of the European Society of Hypertension to provide recommendations on the influence and management of heart rate in clinical practice concluded that there was no available evidence demonstrating an advantage of heart rate measured out-of-office over clinical heart rate, but was of the opinion that, for hypertensive subjects who monitor their BP at home with automatic devices, the reporting of heart rate data together with BP may provide useful information (44). An ongoing analysis of the data in the Dublin Outcome Study confirms that ambulatory heart rate predicts mortality risk. In particular, nighttime heart rate, as is the case with nocturnal BP, is the strongest predictor of outcome. In keeping with previous studies, an increased heart rate also predicted non-cardiovascular deaths, suggesting that an increased heart rate is a nonspecific marker for all-cause mortality (43).

Several complex statistical and chronobiological methods have been proposed for the analysis of circadian BP recordings (45). Cusum-derived statistics are simply calculated from ambulatory data but have never gained popularity in clinical or research practice (45).

WINDOWS OF THE 24-H CIRCADIAN PROFILE

The predictive value of ABPM, and its superiority to office BP measurements, has been demonstrated in prospective studies, which have been well summarized by Giles (1,2). This being so, it is of interest to look more closely at the information that may be derived from 24-h ABPM recordings. The 24-h period

can be divided into a number of windows, each of which yields information about BP change, and each of which provide patterns of BP behavior that may be associated with varying risk. The dabl® ABPM program (dabl Ltd., Blackrock, County Dublin, Ireland) has been designed to allow demarcation of these windows and separate or combined statistical analyses to be performed on the BPs within these windows (46–48) (Figure 7.3).

WHITE COAT WINDOW

The white coat window is the window that extends from the beginning of ABPM recording and lasts for 1 h. Ideally, ABPM recording should begin no later than 9 AM, but, when this is not possible, the dabl®ABPM program adjusts for a later time for ABPM recording to commence (48). During the white coat window, BP may be influenced by the medical environment. The most popular definition of white coat hypertension is that BP measured by conventional techniques in the office, clinic, or surgery exceeds 140 mmHg systolic or 90 mmHg diastolic, but, when ABPM is performed, the average BP is less than 135 mmHg systolic and 85 mmHg diastolic during the daytime period. Currently, an average daytime ABPM of less than 135 mmHg systolic and 85 mmHg diastolic is generally considered normal and levels less than 130/80 mmHg are considered optimal (49). However, it has been shown that the white coat window on ABPM recordings can not only diagnose the white coat phenomenon, but also allows identification of a white coat hypertensive subgroup, with significantly higher pressures, who may be at greater risk and in need of antihypertensive medication (47). ABPM remains the method of choice for diagnosing white coat hypertension (25,47,50).

DAYTIME WINDOW

The daytime window follows the white coat window and is the period when the subject is away from the medical environment and engaging in usual activities (47). For almost all subjects with hypertension, BPs during this window are lower than conventionally recorded pressures in the office, clinic, or surgery setting (50,51). However, BPs during this period are subject to stress, activity, arm movement, the effect of exercise, and other activities, such as driving, all of which may have an influence on the mean level of BP recorded (52). These effects are largely absent from BP measured during the nocturnal period (26,53).

VESPERAL WINDOW

In the normal individual there is a decline in BP in the vesperal window from daytime levels of BP to reach a plateau during the nighttime period. This period (9:01 PM to 0:59 AM on the basis of ABPM commencing at 9 AM) is not included in the estimation of day and night mean pressures because this period represents time during which bed rest is inconsistent and, therefore, cannot be categorized reliably (54). In hypertensive patients (or some normotensive patients with cardiovascular disease) the decline in the vesperal window may be absent (non-dipping) so that BPs do not reach basal levels (26,27,55,56). BP may even rise in the vesperal window to reach levels that are higher than daytime levels (reverse dipping) (57). Alternatively there may be a marked fall in BP during the vesperal window to give the phenomenon of extreme dipping (58). Therefore, what happens to BP in the vesperal window predicates the level of BP in the basal window.

BASAL WINDOW

The nighttime window follows the vesperal window and is the period between 1:00 AM and 6:00 AM (47). BPs in this window are most likely to coincide with sleep or, if not with actual sleep, with the greatest cessation of activity and are likely, therefore, to represent a steady state (46). I have

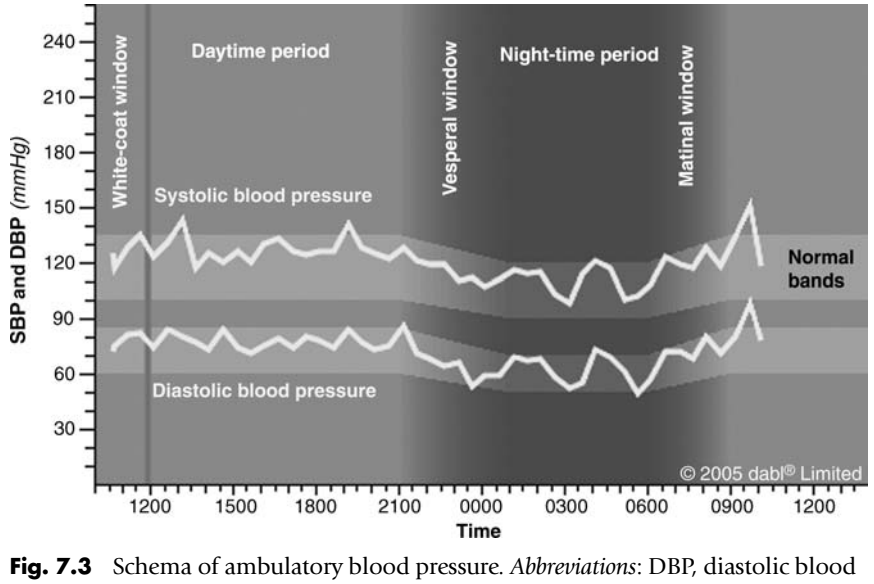

Fig. 7.3 Schema of ambulatory blood pressure. *Abbreviations*: DBP, diastolic blood pressure; SBP, systolic blood pressure. *Source*: Plot generated by dabl ABPM, 2006 (http://www.dabl.ie).

applied the term "basal" to this window in acknowledgement of the seminal paper written by Horace Smirk in 1964 (15). As previously outlined, the compelling conclusion from Smirk's analysis was that basal BP was superior to casual pressure in predicting outcome (14,15). This evidence is very similar to recent evidence from my department (26) and others (56), showing that nighttime BP is superior to all other BP measurements in predicting cardiovascular outcome and mortality, which suggests that nighttime BP obtained by ABPM is similar to the basal BP described by Smirk. Moreover, it has also been shown that the use of a mild sedative during ABPM may help in identifying patients with a very high cardiovascular risk; namely, those patients who continue to manifest a blunted nocturnal dip despite sedation (59).

Valuable though the information derived from the basal window may be, there are a number of methodological limitations to recording BP at night. These include different criteria for defining dipping/non-dipping status, arbitrary dichotomization of a continuous and variable measurement (night-to-day ratio), inappropriate selection of cases (non-dippers) and controls (dippers), insufficient sample size, poor reproducibility of the night-to-day ratio, a "regression-to-the-mean" phenomenon when ABPMs are repeated in subjects classified as extreme dippers or non-dippers on the first ambulatory recording, the influence of daytime physical activity on the dipping phenomenon (27,60), and the influence of sleep disturbance and sleep apnea (53,60). Ironically, despite doubts about reproducibility of the night-to-day ratio, it may be that nighttime BP is more standardized and consequently more reproducible than daytime BP (sleep being a more stable state than activity), and that it is this feature that gives nocturnal BP its predictive value. In clinical practice when the sleep and awakening periods are clearly defined, nocturnal changes in BP are surprisingly reproducible (61,62).

MATINAL WINDOW

The matinal window extends from the end of the basal window to the commencement of daytime activities following rising. This period (6:01 AM to 8:59 AM) is not included in the estimation of day and night mean pressures because this period represents time during which bed rest is inconsistent and, therefore, cannot be categorized reliably (54). However, the magnitude of the rise in BP in the matinal window may yield most valuable prognostic information. In normal subjects, a modest rise in BP occurs in the matinal window, preceding awakening from sleep to merely restore the previous daytime level of BP (46). This pre-awakening rise in BP in hypertensive patients may exceed the daytime average—the pre-awakening or morning surge—and this phenomenon is associated with a poor cardiovascular outcome (58).

PATTERNS OF ABPM

Within the windows of the 24-h BP profile, several variations of BP behavior may be discerned, allowing differentiation of patients into sub-forms and patterns (25,63–65). ABPM may also be used to stage the severity of BP—the higher the initial 24-h ABPM, the more frequent the occurrence of cardiovascular events (19). The most commonly used aggregate to denote levels of ABPM is the mean 24-h BP (25). However, though this may be an acceptable estimate of the BP load over the 24-h period, the information deriving from individual windows of the 24-h profile is such that critical consideration has to be given to the association of ABPM patterns with cardiovascular outcome (Figure 7.4).

WHITE COAT HYPERTENSION

The risk associated with white coat hypertension remains controversial but there is general agreement that the condition should not be regarded as benign, with the risk of developing sustained hypertension at some time being almost inevitable (66,67) (Figure 7.5).

WHITE COAT EFFECT

White coat hypertension must be distinguished from the white coat effect, which is the term used to describe the increase in BP that occurs in the medical environment, regardless of the daytime ABPM . In other words, the term indicates the phenomenon, found in most hypertensive patients, whereby clinic BP is usually greater than the average daytime ABPM, which is nonetheless increased above normal. The importance of the phenomenon is that patients diagnosed as having severe hypertension by conventional measurements may have only moderate or mild hypertension on ABPM because of a marked white coat effect (65) (Figure 7.6).

MASKED HYFPERTENSION

This phenomenon denotes subjects classified as normotensive by conventional office or clinic measurement, but who are hypertensive with ABPM or self-measurement. The prevalence of masked hypertension in adults seems to be at least 10%, and may indeed be higher, with a tendency to decrease with age. Adult subjects with masked hypertension have increased target organ involvement as denoted by left ventricular mass and carotid atherosclerosis. As might be expected when target organ involvement is increased, the likelihood that cardiovascular morbidity will also be greater is indeed the case. The logical extension of this line of reasoning is that future studies will also show cardiovascular mortality to be increased. The problem for clinical practice is how to identify and manage these patients who, it is estimated, may number as many as 10 million people in the United States (23,65).

AMBULATORY HYPOTENSION

Hypotension is particularly common in the elderly, who may have autonomic or baroreceptor failure, and who may also experience post-prandial and postural hypotension—conditions which may lead to risk from falls and accidents. ABPM may also be useful in identifying hypotensive episodes

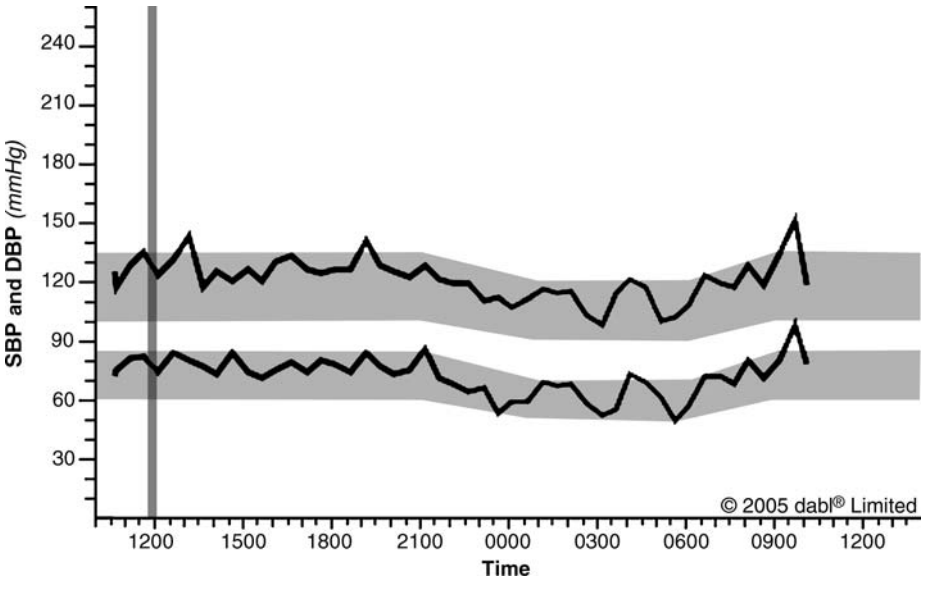

Fig. 7.4 Normal ambulatory blood pressure monitoring (ABPM) pattern. On the basis of the data recorded and the available literature, the ABPM pattern suggests normal 24-h SBP and DBP (128/78 mmHg daytime, 110/62 mmHg nighttime). *Abbreviations*: DBP, diastolic blood pressure; SBP, systolic blood pressure. *Source*: Plot and report generated by dabl ABPM, 2006 (http://www.dabl.ie).

in young patients in whom hypotension is suspected of causing symptoms (23,25,65). In treated hypertensive patients, ABPM may also demonstrate drug-induced decreases in BP that may have untoward effects in those with a compromised arterial circulation, such as individuals with coronary and cerebrovascular disease (68) (Figure 7.7).

DAYTIME SYSTO-DIASTOLIC HYPERTENSION

Many patterns of BP behavior can be discerned from ABPM, but by far the most common pattern is systo-diastolic hypertension (63). Usually, daytime BP levels are lower than clinic

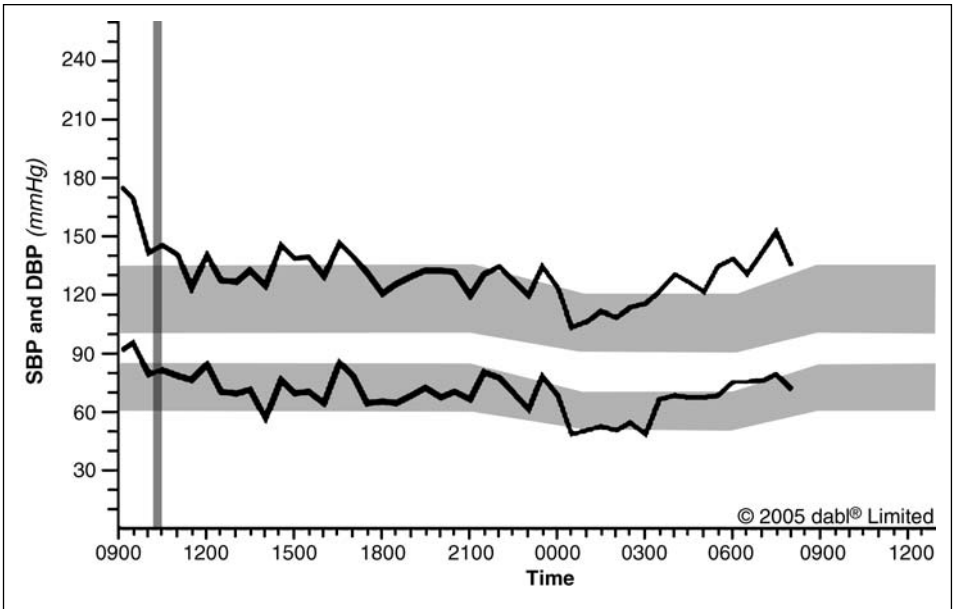

Fig. 7.5 White coat hypertension. On the basis of the data recorded and the available literature, the ambulatory blood pressure monitoring pattern suggests white coat hypertension (175/95 mmHg) with otherwise normal 24-h SBP and DBP (133/71 mmHg daytime, 119/59 mmHg nighttime). *Abbreviations*: DBP, diastolic blood pressure; SBP, systolic blood pressure. *Source*: Plot and report generated by dabl ABPM, 2006 (http://www.dabl.ie).

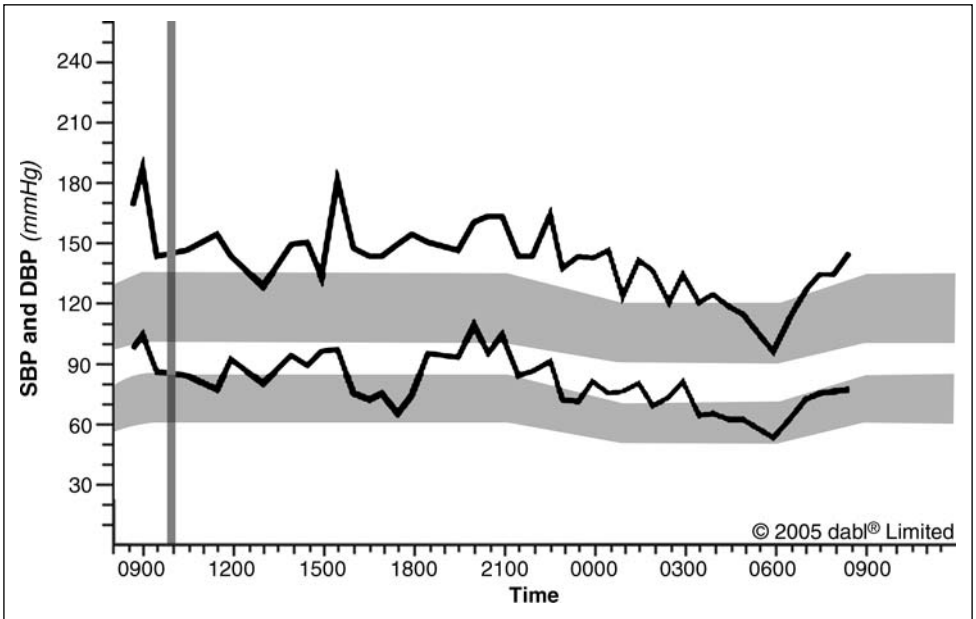

Fig. 7.6 White coat effect. On the basis of the data recorded and the available literature, the pattern suggests mild daytime systolic hypertension (149 mmHg), borderline daytime diastolic hypertension (87 mmHg), borderline nighttime systolic hypertension (121 mmHg), and normal nighttime diastolic hypertension (67 mmHg) with white coat effect (187/104 mmHg). *Abbreviations*: DBP, diastolic blood pressure; SBP, systolic blood pressure. *Source*: Plot and report generated by dabl ABPM, 2006 (http://www.dabl.ie).

readings—the white coat effect. Generally, mean daytime levels of BP are superior to clinic BPs but inferior to nocturnal BP in predicting outcome (26,68,69).

ISOLATED SYSTOLIC HYPERTENSION

Isolated systolic hypertension can, of course, be apparent on clinic BP measurement, but it can be overestimated, and ABPM allows for confirmation of the diagnosis, as well as predicting outcome more accurately. The results of the ABPM sub-study of the Systolic Hypertension in Europe Trial showed that systolic BP measured conventionally in the elderly may average 20 mmHg more than daytime ABPM, thereby leading to inevitable overestimation of isolated systolic hypertension in the elderly and probable excessive treatment of the condition. Moreover, results from this study also show that systolic ABPM was a significant predictor of cardiovascular risk over and above conventional systolic BP (70). In women with cardiovascular disease, systolic BP was the BP measure most strongly related to the risk of secondary cardiovascular events (71) (Figure 7.8).

ISOLATED DIASTOLIC HYPERTENSION

Isolated diastolic hypertension, which can be present on clinic measurement, can be more readily studied on ABPM. The prevalence of the condition in one study was 3.6% (63). There are few studies to date on the prognostic relevance of the condition, but the consensus from a review of the literature is that, if the systolic BP is normal, high diastolic BP is not associated with an adverse prognosis (72).

DIPPING AND NON-DIPPING

The "dipper/non-dipper" classification was first introduced in 1988, when a retrospective analysis suggested that non-dipping hypertensive patients had a higher risk of stroke than the majority of patients with a dipping pattern (55). Whether this classification is associated with adverse outcome has been the subject of much debate (60). On balance, most large-scale prospective studies currently support the concept that a diminished nocturnal BP fall is associated with a worse prognosis (25,27). For example, blunted nighttime dipping of BP is independently associated with angiographic coronary artery stenosis in men (73). In elderly people with long-standing hypertension, a blunted nocturnal dip in BP is independently associated with lower cognitive performances (74). Among elderly patients with recently diagnosed isolated systolic hypertension, those with a non-dipping nocturnal pattern have been shown to have significantly higher left ventricular masses on echocardiography than dippers (75). A non-dipping nocturnal pattern is also associated with renal and cardiac target organ involvement (76). It has been well documented that, in hypertensive subjects, non-dippers are more likely than dippers to suffer silent, as well as overt, hypertensive target organ damage. However, it has also been demonstrated that a non-dipper status is associated with target organ damage in normotensive subjects (76). Moreover, nocturnal BP is now known to be an independent risk for cardiovascular outcome over and above all other measures of BP (26,28). For example, in the Dublin Outcome Study, for each 10 mmHg increase in mean nighttime systolic BP, the mortality risk increased by 21% (26). In a Japanese population, a diminished nocturnal decline in BP was an independent risk factor for cardiovascular mortality, with each 5% decrease in the decline in nocturnal

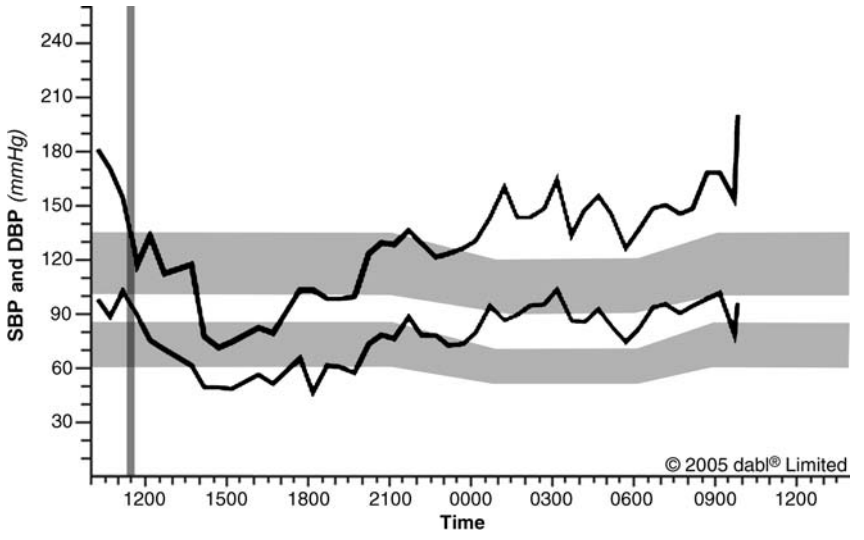

Fig. 7.7 Ambulatory hypotension. On the basis of recorded data and available literature, ambulatory blood pressure monitoring pattern suggests low daytime SBP (100 mmHg), normal daytime DBP (61 mmHg), and moderate night-time systolic and diastolic hypertension (146/89 mmHg) with white coat effect (200/102 mmHg). *Abbreviations*: DBP, diastolic blood pressure; SBP, systolic blood pressure. *Source*: Plot and report generated by dabl ABPM, 2006 (http://www.dabl.ie).

systolic/diastolic BP being associated with an approximately 20% greater risk of cardiovascular mortality (28).

REVERSE DIPPING

In some patients, BP rises above the daytime pressures rather than falling during the night. These patients (also referred to as risers or extreme non-dippers) have the worst cardiovascular prognosis, both for stroke and cardiac events (77) (Figures 7.9 and 7.10).

EXTREME DIPPING

Patients with a marked nocturnal fall in BP, known as extreme dippers, are at risk for non-fatal ischemic stroke and silent myocardial ischemia. This is particularly likely in extreme

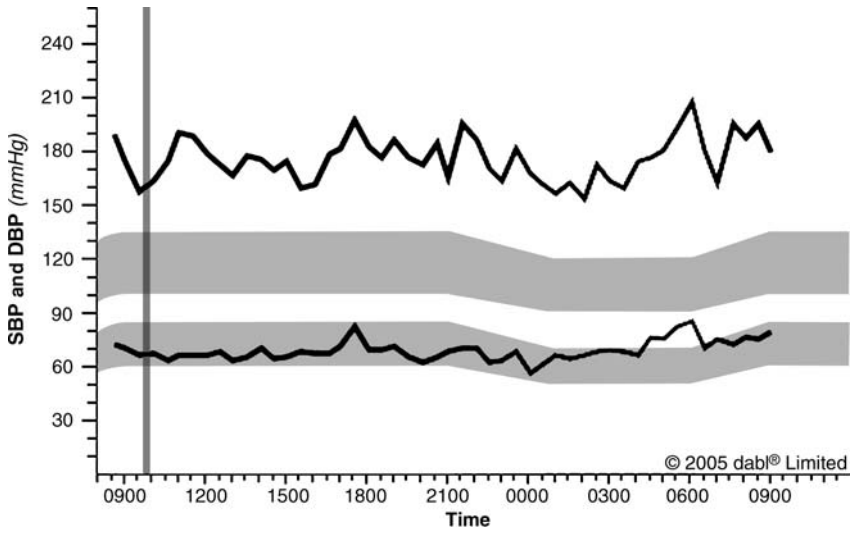

Fig. 7.8 Isolated systolic hypertension. On the basis of recorded data and available literature, the pattern suggests severe 24-h isolated systolic hypertension (176/68 mmHg daytime, 169/70 mmHg nighttime). *Abbreviations*: DBP, diastolic blood pressure; SBP, systolic blood pressure. *Source*: Plot and report generated by dabl ABPM, 2006 (http://www.dabl.ie).

dippers who already have atherosclerotic arterial stenosis, and in whom excessive BP reduction is induced by injudicious antihypertensive medication (77). This possibility was originally enunciated by Floras, as long ago as 1988, when he postulated that patients with critical coronary stenoses or hypertrophied ventricles could have impaired coronary vasodilator reserve and would, therefore, be at greatest risk of myocardial ischemia or infarction if subendocardial perfusion pressure fell below the lower threshold of blood flow autoregulation. This was most likely to occur during sleep, when excessive antihypertensive treatment might cause unrecognized nocturnal hypotension leading to coronary artery hypoperfusion, thereby offering an explanation why treatment had not diminished the risk of myocardial infarction in patients with hypertension (78). Extreme dipping is closely associated with an excessive morning surge in BP, which is associated with cerebral infarction and a high risk of future stroke (77).

SIESTA DIPPING

A siesta dip in BP on ABPM is common in societies in which an afternoon siesta is an established practice. But, in many elderly patients, regardless of cultural practice, a siesta is often a part of the daily routine. There is evidence that ignoring the dipping pattern associated with a siesta distorts the day/night ration of ABPM (79,80), and it should therefore be taken into account in assessing overall 24-h circadian patterns. The magnitude of the siesta dip may have prognostic implications, though the evidence to date is scarce (81).

NOCTURNAL HYPERTENSION

Although daytime ambulatory hypertension is a good predictor of outcome, a number of studies have shown that ambulatory nocturnal hypertension is associated with a worse cardiovascular outcome (26,28,82). Further confirmation of the importance of nocturnal hypertension comes from a recent study showing that a non-dipping pattern and increased nighttime diastolic BP predicted the occurrence of congestive heart failure independently of antihypertensive treatment and established risk factors for cardiac failure. Furthermore, this association was present even after adjusting for office BP measurement, thereby showing that ABPM once again conveys important information that cannot be obtained with conventional measurement (83).

THE MORNING SURGE

Cardiovascular events, such as myocardial infarction, ischemia, and stroke, are more frequent in the morning hours soon after waking than at other times of day (1). Circadian variations in biochemical and physiological parameters help explain the link between acute cardiovascular events and the early morning BP surge (1,2). The clinical consequences of these hemodynamic and neurohumoral changes are numerous. Transient myocardial ischemia and peak ischemic activity has been documented. The occurrence of stroke and heart attack is commoner in this period than at any other time of the day (2). Kario et al. have shown that, in older hypertensive subjects, a morning surge in BP—defined as a rise in BP greater than 55 mmHg from the lowest nighttime reading—carries a risk of stoke almost three times that seen in patients without a morning surge. A pattern of morning surge in BP was also associated with the presence of more clinically silent cerebral infarction (84). Higher carotid internal-medial thickness and circulating inflammatory markers coexist in hypertensive patients with morning BP surge, and might contribute to the increased cardiovascular risk in these patients (85).

CAN DRUGS BE TARGETED TO REDUCE BP IN CIRCADIAN PERIODS OF GREATEST RISK?

Traditionally BP lowering drugs are taken in the morning, but the scientific rationale for the timing of medication may not always be based on sound evidence. It is surprising how little attention has been given to the possibility of achieving a more beneficial effect on cardiovascular outcome by reducing nocturnal BP, either by nighttime dosing, or by designing drugs specifically to reduce nocturnal BP (24). The practice of morning dosing of medication may have had more to do with the practice of conducting antihypertensive drug trials at morning clinics and being able to make an assessment of efficacy based on BP effect some hours after dosing than with scientific evidence based on the pharmacodynamic realities of the drug under study. This lapse in scientific reasoning was well illustrated in the Heart Outcomes Prevention Evaluation (HOPE) study (86). In the main study, the group receiving ramipril had an approximately 35% reduction in cardiovascular events, despite an insignificant reduction in BP of 3/2 mmHg; the outcome benefit was attributed to angiotensin-converting enzyme (ACE) inhibition, which was recommended in all high-risk patients regardless of baseline BP. However, it became evident from later analysis of an ABPM sub-study that ramipril was actually taken in the evening, with outpatient BP measured the following day, some 10–14 h later (87). The reported insignificant change in BP in the main study gave no indication of a "whopping" 17/8 mmHg reduction in BP during the nighttime period, which translated into a 10/4 mmHg average reduction in BP over the entire 24-h period (88).

Interestingly, from an historical perspective, the first paper to describe the effects of antihypertensive medication on 24-h BP was in 1982, when Floras and his colleagues demonstrated, using direct intra-arterial BP measurement, that atenolol and slow-release propranolol lowered nighttime BP, whereas metoprolol and pindolol did not (89). A few years later, we presented data showing a discrepancy between antihypertensive drug efficacy as judged by clinic and noninvasive ambulatory daytime measurement, and concluded that "noninvasive ABPM should be considered an essential part of the evaluation of antihypertensive drugs" (90). Why, we might ask, have we had to wait nearly a quarter of a century to explore the therapeutic potential of nocturnal BP lowering and the differing effects of drugs on ambulatory BP?

Efficacies of the various classes of antihypertensive drugs for restoring normal dipping are not well studied, but diuretics, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin-1 receptor blockers and calcium channel blockers appear to be superior to alpha and beta-blockers

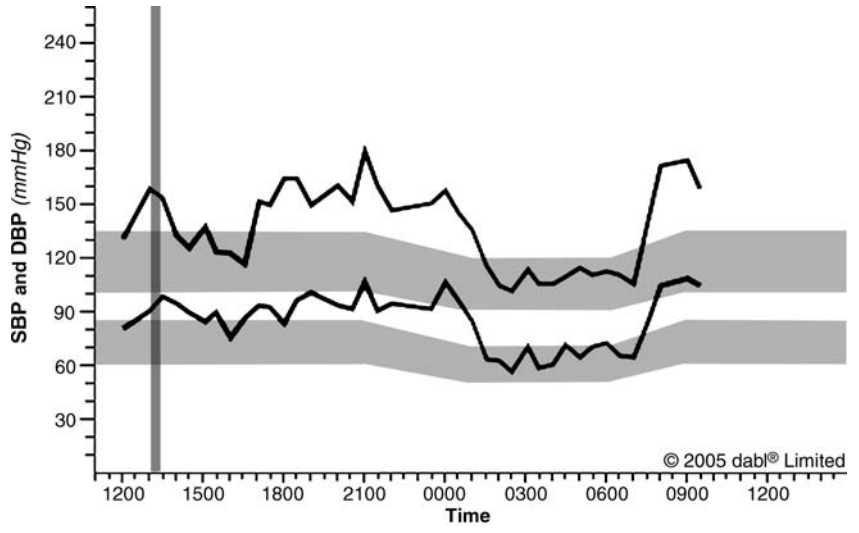

Fig. 7.9 Hypertensive dipper: On the basis of the recorded data and available literature, ambulatory blood pressure suggests mild daytime systolic and diastolic hypertension (147/93 mmHg) and normal nighttime SBP and DBP (111/66 mmHg) with white coat effect (158/90 mmHg). *Abbreviations*: DBP, diastolic blood pressure; SBP, systolic blood pressure. *Source*: Plot and report generated by dabl ABPM, 2006 (http://www.dabl.ie).

(1,9,91). Individualized antihypertensive medication targeting disrupted diurnal BP variation may be particularly protective in the high-risk groups, such as patients with a rise in nocturnal BP and in extreme dippers (57,92).

As much of the morning surge may be mediated by involvement of the renin–angiotensin–aldosterone system (RAAS), it would seem logical to assess agents targeting angiotensin II (1,93,94). Another mechanism worthy of manipulation to enhance nocturnal pharmacological therapy is dietary potassium supplementation and sodium restriction to restore normal dipping (9).

The consistent lowering of nocturnal BP by the renin inhibitor aliskiren, in combination with a thiazide diuretic, an ACEI or an angiotensin receptor blocker, opens up potential for these therapeutic strategies to be used to reduce nocturnal hypertension (95).

The evidence to date clearly suggests that pharmacological research should be directed toward designing drugs with the

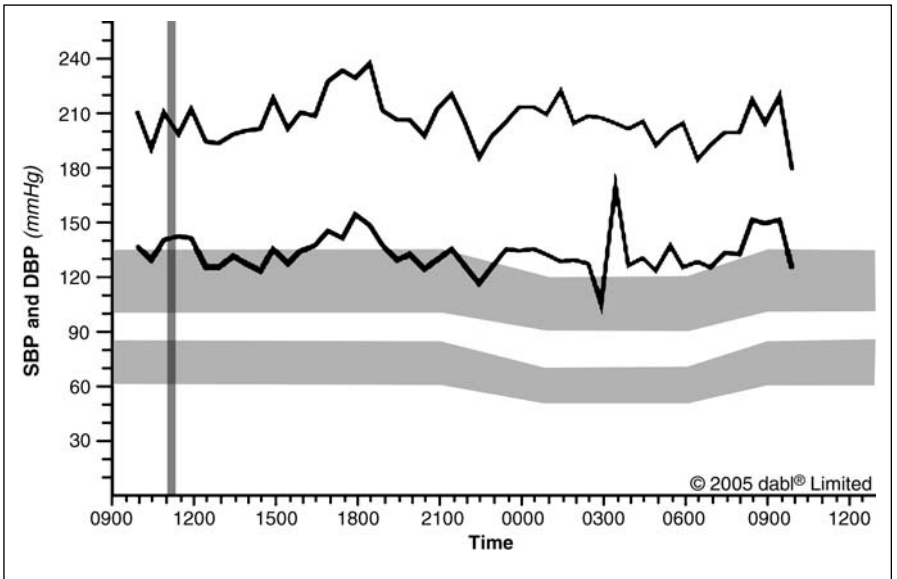

Fig. 7.10 Hypertensive non-dipper: On the basis of the recorded data and available literature, the pattern suggests severe systolic and diastolic hypertension over 24 h (209/135 mmHg daytime and 205/130 mmHg at night). *Abbreviations*: DBP, diastolic blood pressure; SBP, systolic blood pressure. *Source*: Plot and report generated by dabl ABPM, 2006 (http://www.dabl.ie).

primary purpose of modifying the nocturnal manifestations of hypertension.

However, it should also be possible to modify nocturnal BP by using the drugs presently available, but dosing at bedtime rather than in the morning. As has been shown in the HOPE study, the simple expedient of dosing at night rather than in the morning may have a profound effect on nocturnal BP (86–88). Hermida and his colleagues examined the hypothesis that non-dipping in hypertensive patients might be due, at least in part, to the absence of 24-h therapeutic coverage in patients treated with single morning doses, and they showed that, in patients taking bedtime medication, ABPM control was double that of patients taking morning medication. Moreover, in patients with true resistant hypertension, bedtime medication resulted in a significant reduction in the 24-h mean of systolic and diastolic BP, and this reduction was much more prominent during nighttime (96). Bedtime dosing with an ACEI in patients with a non-dipping pattern improves efficacy during the nocturnal period (97).

Antihypertensive medication directed at nighttime BP may not necessarily alter nocturnal patterns for the better. For example, a non-dipping or dipper pattern could be transformed into an extreme dipping pattern with injudicious therapy. The objective should be to reduce BP at the same time as preserving the physiological dipper circadian pattern. This is particularly important in stroke survivors in whom ABPM is mandatory to determine the appropriate dose and the optimum time of administration of antihypertensive drugs so as to avoid the non-dipper, riser, and extreme-dipper circadian profiles induced by treatment (98). Given the extensive evidence for the increased prevalence of cardiovascular events in the early morning hours, antihypertensive drugs that provide BP control at the time of the early morning surge should provide greater protection against target-organ damage and enhance patient prognosis. This period has been dubbed the "blind spot" in current clinical practice (99). Pharmacological research into ways of altering the morning surge is limited, but candesartan has been shown to be superior to lisinopril in decreasing morning BP and the morning BP surge (2,100). Moreover, reduction in the morning rise in BP may be beneficial in preventing target organ involvement in hypertension (101).

CONCLUSION—ABPM IS INDISPENSABLE TO GOOD CLINICAL PRACTICE

Not for the first time, a review of this nature serves to reinforce the clinical message that is so sadly being neglected: ABPM is indispensable to good clinical practice (12). The advantages for the technique are many. First and foremost, the technique simply gives more measurements than conventional measurement, and the real BP is reflected more accurately by repeated measurements; ABPM provides a profile of BP away from the medical environment, thereby allowing identification of individuals with a white coat response, or masked hypertension, who are in need of careful management; ABPM shows BP behavior over a 24-h period, rather than giving a snapshot of BP performed with an inaccurate technique under artificial circumstances, so that the efficacy of antihypertensive medication over a 24-h period becomes apparent, rather than relying on one or a few conventional measurements confined to a short period of the diurnal cycle; ABPM can identify patients with abnormal patterns of nocturnal BP—dippers and non-dippers, extreme and reverse dippers, and those with a morning surge—all of whom are at high risk, and ABPM can be used to target these potentially dangerous patterns with appropriate drugs; ABPM can demonstrate a number of patterns of BP behavior that may be relevant to clinical management—isolated systolic and isolated diastolic hypertension, post-prandial hypotension, autonomic failure, etc. Finally, and importantly, evidence is now available from longitudinal studies that ABPM is a much stronger predictor of cardiovascular morbidity and mortality than conventional measurement—in other words, ABPM identifies patients with hypertension (and subjects whose BP is normal) who are at risk of future cardiovascular events. Moreover, the evidence is growing that nocturnal BP measured by ABPM may be the most sensitive predictor of cardiovascular outcome, from which it follows that the measurement of nighttime BP should be an important part of clinical practice. However, there are those who would disagree. Pickering argues that, until more evidence is available, "it would seem reasonable not to recommend routine measurement of the nighttime BP" (102). This recommendation, in my view, flies contrary to the evidence. But, arguable though this might be, surely we can only learn about the importance of nocturnal BP by measuring it! Had I decided in my clinical practice not to record nighttime BPs when I began recording ABPM in the 1980s I would not now have the data from some 20,000 patients in the Dublin Outcome Study that has permitted analyses to show that nocturnal BP is superior to all other measurements in predicting cardiovascular outcome (26). The inevitable conclusion of this review would seem, therefore, that there should now be international acceptance that 24-h ABPM is an indispensable investigation in patients with established and suspected hypertension, and that it should therefore be available to all hypertensive patients.

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BLOOD PRESSURE VARIABILITY: METHODOLOGICAL ASPECTS, PATHOPHYSIOLOGICAL AND CLINICAL IMPLICATIONS

8

Gianfranco Parati, Grzegorz Bilo, Mariaconsuelo Valentini

INTRODUCTION

Blood pressure (BP) is a highly dynamic parameter, which, both in normotensive and hypertensive subjects, is characterized by continuous fluctuations. Recent data provided by experimental and clinical studies have demonstrated that the assessment and detailed quantification of BP variability (BPV) is of pathophysiological and prognostic importance in subjects with hypertension. In fact, independently from absolute mean BP levels, the magnitude of BPV appears to reflect specific patterns of autonomic cardiovascular regulation and to correlate with the presence and severity of target organ damage (TOD) and the rate of cardiovascular events. These associations suggest that the benefits of hypertension treatment, in terms of TOD prevention or regression, and in terms of event rate reduction, might be greater by targeting not only mean BP level reduction but also the attenuation of an enhanced BPV The same benefit appears to characterize the preservation or restoration of a physiological day–night BP profile.

This chapter summarizes the: (*i*) currently available methods to assess BPV, with their specific advantages and limitations; (*ii*) evidence linking BPV with morbidity and mortality in hypertension; and (*iii*) the potential prognostic impact of lowering BPV together with mean BP levels in hypertension treatment.

HOW TO MEASURE BPV

The oscillations which characterize BP under physiological conditions, as a result of the interplay among different cardiovascular homeostatic mechanisms, were first recognized at the beginning of the 18th century by Stephen Hales. However, assessing BPV in a clinical setting became possible only at the end of the 19th century with the advent of the sphygmomanometric technique, introduced by the Italian scientist Scipione Riva Rocci (1).

A further progress in the definition and quantification of BPV was the development of the miniaturized intra-arterial Oxford System in the 1960s (2), which allowed continuous monitoring of BP fluctuations occurring on a beat-by-beat basis in ambulant humans (3)over the 24-h period (Figure 8.1). The rich amount of information on the characteristics of BP changes over 24 h provided by this technique has allowed the detailed description of all components contributing to overall 24 h BP variance. These include fast changes occurring with exercise and under the effects of behavioral and emotional stimuli. They also include more long-lasting changes, such as those occurring between wakefulness and sleep. In particular, the latter component is characterized by several hours of BP decrease during nighttime sleep and by a brisk BP increase in early morning hours, with an additional decrease in the early afternoon during siesta.

The development and diffusion of noninvasive ambulatory BP monitoring (ABPM) techniques (4) in more recent times has allowed intermittent monitoring of BP over 24 h via automated arm cuff inflations in a continuously increasing number of subjects. BP readings are usually obtained through the oscillometric method, while the microphonic technique to record Korotkoff sounds is employed in a minority of devices only. Unfortunately, the time intervals usually scheduled between automated readings by conventional ABPM techniques (usually ranging between 15 and 30 min) do not allow short-lasting BP changes to be quantified. Moreover, overall 24 h BPV, as quantified by the standard deviation (SD) of 24 h average BP values, cannot be reliably assessed in case of between measurement intervals longer than 10–15 min (5) (Figure 8.2). In spite of these methodological difficulties, noninvasive ABPM is now widely used to estimate not only mean BP levels but also BPV in clinical practice (Figure 8.3). Being noninvasive and readily available on a large

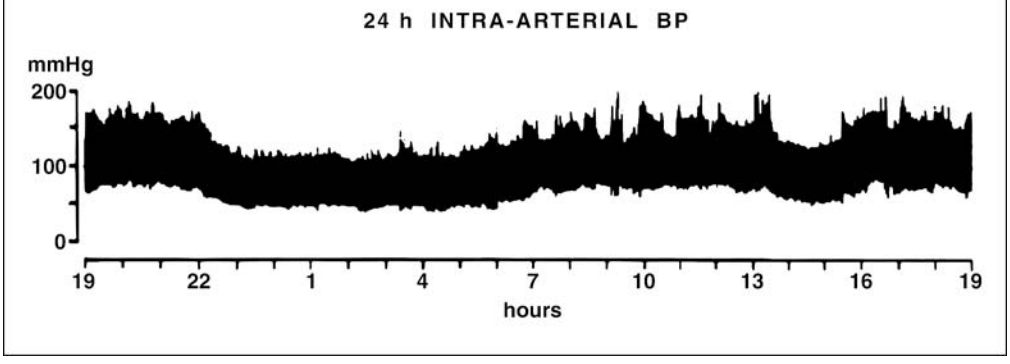

Fig. 8.1 Original 24 h beat-by-beat blood pressure (BP) tracing obtained in an ambulant subject through the Oxford technique, based on insertion of an intra-arterial catheter in a peripheral artery. *Source*: Modified from Ref. 3.

scale, ABPM has allowed the definition of the circadian pattern characterizing a physiological 24 h BP profile in populations of subjects. It has also offered the possibility to quantify its alterations in patients at higher risk of cardiovascular events, strongly supporting the potential role of an enhanced BPV in determining hypertension-related TOD and an increased rate of cardiovascular events More recent progress in the field has led to the development of an innovative approach that is able to overcome the relative inaccuracy of conventional ABPM in assessing BPV. This approach is based on a technique able to monitor BP noninvasively on a beat-by-beat basis at the finger level in ambulant subjects, during their daily activities. This technique, implemented in the Portapres® (Finapres Medical Systems, Arnheim, The Netherlands) device (6), makes use of a servo-adjusted finger cuff inflation system combined with an infrared photoplethysmograph and a hydrostatic height correction tool able to continuously monitor finger BP changes in a calibrated fashion in ambulatory conditions over 24 or 48 h. The quantification of 24 h BP profiles as well as the assessment of fast BP fluctuations provided noninvasively by this approach were found to be similar to those obtained by simultaneous intra-arterial BP monitoring (6,7).

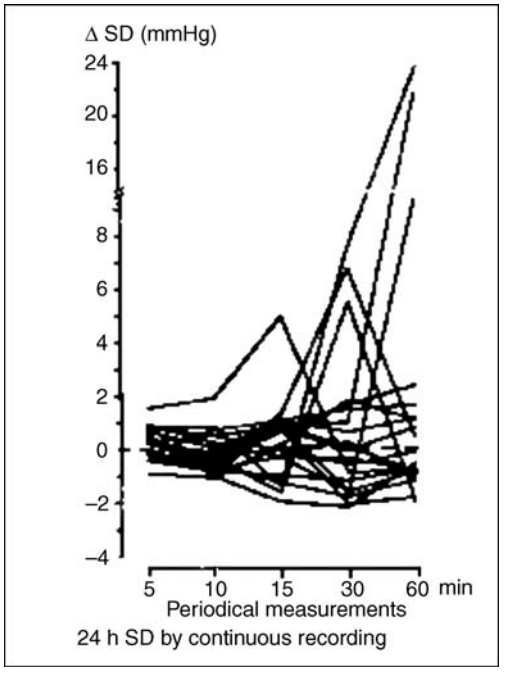

Fig. 8.2 Errors in the calculation of the 24 h mean arterial pressure (MAP) standard deviation (SD) in case of intervals between blood pressure (BP) samples longer than 10–15 min. Data are derived from computer analysis of continuous intra-arterial BP recordings, by considering samples taken at different time intervals, namely every 5, 10, 15, 30, 60 min, i.e., by simulating what happens with discontinuous ambulatory BP monitoring. *Source*: Modified from Ref. 5.

HOW TO QUANTITATIVELY ANALYZE BPV

Several methods have been proposed to obtain a quantitative description of the BP variations occurring over the 24-h period. Such methods include: (*i*) the simple calculation of the BP changes occurring in response either to specific behaviors or to the shifts between day and night (i.e., night BP dipping, morning BP surge); (*ii*) the quantification of statistical indices of BP value dispersion, such as the variance or the SD of average mean BP values over a given recording period; and (*iii*) more complex computations, like spectral analysis, focusing on BP fluctuations in the frequency domain (8,9) (Table 8.1).

At present, the method most commonly employed to compute BPV in both pathophysiological and clinical studies is still based on the quantification of the SD of average BP values calculated either over the entire 24-h period or over the daytime or the nighttime subperiods, respectively.

Of notice, if continuous BP recordings are available, the calculation of the BP SD allows to quantify both the short-lasting and the long-lasting components of BPV. In the pioneering studies based on the use of intra-arterial BP recordings, an approach followed to separately assess short-term and long-term BPV over 24 h was the following. Estimate of short-term BPV consisted in the calculation of the SD of each half hour mean BP value, followed by the calculation of the average of these 48 half-hour SDs. This average value

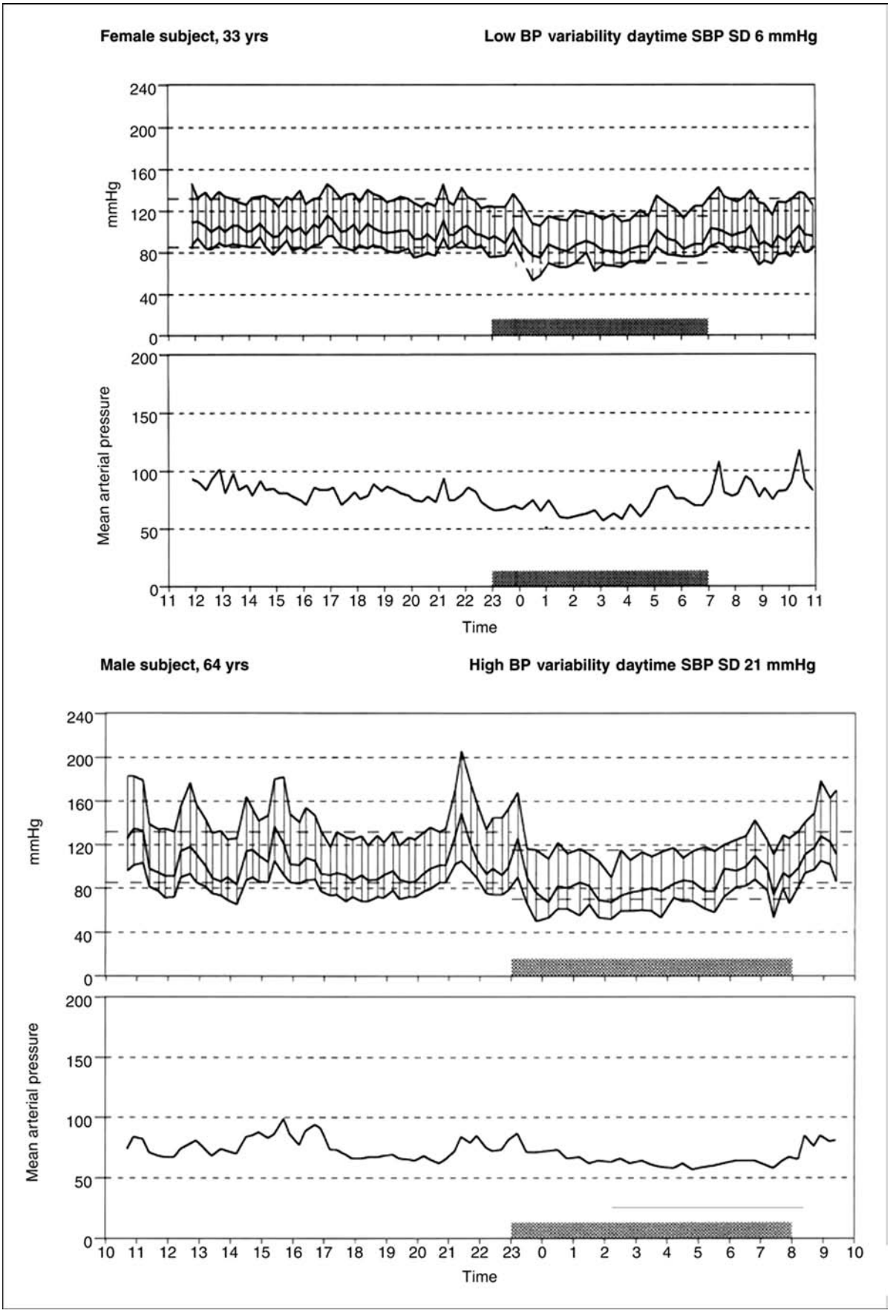

Fig. 8.3 Original tracings of 24 h conventional ambulatory blood pressure (BP) monitoring in two subjects characterized by normal (*upper panel*) or increased (*lower panel*) daytime BP variability.

Table 5.1 Methods for the analysis of blood pressure (BP) variability

Ranges of values over the recording period
Standard deviation (SD) of the average BP over the recorded signal
Coefficient of variation (SD × 100/mean value)
Frequency distribution histograms or curves
Spectral analysis

was defined as "within half hour SD" (3). In the same study, long-term BP changes were assessed by computing the mean BP value for each of the 48 half hours in which the 24 h recordings were subdivided. By subsequently averaging these 48 half hour mean BP values, the 24 h average BP was calculated with its SD, which was taken as a measure of long-term BPV ("among half-hour SD"), mostly reflecting circadian variations (Figure 8.4).

Thanks to these studies, it has been possible to establish that BPV, particularly short-term BPV, increases in parallel with age and with the increase of mean BP levels (3). Moreover, BPV is greater during the daytime and under physical activity and lower during the nighttime or during rest.

BPV AND HYPERTENSION

In studies carried out in both experimental animals and humans, BPV was found to progressively increase with the increase in BP mean levels, hypertensive animals, or subjects, showing a greater BPV than their normotensive counterparts (9). A clear demonstration of this phenomenon was provided by the analysis of 24 h ambulatory intra-arterial BP recordings carried out in a group of normotensive and in a group of hypertensive subjects over 24 h under relatively standardized behavioral conditions (3) thanks to the Oxford technique (10). Hypertensive patients, as compared to normotensive subjects, exhibited greater short-term (within half-hour SD) and long-term (among half-hour SD) BPV. Moreover, within each BP group, the amplitude of BP variations increased in parallel with the increase in mean BP levels over the 48 half-hour subperiods. This indicates that normotensive and hypertensive subjects differ not only in terms of mean BP levels, but also in terms of the amplitude of their BP fluctuations all over 24 h. A research question that has been raised since the time of the first studies on this issue was thus whether the increased cardiovascular risk which characterizes hypertensive patients depends on an increase in mean BP levels only, or also on a combined increased in the degree of BPV.

ASSOCIATION OF BPV WITH TARGET ORGAN DAMAGE AND RATE OF CARDIOVASCULAR EVENTS

Several investigations have addressed the issue of the occurrence of a possible independent association between increased BPV and the cardiovascular consequences of hypertension, over and above the well-known association between these complications and an increase in mean BP levels.

TOD was repeatedly demonstrated to be independently related to the degree of BPV, an enhanced BPV being associated with a more severe TOD and/or with a higher rate of cardiovascular events in both the general population and in selected cohorts of subjects with hypertension. This was shown to be the case when focussing on the degree of BP fluctuations occurring during either the daytime (11,12), the nighttime (13), and the whole 24-h period (14). Probably the first demonstration of the clinical relevance of BPV was

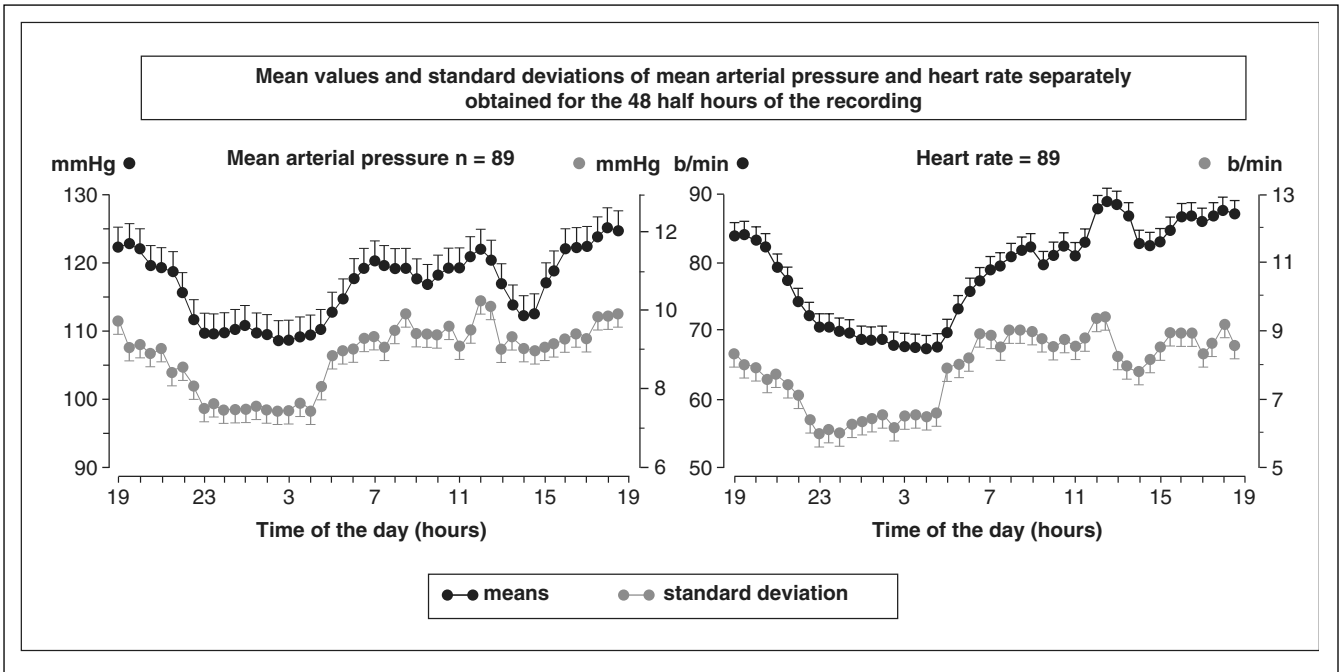

Fig. 8.4 Blood pressure (BP) and heart rate variability over 24 h in a group of 89 hypertensive patients. Black circles refer to average half-hour values (*upper*) and grey circles refer to half-hour standard deviations (*lower*). Data are separately shown for mean arterial pressure (*left panels*) and heart rate (*right panels*). *Source*: Modified from Ref. 3.

provided by a study from our group, which showed the occurrence of an independent association between BPV and TOD in 108 mild-to-severe essentially hypertensive patients, whose BP was invasively monitored for 24 h in ambulatory conditions (14). Both 24 h mean BP and 24 h BPV were independently related to the prevalence and severity of TOD, quantified by an overall score, and such relationship was closer for 24 h mean BP and 24 h BPV than for clinic BP. Of notice, at any given 24 h mean BP value, the prevalence and severity of TOD were linearly related to the extent of short-term and long-term BPV (Figure 8.5). Subsequent longitudinal observations in subjects with high BP (15) provided further support to the concept that BPV has a predictive value in relation to the complications of hypertension, as indicated by the above original cross-sectional findings. The first demonstration of the prognostic value of BPV was again obtained through the intra-arterial assessment of 24 h ambulatory BP and BPV by the Oxford technique in 73 out of the above 108 hypertensive patients, who were subsequently followed up for an average period of 7.4 years. In these patients, baseline long-term BPV (so-called "among half-hour SD" of 24 h mean BP) was found to be a determinant of the occurrence of hypertension-related cardiovascular complications, particularly of an increase in left ventricular mass index (LVMI), over the follow-up period. This relation was independent of the effect on LVMI exerted by an increase in mean 24 h BP levels (Figure 8.6). Other determinants of LVMI in this study were the value of clinic BP at follow-up visits and the entry level of TOD.

These longitudinal observations were confirmed in experimental animals, in which BPV (but not mean BP) had been artificially increased by sino-aortic denervation (SAD), i.e., by surgical interruption of the afferent fibers stemming from the carotid and aortic baroreceptors. Despite stable mean BP levels, the increased BPV determined by this procedure was found to be associated with the appearance of signs of vascular and cardiac damage a few months after SAD (16–20).

The increasing use of 24 h conventional ABPM has allowed for large-scale studies based on parameters derived from analysis of these ABPM recordings ABPM in humans. These studies, in most cases, have further supported the association of BPV with TOD. Making use of this technique, both greater daytime systolic BP (SBP) levels and daytime SBP variability were found to be associated with more advanced vascular damage on fundoscopic examination and with more pronounced left ventricular hypertrophy (on electrocardiogram and chest roentgenogram) (13) in over 700 subjects either with normal BP levels or with hypertension of various severity. Similar results were obtained, again by means of conventional 24 h ABPM, in 1,663 hypertensive subjects enrolled in the European Lacidipine Study on Atherosclerosis (21). Subjects were first divided into quintiles based on 24 h mean BP. Subsequently, quintiles were divided into two subgroups, with BPV either greater or lower than the subgroup average BPV level, respectively. Interestingly, a strong linear relationship was demonstrated between carotid artery intima-media thickness (IMT), assessed from

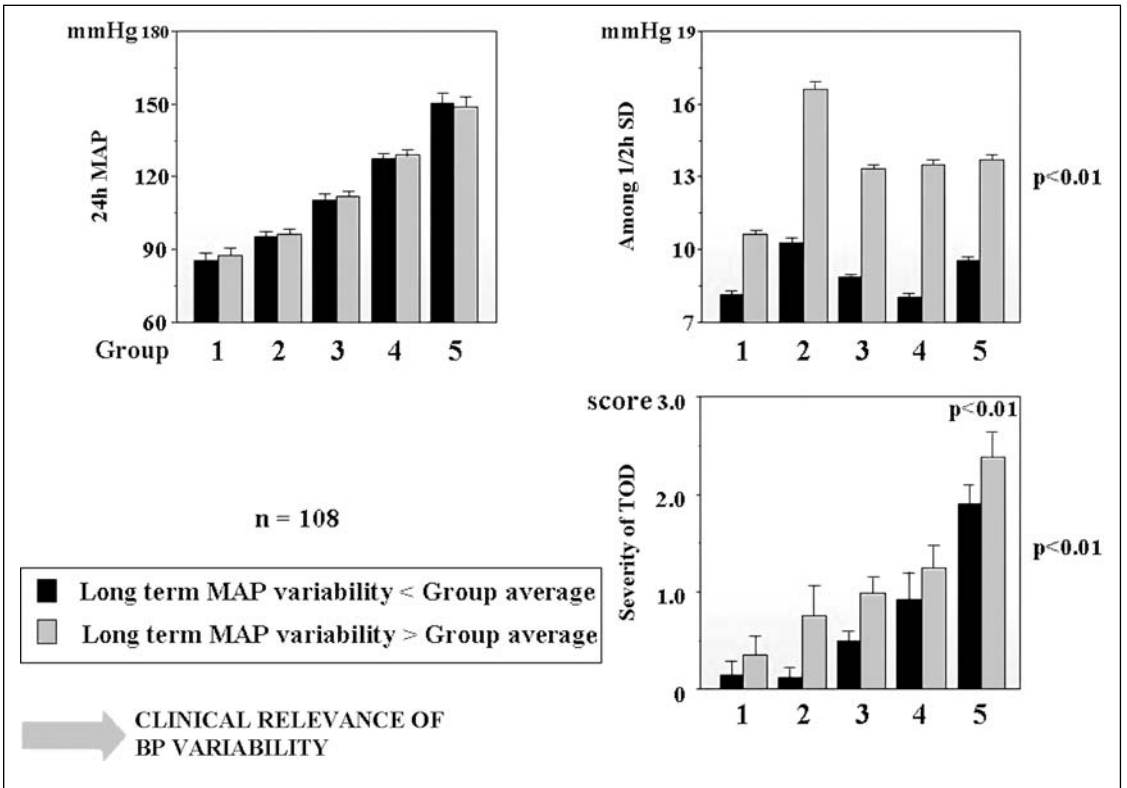

Fig. 8.5 The rate and severity of target organ damage (TOD) was assessed in 108 subjects divided into five groups according to the increasing value of their 24-h average mean arterial pressure (MAP). The subjects in each group were further subdivided into two classes according to whether their among-half-hour standard deviation of MAP (long-term variability) was below or above the average short-term variability of the group. Note that within each group the two classes had a similar 24 h MAP, but that the rate and severity of TOD was less in the class in which long-term variability was lower. *Source*: From Ref. 14.

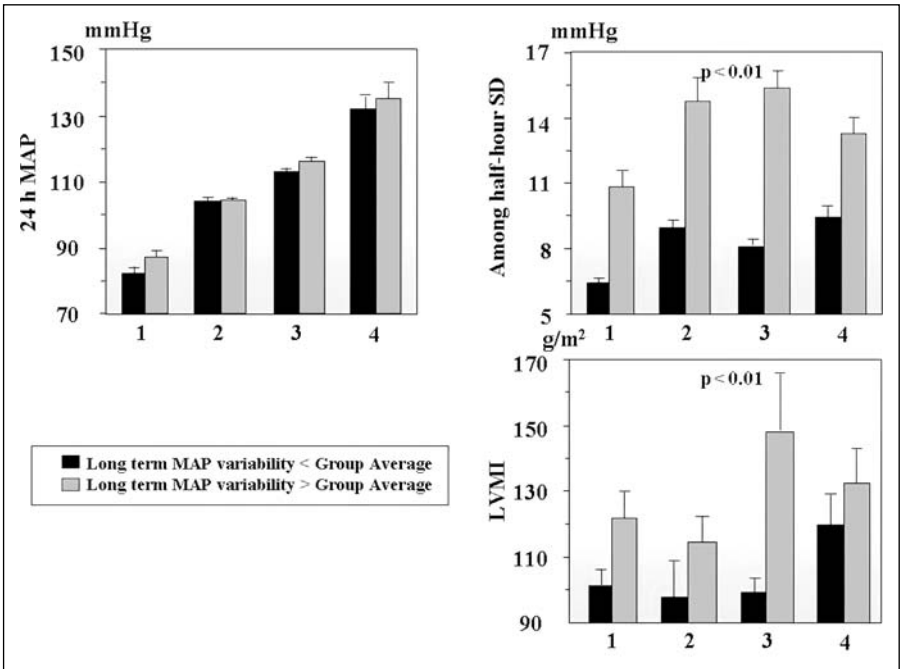

Fig. 8.6 Severity of end-organ damage and left ventricular mass index (LVMI) in 73 subjects divided into four groups according to the increasing value of the 24 h average mean intra-arterial pressure (MAP). The subjects in each group were subdivided into two classes according to whether the among-half-hour standard deviation of MAP (long-term variability) at the initial evaluation was above (*grey bars*) or below (*black bars*) the average long-term variability of the group. Within each group the two classes had similar 24 h MAPs, but the severity of end-organ damage and LVMI assessed at the follow-up evaluation were lower in the classes in which long-term variability was lower. For each class, the severity of damage was expressed as the average score for all subjects in that class or as the average value of LVMI (echocardiography). $P < 0.01$, difference between all pairs of classes. *Source*: From Ref. 15.

repeated ultrasound examinations, and overall 24 h SBP and PP variability. As expected, the same linear association was demonstrated between IMT and 24 h, day and night, mean SBP levels. Overall, the results of this study are extremely relevant from a clinical standpoint, as they support the role of both 24 h BPV and 24 h mean BP levels in determining the large artery damage.

Data on the association of BPV with TOD have also come from the PAMELA (Pressioni Arteriose Monitorate E Loro Associazioni) study (22) in which BPV was computed by analysis of 24 h ABPM performed by validated oscillometric BP measuring devices, with automated cuff inflations scheduled at 20 min intervals. LVMI was assessed by echocardiography in a random sample of 1,648 untreated subjects selected from the general population of a wide area north of Milan. From these recordings, 24 h mean SBP and diastolic BP (DBP) levels and their 24 h SD (overall variability) were assessed. Computer analysis of ABPM recordings also allowed the calculation, by Fourier analysis, of the amplitude of those cyclic components of BPV capable of accounting for over 95% of the overall BPV. Finally, the proportion of overall 24 h SBP and DBP variability that was not explained by the two main cyclic components identified by the Fourier approach (residual variability) was also calculated. Both 24 h mean SBP and DBP and their "residual" BPV were significantly and independently related to LVMI, thus demonstrating that also in the general population BPV, in this case mostly its faster components, play a role that can be clinically relevant.

The contribution of BPV to the incidence of cardiovascular events was also suggested by studies including large samples of subjects, thanks again to the possibility to perform noninvasive 24 h ABPM. In 286 hypertensive patients followed up for over 3 years, Sander et al. (11) performed 24 h ABPM and assessed the IMT of the common carotid artery by ultrasound. The degree of BP variation over 24 h and the daytime period was also assessed. At the end of the follow-up period, independently of traditional risk factors, the vascular lesion had progressed more rapidly in case of greater SBP variability. Moreover, daytime SBP variability was the best predictor of IMT progression on multivariate analysis and was associated with a greater risk of events of cardiovascular origin (Figure 8.7).

Finally, the performance of 24 h ABPM and subsequent longitudinal observations carried out in the general Japanese population of Ohasama have offered a clear demonstration that both increased SBP variability and decreased HR variability are significant and independent predictors of cardiovascular mortality (12), confirming what had already been demonstrated in hypertensive subjects (23,24) (Figure 8.8).

An overview of all these studies thus allows us to conclude that BPV may have prognostic relevance.

Overall, studies exploring alterations in 24 h BPV have demonstrated that an increase in the degree of BP fluctuations over 24 h is associated with both TOD and increased rate of cardiovascular events (25). In particular, an association with

these complications has been reported for an increased frequency and amplitude of BP variations occurring during the daytime (11,12), the nighttime (26), or during the entire 24 h period (15). Additionally, prognostic implications have also been reported for alterations in the BPV components related to the BP transition between the daytime and nighttime. This includes alterations in either the degree of nocturnal BP decline and the morning BP surge. Studies evaluating the shift between wakefulness and sleep have demonstrated that a blunted nocturnal BP fall (i.e., a non-dipping status) is associated with an increased risk of stroke (27–30), whereas conflicting results are available on the prognostic implications of an excessive BP fall at night (known as extreme dipping) (31,32). Most (31,33,34), although not all (27), of the studies evaluating the BP changes between sleep and wakefulness have also demonstrated an association between a steeper morning BP surge and a higher risk of cardiac and cerebrovascular events. Moreover, in a large population followed up for several years, a significant morning BP surge and an extreme BP dipping pattern (nocturnal BP fall >20% of daytime levels) have been found associated with each other, as well as with a greater prevalence of hemorrhagic stroke. Conversely, a non-dipping or an inverse dipping status was associated with a greater prevalence of cerebral infarctions (35).

PROBLEMS WITH THE ASSESSMENT OF BPV AS AN ADDITIONAL RISK FACTOR

Although the available evidence linking BPV and prognosis in patients with arterial hypertension is quite intriguing and has suggested the possibility of broadening the traditional goals of hypertension treatment, a number of limitations pertaining to the quantification of BPV throughout the 24 h period still affect the full assessment of its clinical relevance. First, the different methods used to quantify BPV might be responsible for some of the discordant findings observed so far. These variable methods comprise the assessment of BPV in absolute or in normalized units by using either the SDs of mean BP values or their coefficients of variations (i.e., SD × 100/mean BP level). They also include the different choice of assessing BPV all over the entire 24-h period by computing the conventional SD of average 24 h BP or its weighted value (36), or of focusing on the daytime or on the nighttime periods only. Second, the daytime and nighttime subperiods are often differently defined. In some of the investigations, the information coming from individual patients' logbook was adopted to separate the daytime from the nighttime; while, in some other studies, fixed criteria for separating the day and night periods were followed. This was done by considering either the whole 24 h recording period (wide fixed criteria) or by skipping transitional periods, i.e., by excluding a few hours in the evening and in early morning (narrow fixed criteria). Third, limited information is available on the reproducibility of different BP variability patterns. In particular, in serial 24 h ambulatory BP recordings, the reproducibility of the nocturnal BP dipping and of the morning BP surge was very poor, not exceeding 60% in one investigation (37). Fourth, the entity of the nocturnal BP fall, regarded as a desirable pattern of 24 h BPV, correlates with that of the morning BP rise, which is characterized by an opposite prognostic meaning. This means that two phoenomena having a different clinical impact are closely interrelated, which calls for new approaches to their quantification. Fifth, the prognostic role of BPV was evaluated in studies that enrolled subjects coming sometimes from the general population (32) and sometimes from groups of hypertensive patients under different treatment (31). Finally, although there is no question on the superiority of continuous BP monitoring over intermittent techniques in the detailed assessment of both fast and slow BPV components, in clinical studies only intermittent ABPM devices are commonly available, which means that fast BP changes cannot be assessed, and even slower BP fluctuations can only roughly be quantified. Use of discontinuous ABPM might explain some of the discrepant results obtained on the clinical relevance of BPV (38), possibly due to methodological differences in setting the frequency of the discontinuous automated BP measurements (Table 8.2).

BPV AND ANTIHYPERTENSIVE TREATMENT

Both an increase in TOD and in the frequency of cardiovascular complications are associated with enhanced BPV in subjects with increased BP levels. This association seems to support the concept that, in the management of patients with arterial hypertension, both the reduction of overall 24 h BPV and the normalization of deranged variability patterns could become additional targets of antihypertensive treatment besides mean 24 h BP reduction per se.

In practice, this suggests that a smooth reduction in BP all over the 24 h is a desirable result, facilitating achievement of a less pronounced 24 h BPV. Moreover, the above data also suggest that the correction of a steep morning BP surge might decrease the rate of cardiovascular events, in particular of hemorrhagic stroke, and that the restoration of the proper BP decline in non-dipper patients and in patients with an inversion of the nocturnal physiological BP dipping status might prevent the occurrence of ischemic strokes.

Nevertheless, a definitive demonstration that the correction of deranged BPV patterns can have a positive impact on prognosis is still missing in humans. Only data obtained in experimental animals appear to be available at the moment. In spontaneously hypertensive rats (39) treated with nitrendipine (reducing both mean BP and BPV), TOD showed a greater regression compared to spontaneously hypertensive rats treated with hydralazine (similarly reducing BP

Table 8.2 Problems in assessing the clinical relevance of blood pressure variability (BPV)

Limited reproducibility of BPV
Lack of BPV normal reference values and their dependence on subjects' behavior during BP monitoring
Limitations of conventional discontinuous, low frequency, ambulatory BP monitoring in assessing BPV (oversmoothing, aliasing, overmodeling, failure to assess fast BP changes)
Possible different impact of BPV on vascular and cardiac targets
Inclusion of different populations of subjects in different studies (differences in age, gender, ethnicity, BP levels, presence or absence of antihypertensive treatment)
Need of evidence from intervention trials that reduction of overall BPV, improvement of nocturnal BP decline, and/or buffering of a steep morning BP surge by treatment might lead to reduction in cardiovascular morbidity and mortality

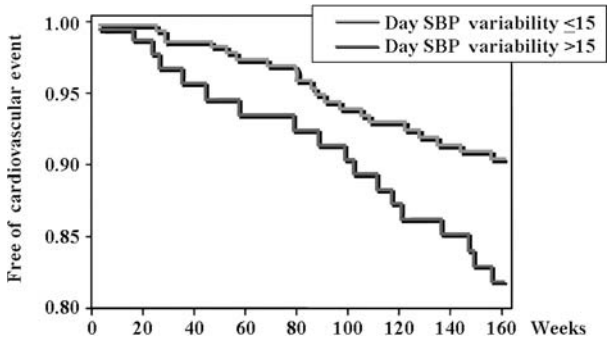

Fig. 8.7 Kaplan–Meier survival analysis for fatal and nonfatal cardiovascular morbid events in patients with increased (>15 mmHg) and normal (≤15 mmHg) systolic blood pressure (SBP) variability. *Source*: From Ref. 11.

but without any effect on BPV). Moreover, TOD showed a stronger correlation with BPV than with mean BP levels in the group receiving nitrendipine.

On the background of the above considerations, antihypertensive drugs should thus lower not only mean BP levels but also BPV. Medications often fail to obtain a decrease in short-lasting BP fluctuations because of their inability to overcome the autonomic nervous system contribution to the amplitude and speed of BP changes (8). However, they may at least succeed in decreasing the overall 24 h BPV if they smoothly exert their antihypertensive effect during the dosing interval, providing us with a homogenous downshift in the 24 h BP profile, towards lower BP levels. Drugs characterized by long duration and by smooth effect, i.e., an effect without important differences between peak and trough BP changes, have the highest probability of achieving such goals, unlike short-acting drugs, which soon loose their antihypertensive affect after dosing, and thus are responsible for an iatrogenic increase in the amplitude of BP swings between peak and trough times. In particular, if short-acting drugs are scheduled in the morning, they will not provide an adequate BP-lowering effect by the end of the 24 h dosing period, i.e., right at the trough time next morning, when subjects experience the sympathetically-driven increase in BP and HR upon waking and are exposed to the highest risk of cardiovascular and cerebrovascular events (26,31,40,41). According to recent observations, antihypertensive drugs with a short half-life taken in the morning may not adequately control the BP at the end o f the dosing period, i.e., the next morning, in as many as 62–85% of the patients. On the contrary, longer acting drugs, like the angiotensin II receptor blocker telmisartan and the dihydropyridine calcium channel blocker amlodipine (42,43)or nifedipine in its gastrointestinal therapeutic system (GITS) preparation, perform much better in this regard.

To evaluate the overall performance of an antihypertensive medication, not only in terms of mean BP reduction but also in terms of smoothness and duration of antihypertensive affect, a few quantitative indices have been suggested.

TROUGH-TO-PEAK RATIO

The trough-to-peak (T:P) ratio was developed in an attempt to summarize both the duration and the distribution of the BP-lowering effect of an antihypertensive medication during the dosing interval (44). Despite being introduced at a time when the BP-lowering effect of a medication was determined by standardized sphygmomanometric measurement, it is now more commonly extracted from a 24 h ABPM by dividing the trough BP changes, i.e., the BP reduction at the end of the dosing interval, by the peak BP changes, i.e., the BP reduction corresponding to the maximum effect of the drug.

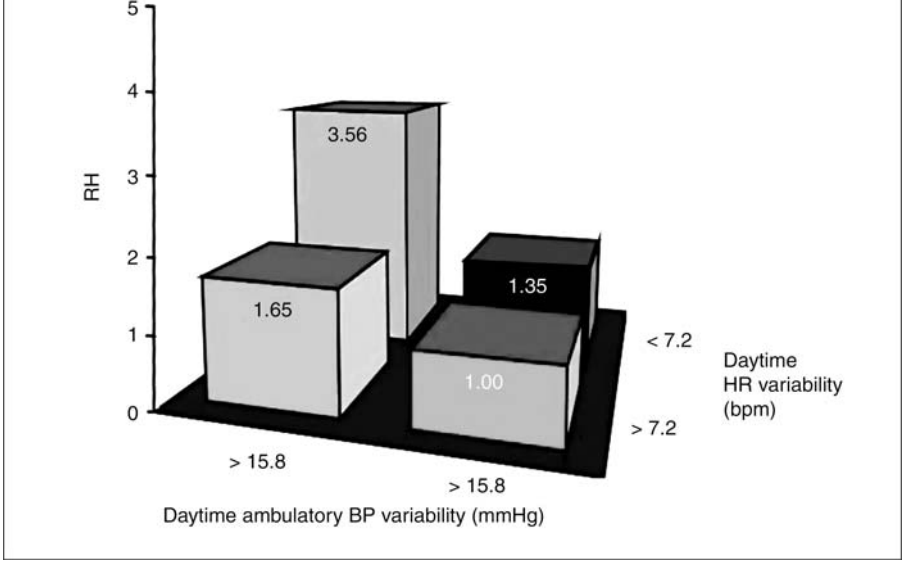

Fig. 8.8 Relative hazard (RH) and 95% confidence interval (CI) for cardiovascular mortality among combinations of daytime ambulatory blood pressure (BP) and heart rate (HR) variability. *Source*: From Ref. 26.

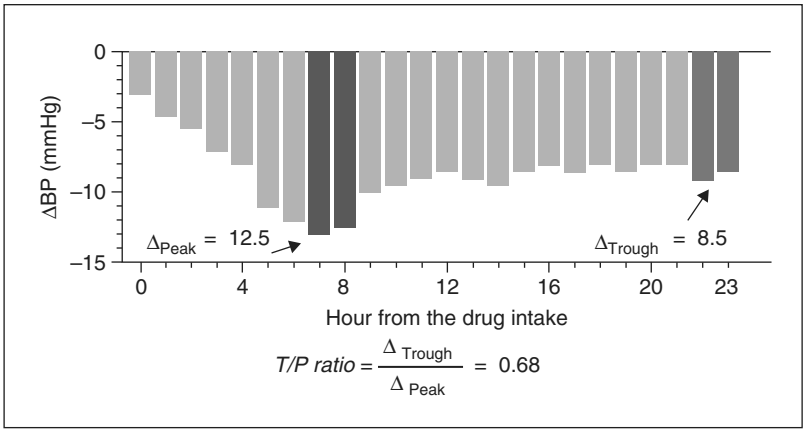

Fig. 8.9 Calculation of the trough/peak ratio (T/P) from hourly blood pressure (BP) values obtained before and during treatment by 24 h ambulatory BP recordings. *Source*: From Ref. 46.

Although the ideal antihypertensive medication providing a homogeneous BP-lowering effect throughout the dosing interval is characterized by T:P ratio equal to 1, medications with a T:P ratio down to 0.5 are commonly approved by the United States Food and Drug Administration (45).

A few limitations make the T:P ratio a rather imprecise index of the overall entity and homogeneity of the BP-lowering effect of an antihypertensive medication (9). First, it can be affected by BP variations occurring either spontaneously or as a result of patients' posture and behaviours; additionally, it concentrates only on two short time intervals, thus potentially missing valuable information relative to the remaining part of the 24 h period (Figure 8.9). Finally, a compound with a negligible BP-lowering effect both at peak and at trough times, like placebo, can have a T:P ratio as high as 1 (46).

SMOOTHNESS INDEX

In an attempt to overcome the limitations of the T:P ratio, a new index aimed at assessing the distribution of the antihypertensive effect of a given drug all over the 24 h, termed the smoothness index (SI), was introduced (47). As for the assessment of the T:P ratio, in order to calculate the SI, two 24 h ABPMs are needed: before and during treatment with

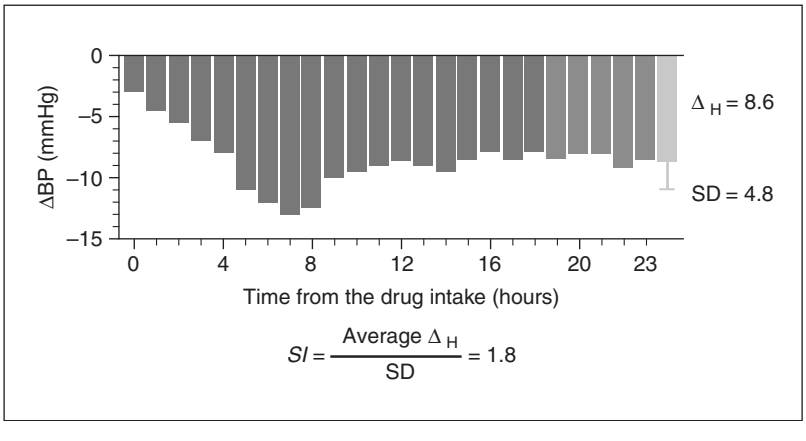

Fig. 8.10 An example of the calculation of the smoothness index (SI). ΔH = average of the 24 h blood pressure (BP) changes between baseline and treatment. SD = standard deviation of the average of the 24 h BP changes. *Source*: From Ref. 47.

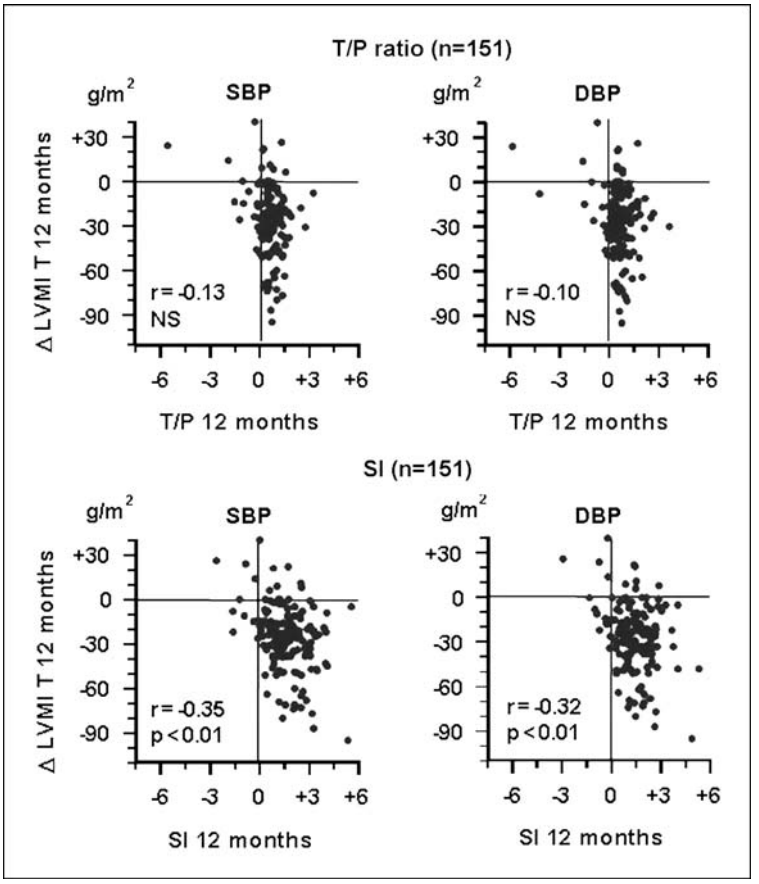

Fig. 8.11 Individual values (*dots*) of the trough:peak (T/P) ratio (*upper panels*) or the smoothness index (SI, *lower panels*) and the treatment-induced reduction in the left ventricular mass index (LVMI). Data obtained after 12 months of treatment are shown separately for systolic (SBP) and diastolic (DBP) blood pressure. The *r*-values between SI and LVMI are negative because an increase in SI was associated with a greater reduction in LVMI. *Source*: From Ref. 47.

an antihypertensive medication. Mean BP changes induced by treatment are calculated for each of the 24 individual hours. Then the average of these 24 h BP changes with the corresponding SD are computed. The SI is the ratio between the average of the hourly BP changes determined by the medication under evaluation and its SD (Figure 8.10). Available data suggest that the SI, compared to the T:P ratio, is a more accurate measure of the entity and distribution of the BP-lowering effect of an antihypertensive medication. Moreover it is more reproducible and displays a stronger correlation with drug-induced TOD regression (Figure 8.11) (47,48).

CONCLUSIONS

Evidence is available that an increased BP variability may represent a determinant of morbidity and mortality in subjects with hypertension, independently of an elevation of mean BP levels. In particular, heavy prognostic implications have been described for increased frequency and amplitude of BP variations occurring during the whole 24 h period, during the daytime, and the nighttime, separately considered for selected abnormalities of the physiologic nocturnal BP fall and morning BP surge.

An antihypertensive regimen capable of decreasing BPV as well as mean BP levels may provide greater cardiovascular protection than a regimen that simply decreases mean BP levels in an uneven fashion over the 24 h, and preliminary data collected in humans seem to support this concept. Interventional trials specifically designed are needed to definitively prove that controlling both mean BP levels and increased BPV provides hypertensive patients with greater prevention of TOD occurrence and progression and of cardiovascular events. Availability of such a demonstration, on the background of the evidence already available on the risk associated with an increased BPV, would be required in order to broaden targets of antihypertensive therapy from the simple control of mean BP levels to the integrated control of both elevated BP levels and increased BP fluctuations.

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Etiological and pathophysiological aspects

SECTION 3

HEMODYNAMICS OF HYPERTENSION 9

Per Omvik, Per Lund-Johansen

HEMODYNAMIC VARIABLES

Generation of hydrostatic pressure in the arterial system—blood pressure (BP)—is the result of two processes: the pumping of blood from the heart into the arteries—cardiac output (CO)—and the resistance against the blood flow through the vascular system—the total peripheral resistance (TPR). In its simplest form, the relationship between BP, CO, and TPR may be expressed as

$$BP \approx CO \times TPR \quad (9.1)$$

CO is derived directly from two components: the blood volume ejected by each stroke—the stroke volume (SV)—and the number of strokes per time unit—the heart rate (HR). Thus, the above central hemodynamic formula may be rewritten as

$$BP \approx SV \times HR \times TPR \quad (9.2)$$

A number of known physiological variables may influence one or more of the factors of Equation 9.2 (Table 9.1). Most of these variables are extensively discussed in other chapters in this book.

During the course of each cardiac cycle, the intra-arterial pressure is determined by the volume ejected into the arterial tree, the vascular resistance, and the elasticity of the arterial walls. The highest BP in each cardiac cycle—the systolic pressure—occurs when the aortic valves open at the peak of the left ventricular contraction. A pressure wave propagates blood forward in the arterial tree toward the capillary bed, with a marked pressure drop at the arteriolar level. The form, the peak, and the speed of the pressure wave are partly determined by the compliance of the arterial walls and vary along the length of the arterial tree (1). Stiffer arterial walls, e.g., as seen with atherosclerosis, causes an exaggerated rise in intra-arterial pressure during systole and may thus account for isolated systolic hypertension (ISH) (see discussion in Chapter 19).

In the steady state, BP shows a slight oscillating pattern due to respiration and reflex mechanisms, but the overall level of BP during undisturbed resting is still quite stable. Conditions like change in body position, physical activity, respiration, mental stress, transition from sleep to wakefulness, and effects of nicotine or drugs may lead to instant and large changes in BP. At the end of physical and/or mental excitement, BP rapidly returns to its usual level. Thus, as actually emphasized by the inventor of the sphygmomanometer, Scipione Riva-Rocci in 1896, a clinically useful BP must be recorded under strictly standardized conditions (2).

BP may also increase more slowly to reach an abnormal high level—hypertension—either by known disease processes (secondary hypertension), or by unknown mechanisms (primary hypertension). Defined levels of hypertension are discussed in Chapter 1. However, any change in BP, whether acute or chronic, must be expressed by a change in one or more of the three components on the right-hand side of the equation sign in Equation 9.2: SV, HR, or TPR. Thus, hypertension can be defined as a hemodynamic disorder, which reflects a disturbance in the balance between CO and TPR.

METHODS OF CENTRAL HEMODYNAMIC MEASUREMENTS

The most precise measurement of BP is obtained by intra-arterial recording using a pressure transducer, which permits detection of immediate beat-by-beat pressure changes, e.g., during variation in physical activity or by other interventions. Intra-arterial recordings may also be carried out at different sites within the arterial tree to obtain hemodynamic information from specific segments of the vascular system. Other modes of BP measurement, including external measurement

Table 9.1 Components known to influence blood pressure control

Body fluid volume
Electrolytes
Kidney
The renin–angiotensin–aldosterone system
Hormones
Nervous/sympathetic systems
Peripheral vessels/endothelium
Heart

and ambulatory monitoring as used in clinical practice, are discussed in Chapter 21.

CO may be measured by a number of techniques, ranging from the Fick principle, to dye dilution, and noninvasive methods (Table 9.2). An extensive review of the methods is published by an expert group from the European Society of Cardiology (3). While noninvasive techniques like echocardiography are easily available, the Fick method, dye dilution, and the thermodilution technique are considered the most accurate for measurement of CO (4). One advantage of the dye dilution technique using cardiogreen (indocyanine) is its usefulness both at rest and during exercise. The repeatability is in the order of 5%, and dye dilution has been referred to as the "golden standard" (4). Limitations are that the technique is invasive and gives the mean value over 10 to 30 s (not beat-to-beat values).

By most methods, the CO is measured as volume per time unit, usually l/min. CO (e.g., by dye dilution) may in turn be used to calculate the SV when HR is known (preferably by electrocardiogram):

$$SV = CO / HR \quad (9.3)$$

By some noninvasive techniques (e.g., echocardiography) the situation is reversed: the SV is the variable being measured and the CO is then obtained by calculation:

$$CO = SV \times HR \quad (9.4)$$

TPR cannot be measured directly, but is derived by calculation as the ratio between the mean arterial pressure (MAP) and CO:

$$TPR = MAP/CO \quad (9.5)$$

The TPR in Equation 9.5 is usually transformed by a constant (1,332) to be expressed by the unit dyn s/cm^5. Indexed values for TPR, as well as for CO and SV, are obtained by relating data to body surface area (BSA). The corresponding variables are designated cardiac index (CI), stroke index (SI), and total peripheral resistance index (TPRI). Indexed hemodynamic variables allow comparison of results between different trial populations and between different laboratories.

Table 9.2 Available methods for measurements of cardiac output

Fick method
Dye dilution
Thermodilution
CO_2 rebreathing
Pulse contour
First passage radionucleotide
Doppler
Echocardiography
Impedance cardiography
Systolic time intervals
Magnetic resonance imaging
Ultrafast (cine) computed tomography
Positron emission tomography

The calculation of TPR is based on Poiseuille's law, but the exact nature of TPR is still uncertain. Strictly, calculation of TPR according to Equation (9.5) is only applicable to a steady, nonpulsatile flow through rigid tubes. It is presumed that vascular resistance is mainly determined by the diameter of the arterioles and that changes in resistance reflect changes in cross-sectional vascular area. As discussed by Folkow, even minute changes in diameter may cause large differences in resistance (5). By an ingenious technique Mulvany and coworkers have been able, in isolated arterioles, to directly study factors that may be of importance in the control of arteriolar diameter (6). However, the vascular resistance is also influenced by other variables like the length of the resistance vessels and the blood viscosity (7).

HEMODYNAMICS OF NORMOTENSION

Evaluation of central hemodynamics in hypertension requires comparative data from healthy, normotensive individuals. Invasive hemodynamic measurements have been carried out only in a limited number of small-scale studies in healthy subjects, mostly in men aged 20–40 years (8–14). The total number of individuals in these studies is approximately 200. Although on an individual basis there was great variability in the results, the differences in the mean values from the studies were rather small. The weighted mean values of the hemodynamic variables in the rest supine position from these studies are shown in Table 9.3.

AGE

Cross-sectional studies from most industrialized countries have shown that BP, particularly systolic arterial pressure (SAP), increases by age (15–17). There is also some increase in diastolic arterial pressure (DAP), but it reaches a peak at the age of 60 and then levels off or even tends to fall slightly. The pattern of increasing BP with age is modified by factors like obesity and physical activity and it is also slightly different between the two genders, with more marked increase in SAP in women compared with men over the age of 50 (17,18). Most invasive studies have shown that, hemodynamically, the increase in BP at higher ages is due to an increase in TPR, while SV and CO are reduced (9,19–22). However, in normotensive subjects between the ages of 18 and 50 years of age, hemodynamic data from cross-sectional studies are rather similar in young and older age groups. Age-related changes in central hemodynamic variables from a cross-sectional study in normotensive and hypertensive subjects from our laboratory from the 1960s are shown in Figure 9.1 (9).

Few studies on the spontaneously occurring changes in central hemodynamics over time have been published. In a 5-year follow-up study from Sweden in young men there were virtually no changes in BP, HR, CO, or TPR, which is in agreement with the cross-sectional data from our laboratory (9,14).

EXERCISE

Hemodynamic response to exercise is often used in clinical practice for evaluation of cardiac pump function. However, systematic exercise hemodynamic studies in normotensive

Table 9.3 Central hemodynamics at rest supine in NT subjects. Mean values from seven studies

MAP[a]; mmHg	85.6
CI; l/min/m^2	3.30
TPRI; dyn s/cm^5 m^2	2118
HR; *beats/min*	66.7
SI; ml/stroke/m^2	51.1

[a]MAP = DAP + ⅓(SAP− DAP). In invasive studies, MAP is obtained by electrical damping of the intra-arterial pressure curve (9).
Abbreviations: CI, cardiac index; DAP, diastolic arterial pressure; HR, heart rate; MAP, mean arterial pressure; NT, normotensive; SAP, systolic arterial pressure; SI, stroke index; TPRI, total peripheral resistance index.

subjects using invasive techniques are scarce. In a study of 33 normotensive men aged 19–49 years (mean 31) from our laboratory, we found an increase in SAP of 34.3 mmHg at a steady state dynamic (bicycle) workload of 100 W compared to the rest sitting situation (9). The corresponding increase in DAP was 3.8 mmHg. CI increased by 6.0 l/min/m^2, SI by 28.4 ml/stroke/m^2, and HR by 53 beats/min. The TPRI fell by 1,308 dyn s/cm^5/m^2 (Figure 9.2). More data on BP during exercise are found in Chapter 23.

CENTRAL HEMODYNAMICS OF ESSENTIAL HYPERTENSION

In nearly all the studies performed in middle-aged subjects with established, uncomplicated hypertension, the CO during rest has been normal or slightly reduced, while the TPR has been increased. Increased TPR is referred to as the hallmark of hypertension, and the resistance has been found increased in all vascular beds (renal, cerebral, pulmonary, myocardial, splanchnic, muscular, and skin) in clinical as well as in experimental hypertension (24–32). In elderly subjects, particularly with ISH, the aortic compliance is reduced and responsible for the immediate increase in systolic BP after ejection of blood into the aorta (1,33,34).

However, when it comes to the starting phase of essential hypertension, most invasive studies in young men

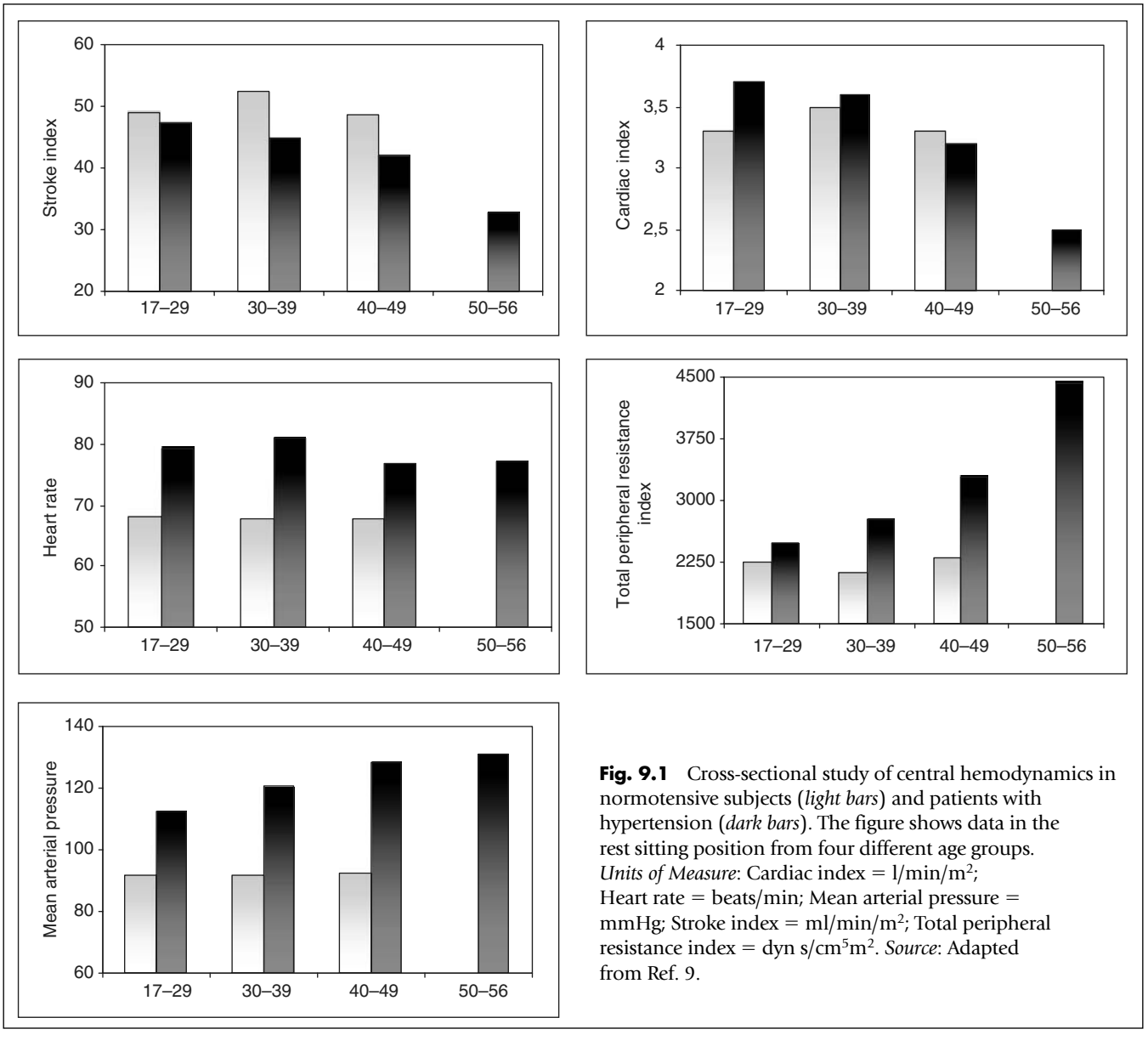

Fig. 9.1 Cross-sectional study of central hemodynamics in normotensive subjects (*light bars*) and patients with hypertension (*dark bars*). The figure shows data in the rest sitting position from four different age groups. *Units of Measure*: Cardiac index = l/min/m^2; Heart rate = beats/min; Mean arterial pressure = mmHg; Stroke index = ml/min/m^2; Total peripheral resistance index = dyn s/cm^{5}m^2. *Source*: Adapted from Ref. 9.

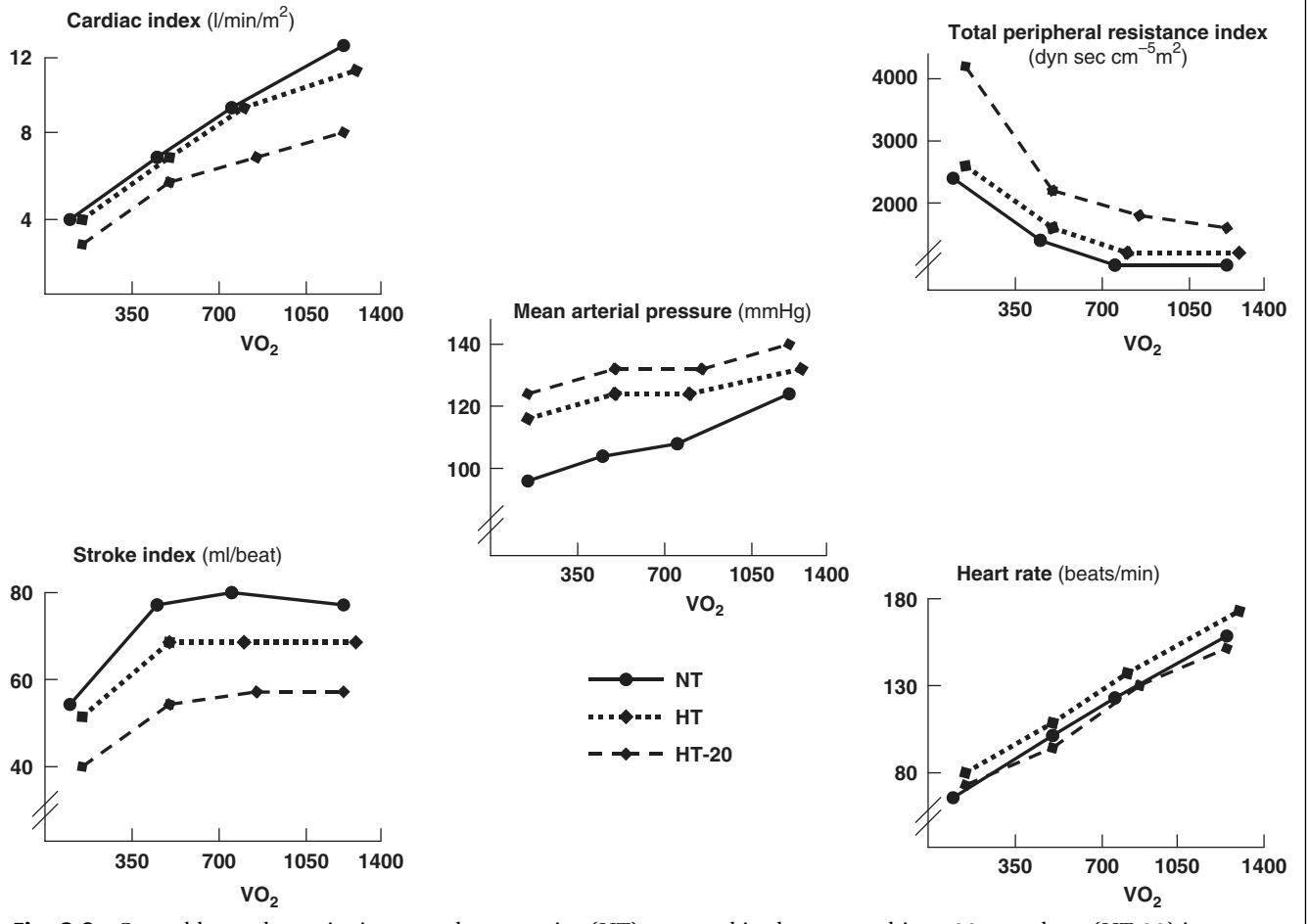

Fig. 9.2 Central hemodynamics in young hypertensive (HT) men and in the same subjects 20 years later (HT-20) in comparison with age-matched normotensive (NT) controls. Data shown at the lowest oxygen consumption (VO_2) values represent measurements at rest sitting, while the remaining data show measurements during steady state dynamic exercise at 50, 100, and 150 W respectively. *Unit of Measure*: VO_2 = ml/min/m^2, measured by the Douglas bag technique (9). *Source*: From Refs. 9,22,23.

(18–30 years) have demonstrated an increased CO (about 15% higher than in age-matched normotensive controls), due to increased HR and normal SV. Figure 9.3 shows the mean values of the seven available studies (8–14). Since oxygen consumption (VO_2) is increased to the same degree as CO, the arteriovenous oxygen difference ($A-VO_2$) is normal, and no over-perfusion of the tissues exists. These hemodynamic disturbances are thought to be due to hyperactivity in the sympathetic nervous system (35,36).

From several noninvasive studies in children with different BP levels there is no consistent evidence for an increase in CO in those with the highest pressures—so it is still uncertain whether the increased CO seen in young males with BP above 140/90 mmHg during invasive studies really represents the cardinal hemodynamic disturbance in the early phase (37–39).

AGE

CROSS-SECTIONAL STUDIES

The hemodynamic basis for the age related increase in MAP in hypertensives is a progressive increase in TPR, which at the age of 50 may be almost twice the value seen at the age of 20 (Figure 9.1). As already mentioned, in ISH, a reduction in aortic compliance is the cardinal disturbance (see also Chapter 19).

CO, which in the resting condition often is increased by 15–20% in young hypertensives, is reduced at higher age. The progressive decline in CO with age in patients with hypertension is associated with reduction in SV, while HR remains increased by 6–10 beats/min compared with normotensive subjects up to the age of 50–60 years.

The true nature of the reduction in cardiac pump function over the years seen in hypertension is not readily apparent. In a group of offspring (mean age 40) from parents, who at a national health screening 27 years earlier had a BP above 140/90 mmHg, a shift of left ventricular diastolic filling from early to late diastole was seen when compared to offspring from parents who were normotensive both at the screening and at the time of the current study (40). Similar findings have been made in other studies, suggesting increased left ventricular stiffness and reduced ventricular filling rate even before development of left ventricular hypertrophy (38,41–43). More details on cardiac damage in hypertension are found in Chapter 17.

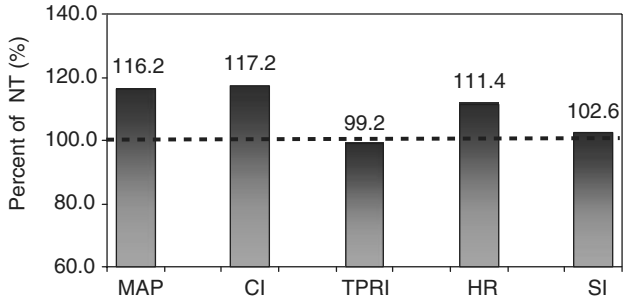

Fig. 9.3 Central hemodynamic variables in young subjects with mild essential hypertension. Data are shown as percent compared with NT subjects (dotted line = 100%) and are the weighted mean values for the supine position at rest from seven studies in a total of 189 NT subjects and 222 HT patients. *Abbreviations*: CI, cardiac index; HR, heart rate; HT, hypertensive; MAP, mean arterial pressure; NT, normotensive; SI, stroke index; TPRI, total peripheral resistance index. *Source*: From Refs. 8–14.

LONGITUDINAL STUDIES

Most follow-up studies on spontaneous changes in central hemodynamics have been of short duration—typically 2–5 years (12,14,22,23,44–48). Generally, BP remained unchanged, while the CO decreased, and TPR, in most cases, showed an increase. Also during a longer follow-up period (10 years) similar results were found (22,48). Like in the cross-sectional studies, the reduction in CO was associated with a reduction in SV on the order of 15%, while HR was almost unchanged. Thus, the progressive decrease in cardiac pump function with age in hypertensives as suggested from the cross-sectional studies is also seen by longitudinal follow-up in individual patients.

A second restudy—with identical invasive methods as in study 1 and 2—after a total of 20 years from the first hemodynamic study, was performed in our laboratory (22,23,48). During the second decade, most patients developed diastolic BP above 100 mmHg and active antihypertensive treatment was initiated in all but 2 patients. Still, it was of interest to evaluate the hemodynamic status without drug effects after 20 years of follow-up and the drug therapy, after consent from the patients, was therefore temporarily discontinued for 1 month before the invasive hemodynamic study was performed for the third time. The principal results were further increases in systolic and diastolic BPs associated with an increase in TPR and further reductions in CO and SV (Figure 9.2) (23).

EXERCISE

Severe muscular exercise increases CO by 300% or more, and dramatically changes the distribution of blood flow—mainly by a large increase in the proportion of the blood flow to working muscles, including the myocardium. Thus, while it could be difficult to detect minor disturbances in the circulatory system in mild hypertensives versus normotensive subjects in the rest situation, such hemodynamic differences could be more clearly unveiled during exercise—when the circulatory system is really challenged.

To obtain accurate BP values during exercise, BP must be recorded intra-arterially (9). This is critical for reliable estimation of diastolic pressure as well as MAP, which is used for calculation of TPR (Eq. 9.5). Likewise, as already discussed above, the use of reliable methods for determination of CO is also crucial.

Several comparative studies on the circulatory system during exercise between hypertensives in different stages and normal age-matched controls have been carried out in the past (9,49–52). In subjects between 18 and 30 years of age with mild or borderline hypertension, the rise in BP during ergometer bicycling with increasing loads was parallel to what was seen in the normotensive controls. HR was slightly higher.

Somewhat surprisingly, the SV in transition from rest to exercise (in the sitting position on ergometer bicycle) did not increase to the same levels as in the normotensive controls (9). In a study from our laboratory, the SI in the hypertensive patients was approximately 15% lower than in normotensive controls during all exercise levels (50, 100, and 150 W). This pattern was also seen in young men with uncomplicated mild essential hypertension. Thus, CI during exercise was no longer higher than in normotensive controls, but actually significantly subnormal, particularly during strenuous exercise (150 W). The oxygen consumption was similar, and, as a consequence, the $A-VO_2$ was increased. TPR, which was numerically normal in the youngest group during rest situation, was significantly higher than normal during exercise at all exercise levels and also in the older age groups (Figure 9.2).

Muscular exercise increases the workload on the heart and the myocardial oxygen need. The product of HR × SAP is a clinically useful index of myocardial oxygen demand (53). When the rate-pressure product is compared in hypertensives and normotensives of similar age, it is seen that, during rest situation in the hypertensive groups, the product is similar to what normotensives are exposed to during 50 W exercise (Figure 9.4) (54). This illustrates the chronic increased burden on the hypertensive heart—also during rest situation.

A few studies performed in subjects with really severe hypertension demonstrated that CI was markedly reduced compared to normotensive controls and also compared to subjects with mild hypertension (55). In transition from moderate to severe exercise, SI actually decreased. This was seen in subjects with no clinical symptoms of heart failure, but these findings could be interpreted as an indication of incipient cardiac failure (9). Studies from other laboratories have shown that the CI in relation to the filling pressure is reduced in patients with relatively severe hypertension (52).

The most important conclusions from the exercise studies are that cardiac pump function and vessel resistance are affected very early in subjects with mild, uncomplicated, essential hypertension. As first pointed out by Tarazi and coworkers, one mechanism responsible for the reduction in the pump function is reduced compliance of the left ventricular wall (56–58). Studies of heart pump function during rest situation by echo-Doppler method in subjects with very mild hypertension have revealed a slight degree of left ventricular hypertrophy and diastolic dysfunction, characterised by reduction in the *E*/*A* ratio. This indicates that the filling of the left ventricle is slightly reduced and more dependent on the atrial contraction in hypertension than in normals (see Chapter 17).

IMPLICATIONS

The causes of hypertension have been sought during the whole of the last century, and Volume 22 of the *Handbook of Hypertension* from 2004 is devoted to this research (59). Except for the limited group of patients in whom a defined disease process can be found to account for hypertension, most patients are still classified as having a form of hypertension without known cause: i.e., primary or essential hypertension (see Chapter 32).

According to the mosaic theory, originally proposed by Irvine Page more than half a century ago, primary hypertension may be caused by disturbance of one or more of a number of control mechanisms for BP (60). However, as discussed above, any mechanism or group of mechanisms that eventually may be shown to explain elevation of MAP must be expressed by changes in either CO and/or TPR. Thus, central hemodynamic variables are cornerstones in the understanding of how hypertension may develop. Since rise in TPR seems to be of fundamental importance in the development of hypertension, research efforts have been directed toward components essential to the control of constriction and/or relaxation of arteriolar smooth muscles. In recent years, with increasing elderly population, ISH has become a major therapeutic challenge.

ANTIHYPERTENSIVE DRUG THERAPY AND CENTRAL HEMODYNAMICS

In addition to enlightening on the pathophysiology of hypertension, measurements of central hemodynamics have been useful tools to understand the mechanisms of action of antihypertensive agents (61,62). Vice versa: by pharmacological challenging of hemodynamic variables, drugs have been used to expose underlying hemodynamic mechanisms of hypertension and, thus, serve as tools to investigate the pathophysiology of the disease. Tables 9.4 and 9.5 show the overall data from 32 invasive studies in our laboratory on central hemodynamic changes at rest and during exercise at 100 W induced by 1-year treatment by the major drug classes of antihypertensive drugs. In these Tables, the drug classes are ranked according to the CI response at rest sitting. Two classes of drugs—one at each end of the rank—are discussed below: beta-blockers and angiotensin receptor-1 blockers (ARBs).

BETA-BLOCKERS

Since their first introduction, it has been known that beta-blockers reduce HR and thereby the CO as well, even in the face of some increase in SV due to a protracted left ventricular filling time (61–63). The BP is reduced due to the reduction in CO, but, because of an increase in TPR, the relative reduction in BP is less than that in CO. The increase in TPR could be viewed as a counter-regulatory effect and could be due to predominant intrinsic mechanisms striving to preserve the elevated BP (64).

A wide range of beta-blockers are available with widely different properties. The degree to which the different beta-blockers increases TPR and reduce CO depends on characteristics of the compounds with regard to intrinsic sympathomimetic activity (ISA) and the balance between beta-1 and beta-2 receptor blocking activity. Some beta-blockers have also been designed with additional vasodilating properties—so-called "dual action" drugs (64).

It was once thought that the increase in TPR during beta blockade was a temporary counter-regulatory response and that with time chronic beta-blocker therapy would even reduce the TPR and the reduction in CO would be abolished. An overshoot of the rise in TPR and a distinct fall in CO after the first administration of a beta-blocker is indeed found, but as exemplified in 1-year and 5-year follow-up studies on the hemodynamic effects of atenolol, the main hemodynamic finding of reduced HR and CO and increased TPR is maintained also on a long-term basis (65,66).

In agreement with these early hemodynamic findings, Mulvany and coworkers in recent morphological studies have shown that beta-blockers, in contrast to angiotensin-converting enzyme inhibitors (ACEI), do not normalize

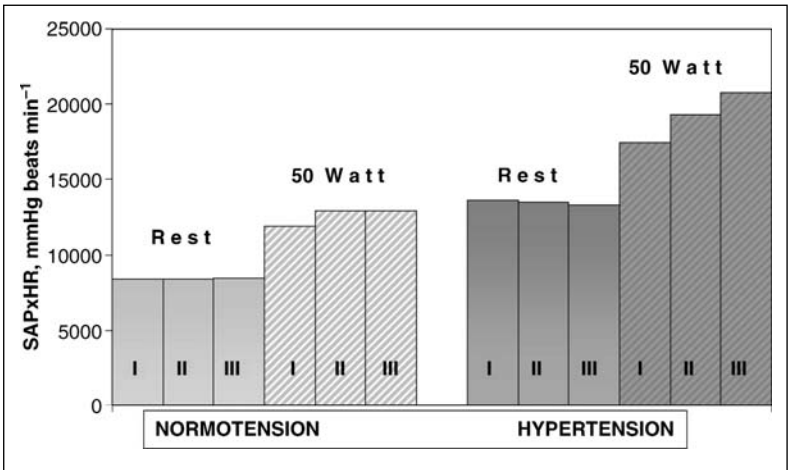

Fig. 9.4 The systolic arterial pressure–heart rate product (SAP × HR) at rest (*solid bars*) and during steady state 50 W bicycle exercise (*lined bars*) in normotensive subjects and hypertensive patients in three age groups: I = 18–29 years; II = 30–39 years; III = 40–49 years. *Source*: From Ref. 54.

Table 9.4 One-year central hemodynamic changes (%) induced by different classes of antihypertensive drugs or low sodium diet. Observations at rest sitting

	Number n = studies; N = patients	MAP (130 mmHg)[a]	TPRI (3905 dyn s/cm² m²)	CI (2.73 l/min/m²)	SI (37.4 ml/ min/m²)	HR (73.2 beats/min)
Beta-blockers	*n* = 7; *N* = 87	−12.8	12.9	−24.2	−3.0	−22.0
Low sodium diet	*n* = 3; *N* = 46	−2.5	7.4	−13.4	−3.5	−9.6
Diuretics	*n* = 4; *N* = 45	−17.7	−6.9	−11.5	−12.3	0.7
Multiple action	*n* = 4; *N* = 52	−15.6	−6.9	−9.9	2.5	−8.2
ACE inhibitors	*n* = 3; *N* = 43	−16.4	−13.9	−3.3	−0.9	−1.5
AT_1-blockers	*n* = 1; *N* = 28	−9.5	−11.5	0.9	3.6	−0.9
Ca-antagonists	*n* = 7; *N* = 111	−13.9	−15.6	1.7	4.3	−2.8
Alpha-blockers	*n* = 3; *N* = 38	−11.9	−17.7	5.5	5.7	0.6

[a]The data in parentheses show overall mean hemodynamic values before treatment in 450 patients with hypertension from 32 studies. *Abbreviations*: CI, cardiac index; HR, heart rate; MAP, mean arterial pressure; SI, stroke index; TPRI, total peripheral resistance index.

resistance arterioles from hypertensive patients (67). Moreover, data from recent clinical studies have shown that beta-blockers are less effective than ACEI or calcium antagonists in reducing risk of stroke, possibly due to less effect on central aortic pressure, and beta-blockers will probably not be used in the future as first-line drugs alone in uncomplicated essential hypertension (68).

ANGIOTENSIN RECEPTOR-1 BLOCKER

The molecular biological aspects of the angiotensin receptor-1 and its blockade are discussed in Chapter 14. Both clinical and experimental studies have shown that angiotensin receptor-1 blockade, in addition to inhibition of the vasoconstrictor action of angiotensin II, is associated with a significant improvement in resistance vessel endothelial function, which conceivably might be expressed in terms of hemodynamic changes (69) (see discussion in Chapter 20).

In a study of 1-year treatment with the ARB losartan in patients with essential hypertension, the hemodynamic response was mainly vasodilatation with a fall in TPR and BP (70). There were almost no changes in CO or SV at rest, whereas during exercise a small increase was seen in SV (Figure 9.5, Tables 9.4 and 9.5). No control subjects were included in the study, but, when compared with hemodynamic values obtained from normotensive subjects in a previous trial as described above, the TPR after 8-month losartan treatment was still above what was seen in normotensive subjects of the same age, and, similarly, the SV both at rest and during exercise was less than in the normotensive subjects. Thus, although the vasodilatation induced by angiotensin receptor-1 blockade tended to normalize the central hemodynamic disturbance of hypertension, in contrast to beta-blockers, there was still a considerable gap between treated hypertension and normotension.

OVERVIEW

The modern selection of antihypertensive agents offers the possibility to modulate central hemodynamics of hypertension, ranging from fall in BP due to marked reduction in CO, which is partly counteracted by some increase in TPR, to vasodilatation with reduction in TPR, and, in some cases, a small increase in CO (Tables 9.4 and 9.5). However, from the tables it may also be seen that none of the available drug classes are even close to fully normalizing the central hemodynamic disturbances of hypertension.

Salt (or more precisely—sodium) has been proposed as an important pathogenic factor in hypertension (71). Thus, conceptually, it could be expected that reduction of salt

Table 9.5 One-year central hemodynamic changes (%) induced by different classes of antihypertensive drugs or low sodium diet. Observations during 100 W dynamic exercise

	Number n = studies N = patients	MAP (147 mmHg)[a]	TPRI (1695 dyn s/cm² m²)	CI (7.07 l/min/m²)	SI (54.7 ml/ min/m²)	HR (132.9 beats/min)
Beta-blockers	*n* = 7; *N* = 87	−12.3	6.6	−17.9	−6.2	−22.6
Low sodium diet	*n* = 3; *N* = 46	−2.6	0.0	−6.0	−1.5	−5.0
Diuretics	*n* = 4; *N* = 45	−14.7	−9.7	−7.0	−5.9	−1.8
Multiple action	*n* = 4; *N* = 52	−15.5	−5.1	−7.7	9.1	−15.9
ACE inhibitors	*n* = 3; *N* = 43	−13.4	−6.0	−7.0	−5.4	−0.5
AT_1-blockers	*n* = 1; *N* = 28	−8.0	−14.5	6.1	9.1	−2.1
Ca-antagonists	*n* = 7; *N* = 111	−11.3	−10.4	−2.2	2.0	−3.8
Alpha-blockers	*n* = 3; *N* = 38	−11.5	−16.5	4.9	4.0	−0.9

[a]The data in parentheses show overall mean hemodynamic values before treatment in 450 patients with hypertension from 32 studies. *Abbreviations*: CI, cardiac index; HR, heart rate; MAP, mean arterial pressure; SI, stroke index; TPRI, total peripheral resistance index.

intake might reduce BP by improving the cardinal hemodynamic disturbance of hypertension—an increased TPR. However, invasive data from our laboratory showed that a small reduction in BP after 9 months of salt restriction caused a reduction in CO, while TPR actually tended to increase (Tables 9.4 and 9.5) (72). This failure to normalize central hemodynamics might be due to the known stimulating effect of sodium deprivation on the renin–angiotensin system and serve as a counter-regulatory mechanism preventing excessive BP fall (73,74).

Some of the large-scale antihypertensive drug trials have shown that ACEI and ARBs may reduce left ventricular hypertrophy more efficiently than other antihypertensive agents and also that development of congestive heart failure (as well as other clinical end-points) is reduced compared with other drugs (75). However, full normalization of left ventricular geometry is usually not seen (76). It is unknown whether this observation and the gap between normal and on-drug central hemodynamic pattern in patients with hypertension is linked, but from a hemodynamic point of view it is obvious that there is still a great potential for improvement in the modes of antihypertensive treatment.

CONCLUSION

Hypertension is a hemodynamic disorder with a pattern changing from high CO and normal TPR in young age and early hypertension, to a normal-to-low CO and high TPR in more established hypertension (22). Early sign of impairment of cardiac pump function in hypertension is most readily seen in SV, particularly during exercise. By drug therapy, it is possible to modulate central hemodynamics on a wide scale from reduction of BP by reducing either CO, TPR, or both. Ideally, a perfect antihypertensive agent, in addition to being without metabolic and subjective side effects, should be able to reduce BP to normal levels by reducing TPR, restoring normal cardiac pump function both at rest and during exercise, and also preventing the reduction in aortic compliance and thereby development of ISH.

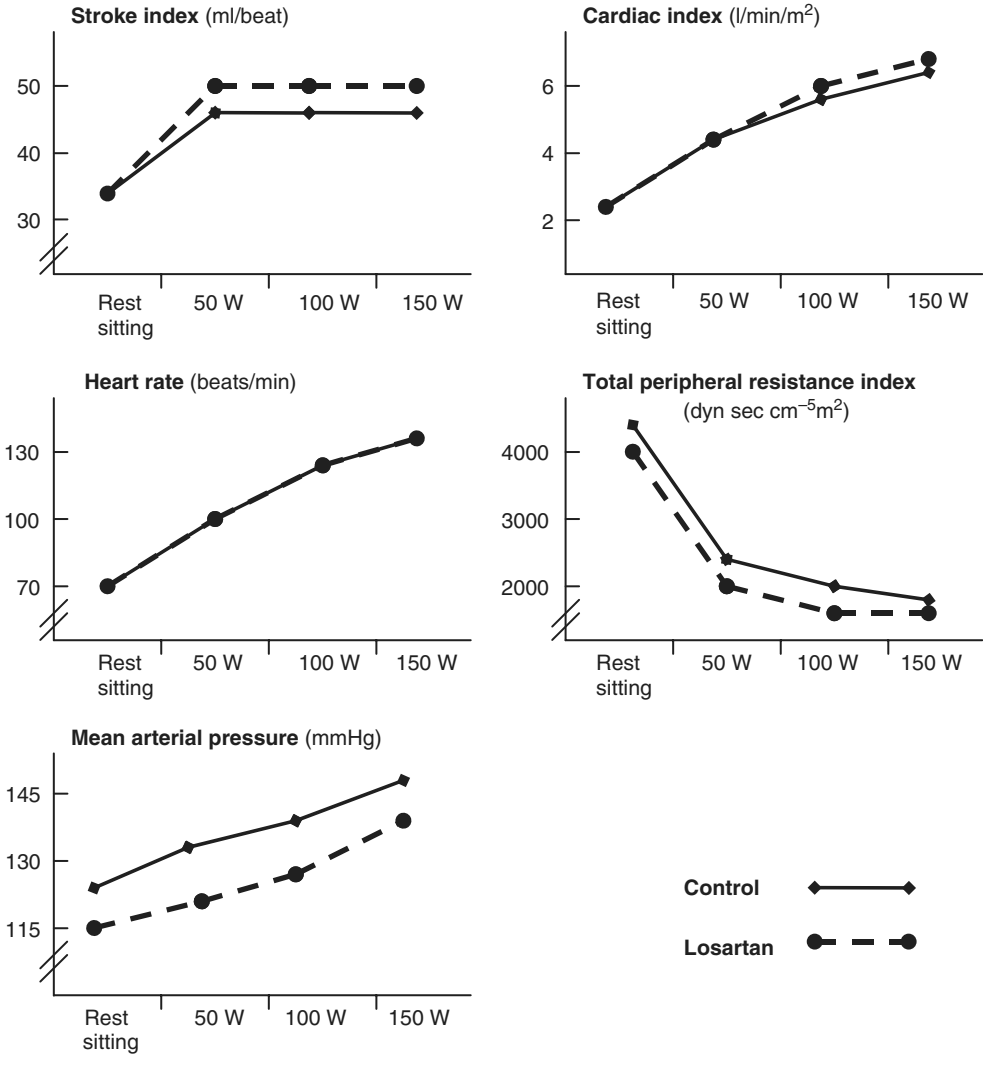

Fig. 9.5 Central hemodynamic effects of losartan in patients with essential hypertension ($n = 28$). Measurements at rest sitting and during steady state dynamic (bicycle) exercise at three workloads before treatment (control) and after 8 months treatment with losartan, respectively. *Source*: From Ref. 70.

But, till now, no hemodynamically ideal drug has been found that can fully normalize the hemodynamic disturbance of hypertension.

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GENETIC FACTORS 10

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EVIDENCE FOR CONTRIBUTION OF GENETIC FACTORS TO THE PATHOGENESIS OF HYPERTENSION—DATA FROM FAMILIAL STUDIES AND EXPERIMENTAL MODELS

The impetus for studies into the influence of genetic factors underlying high blood pressure (BP) has its origins in numerous family-based studies. These examined the prevalence and transmission of hypertension in natural versus adopted offspring; in parent versus offspring; and in identical and nonidentical twin cohorts (1). The overall heritability of hypertension, based on the data from these investigations, ranges from 20% to 55% (2). This familial aggregation of hypertension provided the indirect evidence for contribution of genetic factors to the pathogenesis of high BP. Further support for involvement of genes in the development of hypertension comes from experimental models. The use of rodent models of hypertension, in which environmental factors can be normalized (or indeed manipulated to allow investigations of gene–environment interactions), has been very successful (3,4). One of the key advantages in using genetically hypertensive rat strains is the ability to construct "designer" strains. An example of this is the generation of strains where either discreet chromosomal segments (congenic) or indeed entire chromosomes (consomic) have been introgressed from hypertensive strain into a comparative normotensive strain and vice versa. By monitoring BP and assessing the genetic markers of congenic and consomic substrains, it is possible to capture chromosomal regions (blood pressure quantitative trait loci—BP-QTLs) that may be important in the pathogenesis of hypertension (3,4). Current comparative genomics utilizes information on rodent BP-QTLs in dissection of the syntenic BP-linked regions in human.

MENDELIAN FORMS OF HYPERTENSION

There at least six forms of monogenic hypertension with a clear pattern of Mendelian inheritance. The contribution of these genetic variants to BP variation in the general population is estimated as very small. Nevertheless, studies of these rare forms of hypertension have yielded important pathogenetic insight into regulation of ion handling within the kidney and provided evidence for successful tailoring of the antihypertensive therapy based on genetic testing.

GLUCOCORTICOID REMEDIABLE ALDOSTERONISM

Glucocorticoid remediable hypertension (GRA) is an autosomal-dominant disorder caused by unequal meiotic recombination between aldosterone synthase gene (CYP11B2) and 11-β-hydroxylase gene (CYP11B1) (5). The product of this meiotic misalignment—chimeric gene—consists of CYP11B2 sequences in the coding region and regulatory promoter segments of CYP11B1. In consequence, aldosterone synthase secretion is brought under regulatory control of adrenocorticotrophic hormone (ACTH). Clinically, the phenotype varies from severe early onset hypertension (6) to milder BP elevation with moderate hypokalemia. ACTH suppression by glucocorticoids leads to significant decrease of BP and is currently the most appropriate treatment for patients with GRA (6).

LIDDLE SYNDROME

Liddle syndrome is caused by several mutations within the genes that encode the β or γ subunits of epithelial sodium channel (ENaC) (7,8). The genetic defects result in impaired channel internalization by virtue of Nedd4, an ubiquitin protein ligase and negative regulator of ENaC (9). At a cellular level, ENaCs are accumulated and continuously activated within the plasma membrane of the distal nephron. Early onset hypertension, resistance to most of the classes of antihypertensive treatment, hypokalemic alkalosis, suppressed plasma renin activity, and low plasma aldosterone levels belong to the most common clinical features of the syndrome. Amiloride—a natural antagonist of ENaC—corrects increased reabsorption of sodium through mutated channels,

lowers BP, and corrects hormonal disturbances as well as renal water and electrolyte handling.

TYPE 2 PSEUDOALDOSTERONISM (GORDON'S SYNDROME)

Gordon's syndrome is caused by mutations in two genes encoding serine–threonine kinases (WNK1 and WNK4) (10). The resulting cellular phenotype—overactivation of thiazide-sensitive Na/Cl cotransporter—leads to excessive retention of sodium, potassium, and chloride. Clinically, Gordon's syndrome manifests as hypertension, hyperkalemia, despite normal renal glomerular filtration, and metabolic acidosis. Thiazide diuretics correct metabolic abnormalities and decrease BP in affected patients (11,12).

SYNDROME OF APPARENT MINERALOCORTICOID EXCESS

Apparent mineralocorticoid excess is an autosomal recessive disorder caused by the inactivation of 11β-hydroxysteroid dehydrogenase type II (11β-HSD2) in mineralocorticoid target tissues. The genetic defect leads to impaired conversion of cortisol to cortisone (13,14) and the increased bioavailability of cortisol that activates mineralocorticoid receptor (MR). Suppressed plasma renin activity, hypoaldosteronism, hypokalemia, and metabolic alkalosis are the most typical manifestations of this disorder (15).

AUTOSOMAL-DOMINANT HYPERTENSION WITH BRACHYDACTYLY

Two phenotypic traits of severe hypertension and autosomal brachydactyly have been found to cosegregate in few kindreds around the world. Affected persons are of short stature and exhibit vascular anomalies involving the posterior fossa vessels in the brain (16). This syndrome has been mapped to a 4-cM region of the short arm of chromosome 12p (17,18).

HYPERTENSION ACCELERATED BY PREGNANCY

A mutation in the MR causes early onset hypertension that is accelerated in pregnancy (19). The causative genetic defect associates with alteration of binding of progesterone and other steroids lacking 21-hydroxyl groups to MR. Low plasma renin activity and hypoaldosteronism belong to the most typical hormonal disturbances driven by activation of the MR.

GENETIC DETERMINANTS OF ESSENTIAL HYPERTENSION

Human essential hypertension is a complex, heterogeneous, polygenic disease. Numerous scans of the human genome have provided compelling evidence for existence of several chromosomal regions that are linked to BP (20). These genomic fragments, known as BP-QTLs, are present on almost all human chromosomes (20,21). Most of these BP-linked regions do not overlap across cohorts of distinct ethnic origin (21). However, there are a few exceptions from this population specificity of human BP-QTLs—several chromosomal regions have been actually implicated in more than one investigation. In addition, meta-analyses of genomic screens provided further evidence for consistent clustering of linkage to hypertension in certain regions of the human genome (22,23). These particular chromosomal segments are located on at least four different human chromosomes as shown in Figure 10.1. Of those, the locus within the distal portion of the long arm of chromosome 5 (Figure 10.1) is an excellent model of a common BP-QTL having been linked to BP in two individual scans of the human genome (24,25), at least one targeted chromosomal region study (26), and in the pooled analysis of available screens of human genome (22). In addition, comparative genomics revealed synteny between this region and several BP-QTLs on rat chromosome 18 (27). Therefore, the candidate genes that are located within this common BP-QTL have an obvious positional potential as mediators of the detected linkage and require dissection in further association and gene expression studies (Figure 10.1).

Collectively, the results from genome analyses clearly indicate that human hypertension is a polygenic disorder. The moderate similarity in genetic architecture of BP-QTLs across samples from different populations suggests that apart from strictly population-specific loci, there are at least few common genetic variant(s) that contribute to human hypertension in many populations. Functional importance of these regions is further confirmed by their synteny with rodent QTLs, and genes located within these regions are the most relevant positional candidates in future studies on hypertension (Figure 10.1).

While genetic dissection of human BP-QTLs is progressing toward identification of the ultimate functional variants, it is becoming increasingly clear that at least several causative genes of hypertension may be located outside the classical pathways of BP regulation (20). Firstly, preliminary positional analyses of genes located within QTLs showed that genes with moderate pathophysiological potential to regulate BP were implicated as drivers of linkage to hypertension (28). Secondly, there is a general lack of consistency among investigations on associations between hypertension and common genetic variants (Table 10.1) (29–39). Thirdly, several meta-analyses of available studies on the most pathophysiologically relevant candidate genes including angiotensin-converting enzyme (ACE) gene (36) and β_2-adrenergic receptor gene (ADRB2) (37) have excluded their role as major determinants of BP.

Apart from monogenic diseases, contribution of individual single genetic loci to the overall variation in BP is expected to be modest. However, coexistence of several high risk allelic variants may be associated with an additive increase in BP and the ultimate risk of hypertension (38). Other alleles may exert unmasking effect on potentially neutral variants contributing to the increased cardiovascular risk in hypertensive subjects (39). Finally, two or more variants that are not associated with hypertension as single loci may act in concert, resulting in a substantial elevation of BP (40) and up to 40% increase in the ultimate risk of hypertension (40). Most of the gene–gene interactions that are likely to contribute to human hypertension include variants that belong to the same regulatory pathway (20). Multiple epistatic interactions of genes that encode components of the renin–angiotensin–aldosterone system (41) and beta-adrenergic signaling (39) were shown

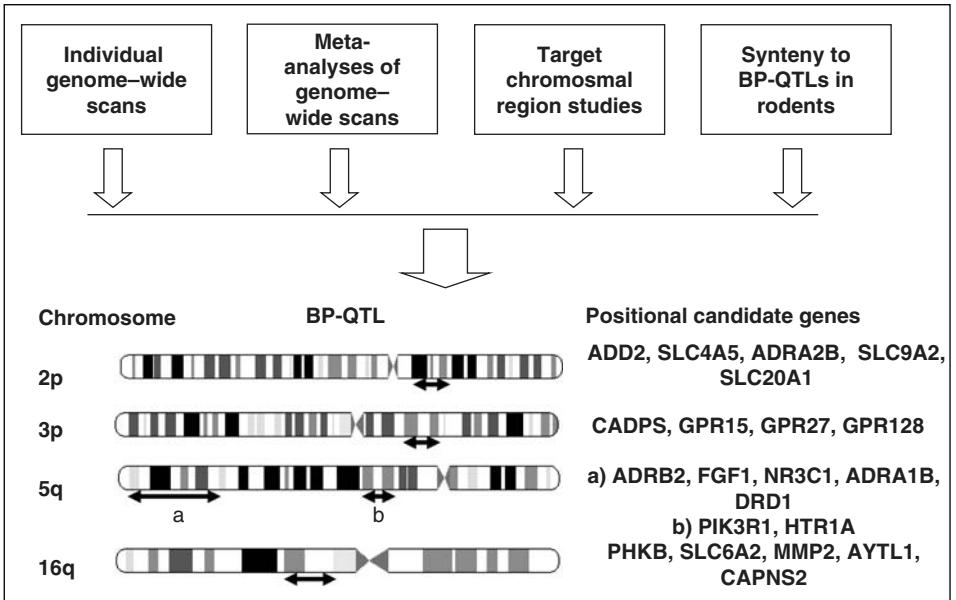

Fig. 10.1 Common human blood pressure quantitative trait loci (BP-QTLs) and new positional candidate genes. The most common chromosomal regions, which were linked to BP in at least two individual hypertension genome-wide searches and at least one meta-analysis of genomic screens, harbor relevant functional candidate genes as well as show synteny to BP-QTLs in rodents, and/or were dissected in target chromosomal region studies. These are listed in the bottom panel. Positional candidate genes within these common BP-QTLS include: adducin 2 (ADD2), sodium bicarbonate cotransporter 4 (SLC4A5), alpha-2B adrenergic receptor (ADRA2B), sodium/hydrogen exchanger 2 (SLC9A2), sodium-dependent phosphate transporter 1 (SLC20A1), Ca2+-dependent secretion activator (CADPS), G protein-coupled receptor 15 (GPR15), G protein-coupled receptor 27 (GPR27), G protein-coupled receptor 128 (GPR128), beta-2-adrenergic receptor (ADRB2), fibroblast growth factor-1 (FGF1), glucocorticoid receptor (NR3C1), alpha-1B adrenergic receptor (ADRA1B), dopamine receptor D1 (DRD1), phosphatidylinositol 3-kinase regulatory subunit alpha (PIK3R1), 5-hydroxytryptamine 1A receptor (HTR1A), beta-phosphorylase kinase (PHKB), sodium-dependent noradrenaline transporter (SLC6A2), matrix metallopeptidase 2 (MMP2), acyltransferase-like 1 (AYTL1), calpain, and small subunit 2 (CAPNS2).

to affect the overall cardiovascular phenotype in hypertensive patients. Other classical genetic networks of BP regulation include variants encoding components of sodium homeostasis system, intracellular signaling, and vasoactive molecules such as endothelins and nitric oxide (30). Novel genetic pathways that may determine familial susceptibility to hypertension include loci that encode growth factors, molecules of oxidative stress (42) and inflammatory response. Joint analysis of multiple loci within each of these networks of molecules is critical for a complete understanding of genetic mechanisms of BP regulation.

Overall contribution of genes to the pathogenesis of hypertension is estimated as 30%. The remaining 70% of interindividual variation in BP is mediated by environmental exposure and its interactions with genes. Interactions between classical environmental factors (such as alcohol consumption and smoking) and genetic polymorphisms are well documented (43). A common allele of the ACE gene was shown to increase BP only in smokers but not in those who did not smoke (43). Furthermore, alcohol consumption was implicated as a factor that interacts with genetic variation in the apolipoprotein E polymorphism in modulation of the overall cardiovascular phenotype (44). Finally, apart from classical risk factors, such as alcohol consumption, stress, smoking, physical activity, other environmental determinants, including diet, social class, exposure to air pollution, and use of common medication (38), may contribute to variation in BP. Accordingly, interactions between these environmental factors and genes must be studied to fully elucidate mechanisms of the pathogenesis of essential hypertension.

Mechanistically, prohypertensive functional variants affect gene expression at the transcriptional and/or translational level and influence the ultimate cellular phenotype in BP regulating tissues. Structural and functional effects mediated by the causative genetic variants at the cellular level are ultimately translated into cardiac output, total peripheral vascular resistance, and renal phenotypes—the major drivers of BP regulation (45). Genetic and environmental heterogeneity, resulting from involvement of different loci and environmental factors, as well as diverse patterns of their interactions, contribute to significant interindividual variation in function and structure of BP regulatory pathways. Therefore, the ultimate cardiovascular phenotype in patients with essential hypertension is polymorphic.

It is expected that identification of genetic signatures of essential hypertension and its complications will have a significant impact on clinical practice. Availability of simple assays that will characterize individual genetic "makeup" will help to identify those with a high risk of hypertension and enable primary prevention. Identification of variants that

Table 10.1 The most common candidate genes and hypertension—summary of findings from association, linkage, and experimental studies

System	Gene	Most common genetic variants	Summary of findings from association studies	Additional information from linkage studies and experimental models	Major ref.
Renin–angiotensin–aldosterone	Angiotensinogen (AGT)	Thr174Met and Met235Thr: exonic single nucleotide polymorphisms (SNPs) leading to nonsynonymous amino acid substitutions within the encoded protein −6(G/A), −20(A/C), −532 (C/T): SNPs in the 5′-flanking sequence of the gene	Both confirmation and exclusion of the association between AGT and hypertension were reported in Caucasian, Asian, and African populations Ethnic origin, sex, and gene–gene interactions influence associations between AGT and hypertension Genetic variation within the AGT was associated with measures of gene expression and circulating levels of AGT in some populations	AGT null mice have significantly lower blood pressure than wild type controls Linkage of the AGT locus to blood pressure was reported	30,35
	Angiotensin-converting enzyme (ACE)	I/D (insertion/deletion) polymorphism in intron 16	Conflicting results on association between hypertension and genetic variation within ACE Associations between hypertension and ACE may be dependent on its interactions with age, sex, other genes, and environmental factors Genetic variation within the ACE is a major determinant of circulating concentrations of ACE	Mice lacking ACE have low blood pressure ACE overlaps with a BP-QTL on chromosome 17 in several investigations	30,36
	Angiotensin II type 2 receptor (AT1R)	1166(A/C): SNP within the 3′-untranslated region −535(A/T): SNP in the 5′-flanking region	Conflicting results on association between AT1R and hypertension were reported mostly in Caucasian and Asian populations	Mice lacking both subtypes of AT1R are hypotensive	30
	Angiotensin II type 1 receptor (AT2R)	1675(A/G): polymorphism in intron 1 3123(A/C): SNP in the 3′-untranslated region	Preliminary results from few case-control studies suggest that AT2R is associated with blood pressure	AT2-null mice have slightly higher blood pressure when compared to the wild type controls	30
	Renin (REN)	17(T/G): SNP in intron 1 1051(G/A): missense polymorphism in exon 9 *Mbo*I RFLP in intron 9	Conflicting results on association between REN and hypertension across populations of different ethnic origin Preliminary evidence for association between genetic variation in REN and plasma renin activity	Genetic variants of REN cosegregated with blood pressure in congenic rats	30
Sympathetic nervous system	β_1-adrenergic receptor (ADRB1)	Ser49Gly, Gly389Arg: exonic SNPs leading to nonsynonymous amino acid substitutions within the encoded protein	Conflicting results on associations between ADRB1 and hypertension Preliminary data suggest that genetic variation within ADRB1 is associated with autonomic function of the heart	ADRB1 null mice develop impaired chronotropic and inotropic responses to receptor agonists	29,30

(*Continued*)

Table 10.1 (Continued)

System	Gene	Most common genetic variants	Summary of findings from association studies	Additional information from linkage studies and experimental models	Major ref.
Sympathetic nervous system	β_2-adrenergic receptor (ADRB2)	Arg16Gly, Gln27Glu: functional missense exonic polymorphisms	Lack of consistency among studies on associations between blood pressure-related phenotypes and ADRB2 does not support its role in the development of hypertension Evidence for associations between ADRB2 polymorphisms and vascular reactivity ADRB2 may affect several metabolic phenotypes in both normotensive and hypertensive subjects	ADRB2 null mice exhibit altered BP-response to exercise Although ADRB2 overlaps with one of the major BP-QTL on chromosome 5, it does not mediate the linkage to blood pressure in this genomic region	26,29,30, 37,39
	β_3-adrenergic receptor (ADRB3)	Trp64Arg: exonic SNPs leading to nonsynonymous amino acid substitutions within the encoded protein	No consistent evidence for association between ADRB3 and hypertension Modest evidence for association between ADRB3 and metabolic markers of adipose tissue		29,30
Intravascular regulation of vasoconstriction–vasodilation balance	Endothelin-1 (EDN1)	Lys198Asn: missense polymorphism in exon 5	Lack of the consistent association between EDN1 and human hypertension	EDN1 knockout mice demonstrate elevated blood pressure	31
	Endothelial nitric oxide synthase (NOS3)	Glu298Asp: nonsynonymous exonic polymorphism	Genetic variation within NOS3 is associated with plasma nitric oxide concentrations and vascular reactivity Genetic variation within NOS3 is not a major predictor of elevated blood pressure There is a weak correlation between NOS3 and risk of coronary artery disease	Mice with targeted disruption of endothelial nitric oxide synthase are hypertensive and insulin resistant	32
Sodium homeostasis	α-adducin (ADD1)	Gly460Trp: nonsynonymous polymorphism within the coding region of the gene	There is moderate support for association between the *Trp* allele of ADD1 and the increased risk of hypertension Association between ADD1 and hypertension is mediated through renal sodium reabsorption	ADD1 polymorphisms account for a significant percentage of blood pressure variation in experimental model of salt-sensitive hypertension There is a moderate support for linkage of ADD1 locus to blood pressure	30,33
	β-adducin (ADD2)	1797(C/T): silent, synonymous polymorphism in exon 15	Modest support for association between ADD2 and human hypertension	ADD2 is located within one of the major common BP-QTL on human chromosome 2	30,34
	Epithelial sodium channel α-subunit (SCNN1A)	2139(G/A): functional SNP within the promoter region of the gene Thr663Ala: missense SNP in the coding region of the gene	Modest support for association between SCNN1A and human hypertension	Variation within epithelial sodium channel α-subunit gene alters sodium handling within the kidney	30

increase the risk of target-organ damage would help to capture high-risk essentially hypertensive patients before the clinical manifestation of cardiac, cerebral, or renal complications (secondary prevention). Finally, genetic markers of response to antihypertensive treatment will help to genetically tailor the most suitable BP-lowering therapy and minimize the risk of adverse effects with a potential to improve compliance and the overall BP control (Figure 10.2).

GENETICS OF SECONDARY HYPERTENSION

Genetic factors also play a major role in the pathogenesis of hypertension secondary to several endocrine and renal abnormalities such as primary pigmented nodular adrenocortical disease, autosomal-dominant polycystic kidney disease (ADPKD), and pheochromocytoma (46). These disorders are not common in the general population—i.e., pheochromocytoma accounts for approximately up to 0.1% new patients with elevated BP (47). However, their prevalence increases among the patients referred to the specialist cardiovascular centers or those with refractory hypertension.

In patients older than 40 years, pheochromocytoma manifests most commonly as a sporadic adrenal or extra-adrenal tumor (48). In those younger than 40 years, pheochromocytoma frequently clusters with familial neoplastic syndromes, including neurofibromatosis 1, multiple endocrine neoplasia (MEN 2), von Hippel–Lindau (VHL) disease, or paraganglioma syndromes (48). Current status of clinical and genetic knowledge about these syndromes is summarized in Table 10.2 (47–53). Unlike essential hypertension, a majority of syndromic pheochromocytoma is caused by a single mutant allele that is transmitted from parents to affected offspring. The spectrum of causative genetic defects includes aberrant splicing, nonsense, and missense mutations, as well as whole gene deletions and intragenic small insertions and deletions (46,47). There is a wide range of molecular techniques, such as fluorescent in situ hybridization (FISH), protein truncation detection, and direct sequencing, that may be used as complementary diagnostic tools in the laboratory work-up. Most importantly, the molecular methods can identify the causative variant based on a single blood sample (46). These genetic tests are indicated in the index patient as a method of identification of the causative defect. A positive result justifies further clinical screening for tumors associated with pheochromocytoma. In rare cases with unequivocal clinical manifestations of pheochromocytoma-associated syndromes, a genetic test may contribute to confirmation of the diagnosis. Moreover, the genetic testing is now available not only to patients with hereditary neoplastic syndromes but also the members of their families. This is particularly important for asymptomatic members of the affected pedigrees, as most of these diseases are inherited in an autosomal-dominant manner. Thus, in the presence of just one mutated allele, the risk of the disease in offspring is 100%. Interestingly, 12–24% of apparently sporadic pheochromocytomas are associated with a germ line mutation in at least one of the genes listed in Table 10.2 (52). Therefore, an obligatory genetic testing is currently being postulated in all patients with pheochromocytoma (52).

Genetic testing has also become a part of the diagnostic work-up in patients with hypertension and chronic kidney disease ever since ADPKD was acknowledged as the most common monogenic renal disease worldwide (54) and elevated BP was recognized as one of the earliest clinical manifestations of this disorder (46). Altogether, approximately 250 single mutations within polycystin 1 (PKD1) and polycystin 2 (PKD2) genes have been identified as causative genetic defects in patients with ADPKD (46). Sequential direct sequencing of PKD1 or PKD2 is used as the most common method of detection of the underlying mutation in an index patient and at-risk family members (46). Although the genetic testing is rarely needed as a method of confirmation of ADPKD diagnosis, it may be particularly helpful in asymptomatic members of affected families. Early genetic diagnosis is associated with several clinical benefits including access to specialist care or screening for other life-threatening

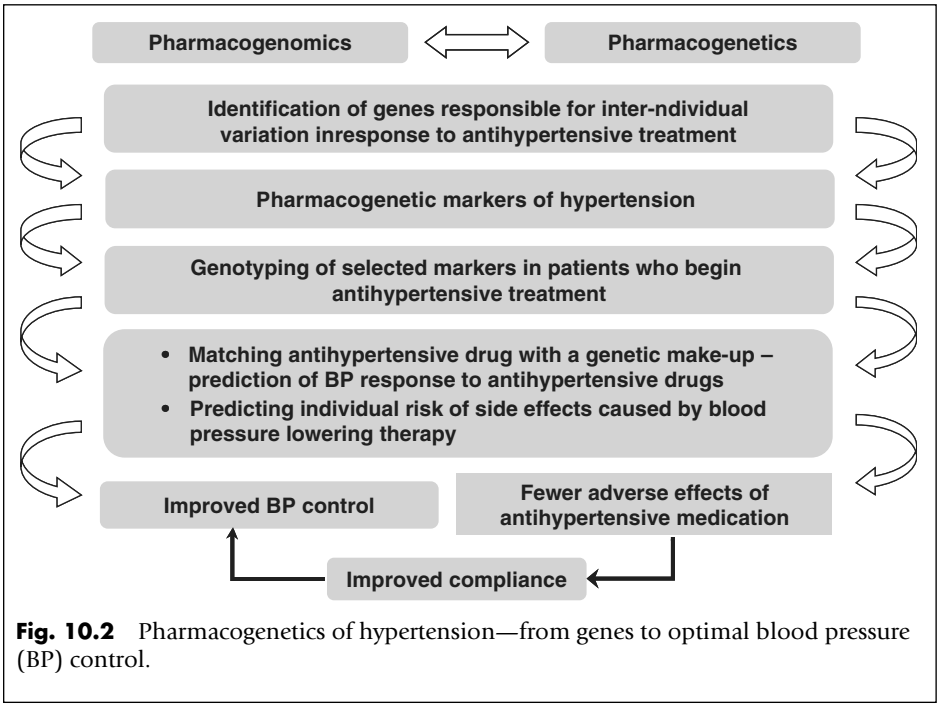

Fig. 10.2 Pharmacogenetics of hypertension—from genes to optimal blood pressure (BP) control.

Table 10.2 Syndromes associated with pheochromocytoma (PHEO)—genetic testing

Syndrome	Clinical manifestation	Clinical characteristics of pheochromocytoma	Causative gene product (gene symbol)	Most common mutations	Methods of genetic testing	Major ref.
Neurofibromatosis 1 (NF1)	*Café au lait macules* Neurofibromas Treckling in the axillary or inguinal regions Optic glioma Lisch nodules (iris hamartomas) Osseous lesions Pheochromocytoma	PHEO does not belong to the standard diagnostic criteria of NF1 Not very common in normotensive patients but the risk of PHEO rises up to 50% in the presence of hypertension Screening for PHEO is recommended once a year in NF1 patients with hypertension	Neurofibromatosis-related protein NF-1 (NF1)	Nonsense, missense, frameshift, splicing mutations Whole gene deletions Small intragenic deletions	Optimized protein truncation testing Direct sequencing Fluorescent in situ hybridization (FISH)	47,49
Multiple endocrine neoplasia type 2A (MEN2A)	Medullary carcinoma of the thyroid Pheochromocytoma Parathyroid adenoma/ hyperplasia	PHEO is diagnosed in 50% of MEN2A cases, usually after medullary carcinoma of the thyroid is confirmed Bilateral PHEO is common Malignant transformation is rare	Proto-oncogene tyrosine-protein kinase receptor ret precursor (RET)	Nonsynonymous substitutions in one of six codons in the extracellular domain of the encoded protein	Mutation scanning Direct sequencing	50,52
Multiple endocrine neoplasia type 2B (MEN2B)	Medullary carcinoma of the thyroid Pheochromocytoma Thickened corneal nerves Mucosal neuromas Marfanoid body habitus	Multiple or bilateral PHEO is very common	Proto-oncogene tyrosine-protein kinase receptor ret precursor (RET)	Nonsynonymous substitutions in codons within the tyrosine kinase domain	Targeted mutation analysis	
von Hippel–Lindau Syndrome (VHL Syndrome)	Retinal angioma Hemangioblastoma of the brain or spinal cord Endolymphatic sac tumors Pheochromocytoma Renal cysts or renal carcinoma	Early onset, multifocal PHEO is common Malignant transformation of PHEO is rare Screening for pheochromocytoma is recommended in all VHL patients aged 5 years or older	von Hippel–Lindau disease tumor suppressor (VHL)	Frameshift, nonsense, missense, and splice site mutations in the exons Complete gene deletions	Direct sequencing Southern blot analysis	51,52
Paraganglioma syndromes	Tumors derived from ganglia of the head, neck, thorax, abdomen, or pelvis	PHEO may coexist with extra-adrenal tumors	Succinate dehydrogenase complex subunits (SDHB, SDHD, SDHC)	Frameshift, nonsense, missense, and splice site mutations in the exons Mutations in SDHD are most common	Direct sequencing	52,53

manifestations of ADPKD (i.e., cerebral aneurysms) (46). However, certain ethical and practical concerns have been raised with regard to genetic testing in subjects at risk of ADPKD (55). PKD1/PKD2 screening was suggested as a source of genetic discrimination in employment and insurance as well as a factor that has a negative impact on the overall well-being in asymptomatic carriers of the causative mutations (55). The potential negative aspects of genetic screening must be clearly considered before the tests are instituted in patients at risk of ADPKD. However, these disadvantages are overshadowed in confrontation with the overall clinical benefit of early diagnosis (46).

Availability of gene testing in patients with secondary hypertension clearly illustrates how clinical management of patients with elevated BP has been improved as a result of progress in genetic research. In addition, familial screening and genetic counseling are emerging as new clinical approaches in affected pedigrees. Progress in genetics of secondary hypertension holds a promise of integration of molecular testing into the standard diagnostic evaluation in patients admitted to the reference hypertension centers.

PHARMACOGENOMICS OF HYPERTENSION

Optimal BP control is achieved in only one quarter of hypertensives, leaving most with suboptimal BP control and an increased risk of cardiovascular complications. This can be attributed to the heterogeneity of the response to antihypertensive therapy, noncompliance, and partly to side effects that contribute to withdrawal of treatment. Though evidence-based guidelines have been devised for the use of these drugs (56), the final choice of therapy remains empirical. Progress toward identifying individual patients' characteristics that predict BP response prior to drug administration has been limited. African-Americans are reported to be more responsive to diuretics and calcium channel blockers (CCBs) and less responsive to beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs) than Caucasian subjects. Neither gender nor age nor measures of body size have been shown to predict response to antihypertensive treatment (57,58).

Pharmacokinetic mechanisms determine the level of the drug in the blood and ultimately at its target, while pharmacodynamic mechanisms are responsible for the interaction of the drug with its target and the subsequent cellular and systemic events. Genetic variation that alters the structure, configuration, or quantity of any of the involved proteins may contribute to interindividual variation in drug response. For the majority of drugs, the frequency distribution for most measures of response is unimodal or Gaussian, consistent with a multifactorial determination, with no single factor having a discernibly large effect on response (59). Single gene polymorphisms with large effects on drug response are now less important as antihypertensive drugs metabolized by the polymorphic enzymes involved in debrisoquine hydroxylation, *N*-acetylation, and catechol-*O*-methylation are no longer widely used (60). Thus, pharmacodynamic mechanisms may play the predominant role in determining interindividual variation in BP responses to common antihypertensive drugs.

So far, restricted genotyping and analytical capabilities have limited pharmacogenetics to association studies of a priori selected candidate genes. Obvious candidate genes are those that encode components of a BP regulatory system targeted by the drug or components of the counter-regulatory systems that oppose the drug-induced fall in BP. The commonly used antihypertensive agents—diuretics, ACEI, angiotensin-receptor blockers (ARBs), CCB, and beta-blockers—have been involved in association studies to predict drug response, but the results have not been consistently replicated.

Variants in genes that encode α-adducin, G protein β_3 subunit, epithelial sodium channel, ACE, angiotensinogen (AGT), angiotensin (AT) type 1 receptor, and aldosterone synthase have been tested so far as potential genetic determinants of response to diuretics (61). None of the polymorphisms have shown a reliable and consistent association with diuretic response, and the initial promising findings regarding α-adducin gene variants (62) have not been consistently replicated in other populations.

There is a significant variability in individual response to beta-blockade by age and ethnicity. Polymorphisms in the β_1-adrenergic receptor gene, G_s protein α subunit gene, G protein β_3 subunit gene, ACE, and AGT gene have been studied in association studies on beta-blocker response, but the results are not overwhelmingly convincing (61).

The most common candidate variants of the renin–angiotensin–aldosterone system that have been examined in order to identify genetic markers of response to ACEI include insertion/deletion polymorphism (ACE), M235T polymorphism (AGT gene), and A1166C (type-1 AT II receptor gene). These studies have failed to demonstrate an interaction between the genetic variants and BP response to ACEI.

There is evidence for associations between the genetic variation within the molecules that metabolize ARBs and BP response to this class of antihypertensive medication. The cytochrome P450 2C9 enzyme metabolizes irbesartan and losartan to an active product with antihypertensive effects (63,64), and it was suggested that individuals with a single CYP2C9*3 allele exhibit decreased response to losartan. The SILVHIA study (65) showed that the CYP2C9*1/CYP2C9*2 genotype was associated with a greater percent change in diastolic BP after treatment with irbesartan than the CYP2C9*1/CYP2C9*1 genotype. The other ARBs are minimally metabolized in the presence of the CYP2C9 genotype. The clinical relevance of these findings must be verified in larger populations.

CCBs do not currently appear to have any significant gene–drug interactions. A majority of CCBs are metabolized chiefly by CYP3A4 but it is not clear whether the genetically mediated interindividual variability in these enzymes actions translates into BP response to CCBs (66). A polymorphism in the CYP2D6 enzyme gene may significantly alter the disposition of diltiazem metabolites but the clinical relevance of this finding remains to be elucidated (67).

Apart from candidate gene approach, panels of genetic markers (microsatellites) were used to search the entire genome for regions linked to BP response induced by antihypertensive medication. As no prior knowledge or assumptions are required about gene function, one attractive feature of this approach is the possibility of identifying new genes outside classical regulatory pathways. Moreover, the relative strength of linkage evidence accompanied by existing knowledge about functions of genes within the linked regions can help to prioritize the subsequent search for functional mutations in the positional candidates. The first genome-wide linkage analysis using partitioning of different pathways of hypertension based on drug response found a

susceptibility locus on chromosome 2p at 90.68 cM in white European nonresponders to AB group of antihypertensives (68).

In the future, statistical and biological models and molecular analysis of target tissues are likely to be critical for studies that aim to elucidate polygenic determinants of drug response. Large clinical trials of uniformly treated and systematically phenotyped patients, high-throughput genotyping methods, and sophisticated bioinformatic analyses will be needed to promote pharmacogenomics from basic science to a clinically useful tool.

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ENVIRONMENTAL FACTORS IN HYPERTENSION 11

Alberto U Ferrari

INTRODUCTION

In the present chapter, the term "environmental" is broadly intended to encompass the wide range of elements believed to implicate in the genesis and maintenance of hypertension but not directly dependent on the subject's genetic characteristics. They may be operationally categorized as dietary, behavioral, and environmental "stricto sensu," although items bridging across such categories exist.

DIETARY FACTORS

Virtually all components of the omnivorous human diet, i.e., protein, fat, and carbohydrates, as well as an array of single dietary "chemicals," including electrolytes, alcohol, vitamins, marine oils, caffeine, fiber, and many others, have been implicated as being able to raise or lower blood pressure (BP) and, thus, to respectively promote or hamper the development of hypertension.

As a result of huge investigational efforts devoted to observational population or cohort follow-up studies, as well as to smaller-sized dietary intervention studies, the emerging consensus is that many "candidate" nutrients have minimal or no long-term BP effect, whereas, for a limited number of dietary components, the ability to affect BP was confirmed, although (probably with the only exception of sodium) the size of the effect of single substances is small. This is by no means to be viewed as a failure, nor does it detract from the crucial importance of continuing our investigation of dietary effects (and of the possible derived dietary interventions and recommendations), because (*i*) at the population level, even small BP differences are known to have sizeable morbidity/mortality implications, and (*ii*) at the individual level, implementation of multiple dietary modifications may end up having nontrivial protective effects against the development of hypertension and of cardiovascular disease at large.

SODIUM

The body of the evidence documenting the role of dietary salt in hypertension is impressive and long-standing. In time-honored observations, the strikingly high prevalence of high BP in Bahamian residents (1) was clearly linked to the excess NaCl content of the drinking water in that area (2); the notion of the "environmental" role of salt interacting with the genetic background to determine the BP levels of individuals or populations has been well established since the 1950s (3).

Throughout the subsequent years, the contribution of even much less extreme variations in dietary salt to BP was uninterruptedly addressed by epidemiological, clinical, and experimental research. Landmark studies in this area have been the Intersalt Study, a huge, international, 32-country effort on >10,000 subjects aged 20–59 years, in whom salt intake was assessed by measurement of 24-h urinary sodium (Na) excretion. The results indicated that a difference in 100 mmol/day of Na intake (6 g of NaCl) is associated with a systolic/diastolic BP difference up to 6/3 mmHg, the relationship holding across the various subgroups considered: normotensives or hypertensives, younger or older aged, men or women; salt intake also affected (steepened) the slope of the BP/age relationship (4). Later analyses of the Intersalt database suggested that the magnitude of the Na-related influence may be even larger than initially estimated (5).

The concepts emerging from the cross-sectional Intersalt data were fully supported by the cohort findings of the Multiple Risk Factor Intervention Trial, in which a 6-year follow-up on >11,000 individuals showed dietary salt (in this case indirectly assessed from dietary records) to be independently and directly related to systolic and diastolic BP, irrespective of the concomitant administration of antihypertensive drugs (6). Evidence from many other studies strengthened and extended the above notions. To list just the major points, this study indicates that the BP lowering properties of Na restriction: (*i*) are also detectable in infants, children, and adolescents (7,8); (*ii*) are at least partly additive to other major dietary modifications, such as those contemplated by the dietary approach to stop hypertension (DASH) diet (see below) (9); (*iii*) play not only a therapeutic but even a preventive role against hypertension (10); (*iv*) are particularly pronounced in subjects of advanced age; and (*v*) show large interindividual and interracial variability, probably in relation to polymorphisms in the many genes implicated in the cardiovascular and renal adaptive responses to variations in Na intake, such as,

e.g., genes controlling the adrenergic or the renin–angiotensin systems.

Despite the bulk of the accumulated evidence in favor of the benefits of Na restriction, concerns have been repeatedly raised as to possible adverse effects of this dietary measure on a variety of outcomes, such as, e.g., insulin sensitivity, serum lipids, fetal growth, cardiovascular homeostatic capabilities, and even general health and total mortality (11,12). At present, the validity or relevance of most of these caveats has been questioned, especially as far as the consequences of moderate Na restriction are concerned, and the expert consensus, widely reflected in various Hypertension Guidelines (13–15), is that, in a salt-conscious diet, the daily intake of NaCl should not exceed 5–6 grams.

POTASSIUM

Demonstrating the inverse relationship between potassium (K) intake and BP has been made difficult by the relatively small extent of K's effect and by the simultaneous and parallel changes in the intake of other elements—especially calcium and magnesium—associated with the dietary modifications that affect K intake. However, the body of the evidence obtained from animal studies, as well as from human observational and intervention studies and their meta-analysis (16,17), now strongly indicates that an increase in dietary K lowers BP in normotensive subjects, and even more so in hypertensive subjects. The order of magnitude of the lowering is 3–5 and 2–3 mmHg for systolic and diastolic pressure, respectively; the effect seems to be similar in males and females, is particularly pronounced in blacks (18), and is interdependent and largely nonadditive to the effect of Na restriction—namely, it is limited in subjects already eating low-salt diets and vice versa, whereas, conversely, salt restriction has smaller BP lowering effects in subjects eating K supplements (19). The current recommendations regarding K intake for the primary prevention of hypertension, as well as a nonpharmacological tool in hypertension treatment, suggest that 4.7 g (120 mmol) are ingested daily, preferably by increasing the fruit/vegetable content of the diet rather than by employing K pills (13).

CALCIUM AND MAGNESIUM

Despite the considerable interest and research efforts devoted to document a possible BP-lowering effect of calcium supplementation, especially during the 1980s and 1990s (20), the consensus has been that, although likely to exist, such effect is minute in size and insufficient to generate a recommendation on the usefulness of calcium supplementation in the prevention or treatment of high BP. Similar views apply to the effects of dietary magnesium (13).

ALCOHOL

The BP-rising effect of a more than moderate intake of alcohol is now well established based on observational and intervention studies (21,22). The effect is dose-dependent and largely unrelated to concomitant factors able to affect BP, such as obesity, age, or other diet components: it is estimated that cutting alcohol intake to below 35 g daily (corresponding to, e.g., two cans of regular beer or two glasses of wine) may lower systolic and diastolic BP by some 3–4 and 2 mmHg, respectively (23). Also, considering the calorie intake/body weight implications of drinking, alcohol moderation represents an important nonpharmacological tool for both prevention and treatment of hypertension.

CAFFEINE, FIBER, PLANT PROTEIN, FISH OIL, CARBOHYDRATES

These and other dietary components received attention by investigators, and are often mentioned by patients, as possible contributors to higher or lower BP levels. Although they may indeed have such potential, no recommendations can at present be made as to their role in hypertension prevention or treatment because of insufficient/inconsistent scientific knowledge (e.g., fiber), small/transient BP effect (e.g., caffeine), unfeasibility/poor tolerability of the dietary modification (e.g., high dose fish oil) (13).

OVERALL DIETARY PATTERNS

A clear-cut reduction in BP is obtained when appropriate modifications of multiple rather than single dietary components are simultaneously implemented. The prototypical study illustrating the effects of this strategy was the DASH study (9), in which over 450 subjects with normal BP, or grade 1 hypertension, were subjected to strictly controlled food and beverage intakes and followed up to determine the BP effects of switching from a control diet (low in fruits, vegetables, and dairy products, and with a fat content typical of the average diet in the United States) to (*i*) a diet rich in fruits and vegetables and an unchanged fat composition, or (*ii*) a "combination" diet rich in fruits and vegetables along with greater amounts of low-fat dairy products to the expense of the amount of saturated and total fat (Table 11.1). Na and alcohol intake were not an object of the investigation and were kept constant throughout, as was body weight (with adjustments of total daily calories as needed). Over an 8-week observation period, the combination diet significantly reduced systolic/diastolic BP by 5.5/3.0 mmHg, with a much more pronounced effect in the subset of hypertensive patients (about a third of the whole population, with a 11.5/5.5 mmHg BP reduction) compared to the normotensive subjects (whose BP was reduced by 3.5/2.1 mmHg). The BP lowering effect of the fruits and vegetables diet was sizeable, but some 50% less pronounced than that of the combination diet.

Table 11.1 Main food groups modified in the DASH (combination) diet

Increased	Decreased
Fruits and juices	Red meat, pork, ham
Vegetables and legumes	Fats, oils, salad dressings
Nuts and seeds	Snacks
Low-fat dairy products	Sweets
Fish	Pop beverages

Abbreviation: DASH, dietary approach to stop hypertension.

Subsequent studies could demonstrate that the BP reduction one can obtain by combining the DASH diet with salt restriction are, at least to some extent, additive (24). This is, on the one hand, of practical importance, as it emphasizes the usefulness of recommending multiple dietary modifications to maximize BP lowering effectiveness (Figure 11.1); and, on the other hand, this raises the mechanistic question of why the combined effects were at least partly redundant (smaller than the sum of the single dietary measures). Although no firm answer is available, the most likely explanation relates to the interactions between the effects of Na restriction and K supplementation; namely, the low-salt regimen attenuated the BP reduction brought about by the K-rich DASH diet, and vice versa.

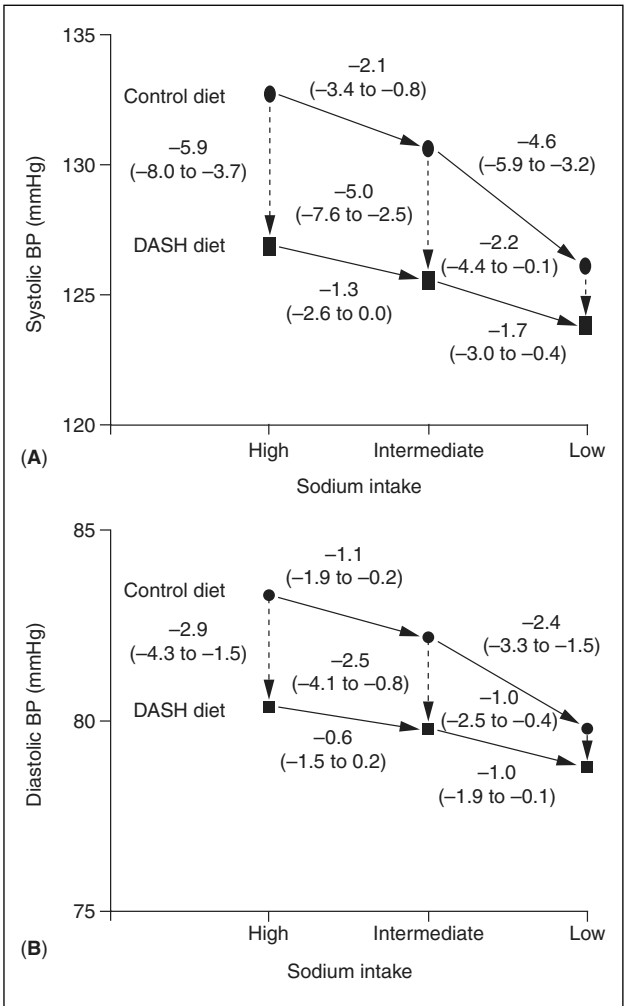

Fig. 11.1 The effect of reduced sodium (Na) intake and the dietary approach to stop hypertension (DASH) diet on systolic blood pressure (BP) (**A**) and diastolic BP (**B**). The mean systolic and diastolic BPs are shown for the high-Na control diet. The mean changes in BP are shown for various Na levels (*solid lines*), and the mean differences in BP between the two diets at each level of Na intake are shown. Unidirectional arrows are used for simplicity, although the order in which participants were given the Na levels was random with a crossover design. The numbers next to the dotted lines connecting the data points are the mean changes in BP. The 95% confidence intervals are given in parentheses. *Source*: Reproduced from Ref. 24.

BEHAVIORAL FACTORS

Lifestyle characteristics (including the above-mentioned dietary ones as well as those reviewed herein) have profound influences on health outcomes and are the determinants of some of the major modifiable cardiovascular risk factors: their successful management would confer strong benefit at virtually no cost, but are faced with the paradox of being very difficult to implement and, especially, to maintain over time at both the individual and the population level.

EXERCISE

Regularly exercising provides therapeutic and preventive benefits for countless health problems, and high BP makes no exception. Most hypertension authorities recommend that 30–60 min of moderate intensity dynamic exercise are performed at least 3–4 times per week, the types of suggested activities spanning from running to swimming, walking or cycling; there is no need of reaching strenuous exercise intensities (which may be indeed contraindicated in large subsets of the hypertensive population), nor are isometric activities, such as weight lifting or body building, recommended.

Documenting the inverse relationship between BP and the amount of physical activity has been difficult in cross-sectional studies because of the many methodological difficulties and confounding factors, but was successfully achieved via longitudinal studies and their meta-analysis (25,26). The magnitude of the systolic/diastolic BP-lowering effect of physical activity is in the order of 5/3 mmHg, with hypertensive patients showing larger responses than normotensive individuals. The usefulness of exercise extends to all age groups, including elderly individuals, in whom, however, caution and graduality are of utmost importance to avoid the risk of negative effects, including acute myocardial infarction and sudden death; the same applies to patients with uncontrolled hypertension or with any serious medical condition.

The mechanisms underlying the exercise-dependent BP-lowering are incompletely understood: shifting from a sedentary to a physically active lifestyle is known to bring about a fall in total peripheral resistance, with some degree of bradycardia, but some increase in stroke volume, and, thus, little or no change in cardiac output. There is evidence that the cardiovascular homeostatic systems implicated in the above hemodynamic modifications include the sympathetic nervous system and the renin–angiotensin system, whose activities are diminished (27,28), as well as the endothelium, whose major vasoactive factors, nitric oxide and endothelin, show reciprocal changes, the former being increased and the latter reduced (29).

OVERWEIGHT AND OBESITY

Excess adiposity has long been known to represent a cardiovascular risk factor, although recent reports support the notion that this relationship is not straightforward (30) and that quantitation of the weight disturbance by body mass index (BMI, by far the most commonly used parameter) may fail to adequately account for the "qualitative" aspects of fat accumulation; more adequate measures would be those reflecting

abdominal adiposity, such as waist circumference or waist-to-hip ratio (WHR) (31). As far as hypertension is concerned, there is, in most of the world's populations, a direct correlation between BP and body weight, and the close relationship between body fat and BP is firmly established and systematically identified in different populations irrespective of how the former is measured (32–34). Table 11.2 shows the dramatic effects of being overweight or more severely obese on the risk of hypertension in the NHANES III Survey; the subgrouping of the population according to age emphasizes that the obesity-related risk of hypertension is particularly high in the younger age range (<55 years) in either males or females.

Conversely, successfully pursuing even a small reduction in body weight (obtained by energy intake restriction, alone or in combination with increased physical activity) is an extremely effective antihypertensive measure, the extent of the fall grossly amounting to 1 mmHg systolic per kilogram of body weight lost (35). This has not only therapeutic but also preventive value in as much as it is seen in both hypertensive and normotensive individuals.

The pathogenic links between obesity and high BP are multifold and far from being understood; they are indeed being given an enormous amount of attention and research efforts, due to the central role of overweight/obesity in the so-called metabolic syndrome (MS), a condition associated with surprisingly heavy implications in terms of future occurrence of cardiovascular events and development of diabetes, as shown in many observational studies, and recently further characterized in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study population (36). Covering the complex features of the MS (not only the pathophysiology, but even its very existence, which, as a disease entity, is a subject of debate) as well as of overweight/obesity in relation to the genesis of hypertension is beyond the scope of this discussion: suffice it to say that improper functioning of virtually every known cardiovascular regulatory mechanism (autonomic nervous system, natriuretic hormones, endothelium, renin–angiotensin system, vascular trophic influences, etc.) has been claimed to contribute to the rise in BP and to the increased cardiovascular risk in addition to the alterations in carbohydrate and lipid metabolism typical of these conditions.

SMOKING

Acute smoking is well known to raise BP, with a consistent 15–20 min elevation occurring after each cigarette smoked (37). In contrast, an association between chronic smoking and a raised BP has been difficult to demonstrate; indeed, many office BP observations indicated that, compared to nonsmokers, regular smokers have a similar or slightly lower BP (38,39). However, those measurements are most likely performed quite apart from any recent smoking, thus not accounting for the acute BP-rising effect of smoking, and ambulatory BP studies did indeed reveal a higher daytime BP in smokers. The difference was, however, of limited magnitude, confined to systolic values, and only observed in older but not in younger patients (40): this indicates that any independent, chronic effect of smoking on BP is small, if any (41). This does not mean, however, that, whatever epidemiological studies may tell, it is most likely that especially heavy smokers have a consistently higher "area under the curve" of their BP values due to the acute effects of each smoked cigarette. Even more importantly, this by no means detracts from the tremendous importance of quitting smoking in either normotensive or hypertensive subjects due to the adverse health consequences of smoking irrespective of its BP effects.

PSYCHOLOGICAL STRESS

Despite the attractive hypothesis that, especially in western countries, intense psychological factors such as mental stress, anxiety, or depression may play a causative role in hypertension, evidence concerning this possibility has been at best controversial (42,43); these factors may indeed provide some contribution to the genesis of coronary heart disease (44) but are likely to do so via mechanisms other than inducing chronic BP elevation. Conversely, treatment of hypertension by means of biofeedback or other stress management techniques provided inconclusive results (45).

ENVIRONMENTAL FACTORS (STRICTO SENSU)

NOISE

Although methodologically difficult because of many hardly avoidable confounding factors, research concerned with the relationship between ambient noise and hypertension provided evidence in favor of such relationship for individuals exposed to both occupational and airport noise, the relative risk compared to nonexposed individuals amounting to some 1.2 per 5 dB(A) increase in ambient noise

Table 11.2 Prevalence and relative risk of hypertension as a function of body weight status in younger and older men and women

	Normal weight prevalence	Overweight RR	Obesity class I RR	Obesity class II RR	Obesity class III RR
Men <55 years	12.1	1.62	2.52	4.50	4.60
Men >55 years	54.4	1.11	1.35	1.47	1.66
Women <55 years	8.5	1.65	3.22	3.90	5.45
Women >55 years	61.7	1.16	1.24	1.42	1.41

Abbreviation: RR, relative risk compared to normal weight.
Source: From the NHANES III Survey, 1988–1994, modified from Ref. 34.

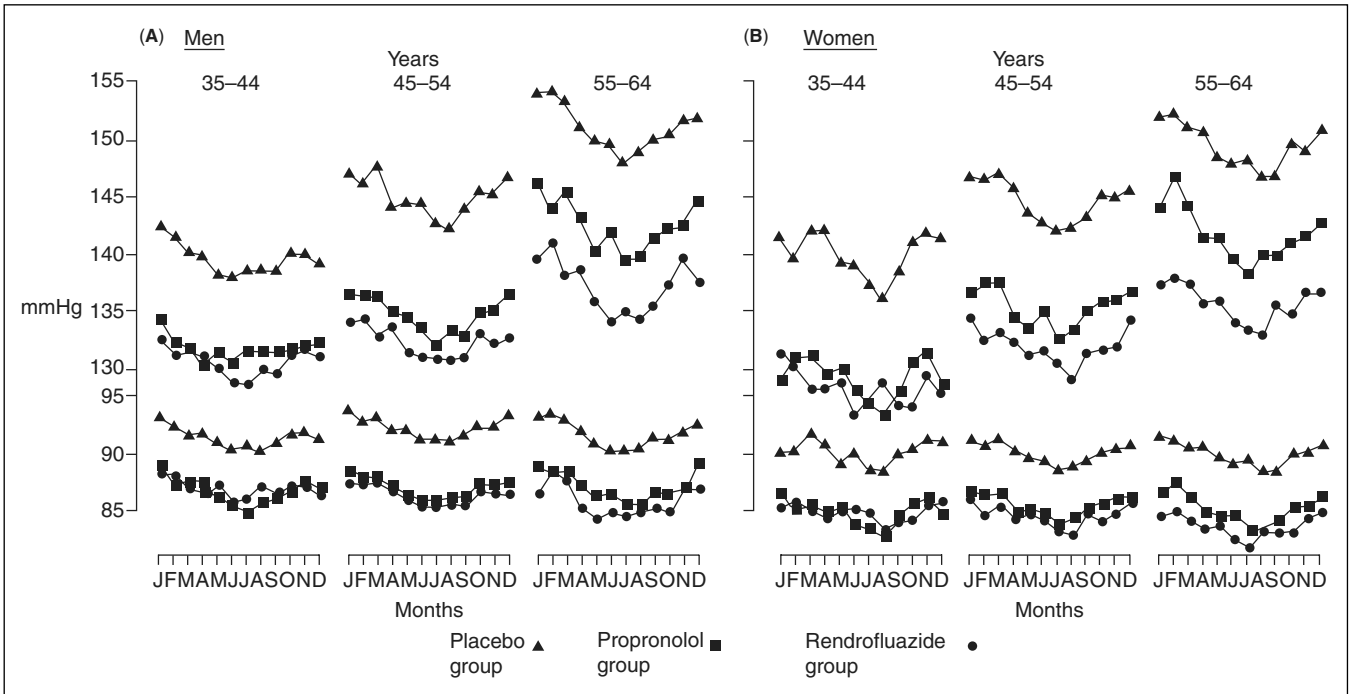

Fig. 11.2 Medical Research Council (MRC) treatment trial for mild hypertension. Seasonal trends in blood pressure in (**A**) men and (**B**) women by age and treatment regimen. *Source*: Reproduced from Ref. 51.

intensity, and with airport noise appearing to be slightly more "hypertensinogenic" than occupational noise (46,47). A large-scale international trial addressing the BP effects of both airport and road traffic noise in the neighborhoods of several European airports is ongoing (48).

POLLUTION

There is a fair amount of evidence that air pollution increases the risk of cardiovascular disease, and this may be in part due to transient rises in BP (49,50). Instead, no available evidence supports the notion that air pollution plays a causative role in chronic hypertension.

SEASONAL VARIATIONS

It is every doctor's experience that the BP values observed during summer are lower than those measured during colder seasons. The seasonal trend has been well characterized in large-scale hypertension studies, as shown in Figure 11.2 (51), and has been confirmed by ambulatory BP studies, which, interestingly, observed that seasonal effect is confined to daytime but not to nighttime BPs (52,53). These phenomena may have important clinical and epidemiological implications, because they can, e.g., warrant downtitration of antihypertensive drug dosage during hot weather, in lack of which many patients, especially the elderly ones, may be overtreated and experience hypotensive symptoms, or may interfere with proper subjects' classification in BP surveys spanning over different seasons. On the other hand, seasonal effects are unlikely to bear any etiologic role in the development and course of the hypertensive disease.

CONCLUSIONS

In summary, reviewing the environmental factors able to affect BP not only reveals important epidemiological, clinical, and pathophysiological features, but also supports the more general biological consideration that our genome is "designed" to subserve a behavior characterized by substantial degrees of physical activity, as well as a diet rich in plant-derived food that is unlikely to be over caloric. The urbanization and acculturation processes typical of western societies led to profound deviations from the above behavioral patterns and opened the way to progressive increase in body mass, higher BP, and propensity to metabolic abnormalities, such as diabetes and dyslipidemia. Efforts by health professionals, politicians, and individuals to obtain an at least partial correction of these behavioral "errors," especially in terms of calorie restriction, avoidance of excess alcohol, proper dietary Na/K intake, and daily amount of physical activity, are and will be a major challenge in the prevention and management of hypertension and cardiovascular disease.

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STRUCTURAL CARDIOVASCULAR CHANGES IN HYPERTENSION 12

Harry AJ Struijker Boudier

INTRODUCTION

The basic structure of the cardiovascular system is determined early in the development of an individual. However, after birth, and even in adult stages of life, the structure of the heart and blood vessels are not static: these structures undergo constant remodeling. Remodeling can be part of an adaptive process in which the altered structure contributes to homeostatic control of, for instance, mechanical forces in the heart and blood vessels. Remodeling can also be part of a pathological series of events in the cardiovascular system and its end organs.

Hypertension is associated with both types of remodeling. In hypertensive individuals, structural changes in the heart and blood vessels have been observed even in the early phase of blood pressure (BP) elevation. In the long-term, these structural alterations form a key factor in the maintenance of an elevated BP. In this chapter, the major structural changes in the heart and blood vessels in hypertension are reviewed. Furthermore, this chapter discusses how these changes contribute to the target organ damage in hypertensive disease.

STRUCTURAL CHANGES IN THE HEART

Hypertension is associated with structural changes in the heart. These changes involve hypertrophy of the left ventricle (LVH), fibrosis of the myocardial interstitium, and coronary angiopathy.

LEFT VENTRICULAR STRUCTURE AND ITS FUNCTION IN HYPERTENSION

Increased arterial BP initially induces concentric LVH with an increase in wall thickness and left ventricular muscle mass. This is a compensatory mechanism to maintain a normal cardiac output and ejection fraction. However, already in this stage there is a decreased coronary flow reserve. With time, the fibers of the hypertrophied muscle become thickened and shortened. In addition, there is a gradual interstitial proliferation of connective tissue. Together, these changes induce an increase in ventricular radius, end-diastolic volume, and systolic wall stress. Due to ventricular dilatation, the LVH becomes eccentric, with a diminishment of ventricle pump indices (cardiac index, ejection fraction). In this stage, there is usually also a strong involvement of coronary macro- and microangiopathy, contributing to a more severely reduced coronary flow reserve.

LVH has become an important parameter in the assessment of hypertensive patients. LVH is a strong independent predictor of cardiovascular morbidity and mortality. In cases of hypertension, it increases the risk of stroke, ischemic heart disease, and, eventually, congestive heart failure (1). The prevalence of LVH in a mild- to moderate-hypertensive population is 20–50% (2,3). There are now various methods to assess LVH in hypertensive patients (4). These include the classical electrocardiogram, echocardiography (both two- and three-dimensional), and cardiac magnetic resonance imaging.

PATHOPHYSIOLOGY OF LVH IN HYPERTENSION

Although LVH is usually regarded as a consequence of chronic elevation of arterial pressure, this may not always be the case. LVH is a pressure-independent predictor of cardiovascular morbidity and mortality. In fact, up to 60% of the variance of LVH may be due to genetic factors independent of BP (5). An increasing number of genes have been identified that contribute to LVH. Among these genes, most target the renin–angiotensin–aldosterone system (RAAS), the natriuretic peptide family, or the adrenoceptor signaling cascade (6).

In recent years, the sequence of events leading from increased myocardial wall stress to LVH has been intensively studied. In this signaling cascade there is a central role for intracellular calcium release, which is an early response to mechanical and humoral myocyte stretch factors, including angiotensin II and endothelin. The increase in intracellular calcium results in activation of calcineurin, which dephosphorylates transcription factors of genes that lead to myocyte hypertrophy, such as beta-myosin heavy chain and beta-skeletal actin (6,7). These novel insights from molecular genetic studies suggest that LVH may be caused both by mechanical (pressure, stretch) and humoral factors, explaining why LVH can occur at least partly independent of pressure elevation.

Another important aspect of the pathophysiology of LVH in hypertension is the question of how LVH leads to heart failure. In this transition, fibrosis of the interstitium of the myocard plays a central role. Fibrosis can be triggered by humoral factors. The RAAS is again a key factor in initiating fibrotic changes in the heart. Other important mediators include matrix metalloproteinases (MMPs) (8), integrins, such as osteopontin (9), and inflammatory cytokines, e.g., transforming growth factor beta. These mediators are now important targets for novel drugs in the regression of LV structural changes.

STRUCTURAL CHANGES IN THE CORONARY VASCULAR BED

In hypertensive patients, coronary vascular resistance and coronary perfusion pressure are increased (10). An increase in coronary resistance has also been reported in hypertensive patients without LVH (11). These observations suggest an important role for coronary microangiopathy independent of LVH. Coronary reserve, a measure of the capacity of the coronary vasculature to respond maximally to vasodilator agents, is significantly decreased in hypertensive patients. The exact clinical consequences of these abnormalities in coronary perfusion are far from clear (12). Presumably, under conditions of increased myocardial oxygen demand, decreased ability to dilate the coronary microvasculature translates into diffuse ischemia and infarction. Such a propensity to ischemia may explain some of the increased risk for coronary events and sudden cardiac death in patients with LVH. In addition, impaired subendocardial blood flow may contribute to diastolic dysfunction and increase the risk and severity of heart failure (12).

The pathophysiology of coronary angiopathy in hypertension is still not completely understood. Several mechanisms may be involved. The first is endothelial dysfunction causing an impaired vasodilator potential of coronary microvessels. The second is a structural inward remodeling of the coronary arterial wall, causing an increased wall/lumen ratio of small coronary arteries and arterioles. This remodeling can occur in combination with perivascular fibrosis and subsequent compression of the outer surface of these small vessels (10). Finally, reduction of the number of small arteries, arterioles, and capillaries (rarefaction) is a further mechanism that induces reduced coronary flow and flow reserve (13,14).

STRUCTURAL CHANGES IN BLOOD VESSELS

Hypertension is associated with a range of structural changes in the vasculature. The nature of the changes and their functional consequences differ per segment of the vascular tree (Table 12.1). The most significant alterations occur on the arterial side and in the microcirculation. With respect to arterial structural changes, a distinction can be made in large arteries (the aorta and its side-branches), small arteries, and arterioles. The large arteries primarily serve a conduit and compliance function, whereas the small arteries and arterioles control vascular resistance. The difference between large and small arteries is also reflected in the heterogeneity of the way in which they remodel in response to a rise in BP. Large arteries adapt to increased pressure by expressing early response genes that lead to vascular smooth muscle cell (VSMC) hypertrophy and an increased wall thickness. Small arteries, on the other hand, rapidly constrict without changing wall material (eutrophic inward remodeling) and thereby normalizing wall stress. Only in severe hypertension, small vessels may also undergo hypertrophic remodeling (15).

Table 12.1 Segments of the vascular tree and their structural change in hypertension

Segment of the vascular tree	Structural change	Functional consequence
Large arteries	Vascular smooth muscle cell hypertrophy	Distensibility ↓
	Extracellular matrix composition	
Small arteries	Inward remodeling	Distensibility ↓
	Extra cellular matrix composition	Resistance ↑
Arterioles	Inward remodeling	Resistance ↑
	Rarefaction	
Capillaries	Rarefaction	Resistance
		Tissue ischemia

The basic architecture of arteries is usually described in terms of cross-sectional arrangement of cells and extracellular matrix. Cells include the endothelial cell layer and VSMCs. The extracellular matrix consists of lamellae of elastic material with intervening layers of VSMCs, collagen fibers, and ground substance (16). However, the distribution of elastin and collagen varies markedly along the longitudinal axis. In the proximal aorta, elastin is the dominant component, whereas in the distal aorta and its side-branches, as well as in the smaller arteries, collagen predominates. The smaller the arteries become, the more VSMC predominate. These differences find their origin in the early development of the vascular system. The reader is referred to the specialized literature for further details on this aspect of vascular development (16).

LARGE ARTERY STRUCTURE AND FUNCTION IN HYPERTENSION

In hypertensive patients, the stiffness of large arteries is usually increased. A complex interplay of genetic, structural, and functional modifications of the arterial wall contributes to the increased stiffness. The major genetic factors that determine arterial stiffness have recently been reviewed by Laurent et al. (17). Epidemiological studies have shown that up to 40% of the variance in indices for arterial stiffness may be genetically determined (18). Furthermore, the relationship between polymorphisms of several candidate genes and arterial stiffness has been investigated. Various candidate genes of the RAAS play a key role in arterial stiffness. However, the contribution of a given gene polymorphism to the variance of a specific phenotype is limited (17). In subjects of the Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO) study we found a much stronger contribution in individuals showing specific combinations of gene variants (19). For instance, the combination of angiotensin-converting enzyme DD subjects homozygous for alpha-adducin Gly 460 was a powerful predictor of increased large artery stiffness.

Another genetic approach, particularly followed by Laurent and coworkers (17) is the study of large artery properties in subjects with monogenic disease or in knockout mice with

phenotypic changes in arterial wall properties. The data obtained following this approach highlights the role of extracellular matrix components, such as fibrillin (17). Furthermore, the data shows that collagen and elastin are not simply passive compounds that can be elastic or rigid, but that they are also involved in the control of VSMC function, such as migration, proliferation, adhesion, and cytoskeletal rearrangement (17) and may thus influence large artery properties in different ways.

Genetic factors operate, at least partly, via the structural composition of the arterial wall. However, nongenomic influences also contribute importantly to the increased large artery stiffness in hypertension. One factor is the elevated BP as such. An elevated pressure shifts the pressure– distensibility relationship toward a lower distensibility value (20,21). This observation led to the conclusion that hypertension-induced large artery hypertrophy is not necessarily associated with increased arterial stiffness (20). Despite increased wall thickness due to VSMC hypertrophy, the stiffness of the artery wall material as assessed by the modulus of elasticity is not increased in hypertensive patients or in the spontaneously hypertensive rat (SHR) (20).

Another source of nongenomic influence on large artery structure and function is a range of humoral and metabolic products. It is beyond the scope of this book to discuss all these products in detail. The RAAS has received most attention in this respect (for a recent review of the relevant evidence, see Ref. 22). Its major mediators—angiotensin II and aldosterone—affect arterial structure considerably and beyond their effects on BP. They activate signal transduction pathways that promote VSMC growth, inflammation, and fibrosis. The cytoskeleton is also involved in structural arterial changes, and evidence shows that many of these changes can be induced by the RAAS (22). Studies in both experimental animals and in humans with hypertension suggest that drugs blocking the RAAS have an impact on early mechanisms of vascular disease, such as endothelial dysfunction and arterial remodeling (22–24).

STRUCTURE AND FUNCTION OF SMALL ARTERIES IN HYPERTENSION

Small arteries primarily contribute to the control of vascular resistance, although they also have a compliance function. Essential hypertension is characterized by an increased peripheral vascular resistance. The structural change in small arteries underlying the rise in peripheral resistance is a narrowed lumen and an increased wall/lumen ratio (25,26). Small arteries in patients with essential hypertension undergo an inward eutrophic remodeling: a reorganization of the VSMC around a narrower lumen. Rizzoni et al. (27) have shown that patients with renovascular hypertension exhibit hypertrophic remodeling of small arteries due to smooth muscle cell hypertrophy, without evidence of hyperplasia. An increased wall/lumen ratio of small arteries was recently reported to be prognostically important in hypertensive patients (28). Furthermore, Schiffrin and coworkers (29) concluded from their observations that small artery structure is one of the first manifestations of target organ damage, occurring before proteinuria or cardiac hypertrophy.

Izzard et al. (26) reviewed the mechanisms of inward eutrophic remodeling of small arteries from essential hypertensive individuals. Their conclusion was that chronic vasoconstriction is the stimulus for a structural reduction in lumen diameter. The nature of the contractile stimulus is still not fully resolved. Neural or humoral factors may be involved, although Izzard et al. (26) favor the myogenic properties of the small arteries as the underlying mechanism. The myogenic vasoconstriction could serve to maintain wall stress at constant value. Patients with type 2 diabetes show a severely impaired myogenic constriction to increases in intraluminal pressure. In these patients, impaired myogenic tone would increase wall stress and thereby promote small artery hypertrophy (26).

In addition to these changes in VSMC structure and function, the extracellular matrix is critically important in the altered properties of small arteries in hypertensive subjects. With chronic vasoconstriction, some degree of cell migration, secretion of fibrillar and nonfibrillar components, and rearrangement of extracellular matrix–cell interactions may occur (25). Collagen deposition is significantly enhanced in small arteries from patients with essential hypertension (30,31). Deposition of collagen and other proteins contributes to media thickening and to reorganization of vessel wall components around an altered lumen (25).

STRUCTURE AND FUNCTION OF THE MICROCIRCULATION IN HYPERTENSION

The largest drop in BP between the aorta and veins takes place in the small arteries and arterioles of the microcirculation. This segment of the circulatory system is usually taken to encompass all blood vessels with a diameter $<150\,\mu m$. Capillaries have a diameter of 3–12 μm. They contribute to only a slight degree of resistance to flow. Their major function is to ensure fluid-metabolite exchange between blood and tissues.

The most consistent structural change in the microcirculation of hypertensive individuals is microvascular rarefaction: a reduced density of vessels in the microvascular network (14,32). Microvascular rarefaction can be functional or structural. Functional rarefaction refers to an abnormal low prevalence of anatomically existing but nonperfused microvessels. Structural rarefaction represents a situation in which the microvessels are anatomically absent. This can be due to either active elimination of microvessels or to a lack of growth during the development of microvascular networks (33). Studies in experimental animal models of hypertension have shown structural rarefaction in many tissues (14,34). In humans, Ruedemann already in 1933 reported that hypertensive patients had an abnormal low number of small conjunctival vessels (35). This observation has been confirmed by various investigators studying different tissues with more sophisticated visualization equipment (36,37). Evidence from both experimental animal models and human hypertension suggests that arteriolar and capillary rarefaction precede the onset of hypertension (14,37,38).

The cause and effect relationships between microvascular rarefaction and hypertension are still under discussion. Various authors have shown that mechanical forces due to increased pressure and/or flow may cause structural arteriolar and capillary rarefaction (34). Recent data suggests a significant role for endothelial cell apoptosis caused by oxidative stress (39). An alternative possibility is a primary defect in angiogenic mechanisms in subjects prone to develop hypertension. Evidence for this mechanism comes from studies in

normotensive humans with a familial predisposition to develop hypertension and who have an abnormally low microvascular density (40,41). The molecular mechanisms of abnormal angiogenesis have recently been studied by Levy and coworkers (34). They imply a crucial role for the endothelial NO and the RAAS. These systems do not only affect vascular tone, but also play an important role in angiogenesis. A recently studied factor in abnormal angiogenesis in hypertension is the bone-marrow-derived endothelial progenitor cell (EPC). Recruitment of these cells contributes to the formation of new microvessels in ischemic or inflamed tissue (42). Imanishi et al. (43) showed accelerated senescence of EPCs in hypertensive animals and humans, suggesting a potential lack of EPC-mediated angiogenesis in hypertensive subjects.

Microvascular rarefaction has two major consequences. Firstly, reduction of arteriolar density increases vascular resistance (44). Secondly, it disturbs the tissue delivery of oxygen and nutrients, thus contributing to target organ damage in hypertension.

CONCLUSION

Structural changes in the cardiovascular system contribute to the initiation and maintenance of BP elevation in hypertensive disease. Furthermore, structural changes in the heart and blood vessels play an important role in hypertension-induced target organ damage. In the treatment of hypertension, prevention of target organ damage is an increas-ingly important goal. We may expect that future therapies will specifically target the structural changes reviewed in this chapter.

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AUTONOMIC ABNORMALITIES IN HYPERTENSION 13

Guido Grassi

INTRODUCTION

The autonomic nervous system has moved toward center stage in cardiovascular medicine, a development supported by a number of evidences. First, an imbalance in autonomic cardiovascular control, with a resultant sympathetic activation and a parasympathetic inhibition, has been shown to be involved in the genesis of life-threatening cardiac arrhythmias and in the development of heart failure, as well as in the occurrence of sudden death, particularly in patients with obstructive sleep apnea (1–3). Second, alterations in autonomic cardiovascular control have been reported in metabolic diseases (diabetes mellitus, obesity, metabolic syndrome) displaying a major adverse impact on cardiovascular morbidity and mortality (4). Finally, in several diseases, most of them of cardiovascular nature (heart failure, acute myocardial infarction, malignant cardiac arrhythmias, renal failure, and acute stroke), an inverse relationship has been described between the degree of the sympathetic activation and the survival rate of the patients (5–9). Further evidence in favor of the renewed importance of the sympathetic nervous system in cardiovascular medicine comes from the data indicating that, in a substantial proportion of patients, essential hypertension has a neurogenic origin, the adrenergic overdrive contributing to the development, maintenance, and progression of the disease.

This chapter provides an overview of the autonomic alterations characterizing essential hypertension. This is done by examining (*i*) the data supporting the so-called "neurogenic hypothesis" of the pathogenesis of hypertension, (*ii*) the mechanisms responsible for autonomic dysfunction, and (*iii*) the consequences in terms of disease progression and end organ damage development, as well as the therapeutic implications of the parasympathetic/sympathetic imbalance.

EVIDENCE FOR AUTONOMIC DYSFUNCTION IN HYPERTENSION

Throughout the years, several techniques designed to quantify autonomic cardiovascular influences in humans have shown them to be altered along the whole clinical course of the hypertensive state. The early stages of hypertension are characterised by a hyperkinetic circulation, i.e., by an increased cardiac output coupled with a resting tachycardia largely dependent on a reduced parasympathetic function (10). Indeed, intravenous atropine (the drug that selectively blocks the effects of the vagal neurotransmitter acetylcholine on cardiac muscarinic receptors) induces, in young, borderline hypertensives, an increase in heart rate and cardiac output of lesser magnitude than that found in age-matched normotensive controls (10). Evidence has also been provided that the blunted parasympathetic tone observed in early hypertensive phases (*i*) is also a hallmark of established hypertension (11) and (*ii*) is not limited to the cardiovascular system, a reduced salivary flow (the control of which is under parasympathetic influences) being reported in subjects with borderline hypertension as well (12). Taken together, these findings support the concept that an autonomic dysfunction involving parasympathetic cardiovascular control characterizes, at the very early beginning, the hypertensive state.

The above-mentioned dysregulation is not limited only to the parasympathetic function, but affects sympathetic cardiovascular control as well. Multifold evidence supports this statement. In a meta-analysis of all published studies, Goldstein reported that, even accounting for some negative results, an indirect marker of sympathetic tone, such as plasma norepinephrine, is significantly elevated in essential hypertensive patients as compared to age-matched normotensive subjects (13). Furthermore, by employing the technique based on the intravenous tracer infusion of small doses of radiolabeled norepinephrine, Esler and coworkers were able to show that the rate of norepinephrine spillover from the neuroeffector junctions is increased in young subjects with a most borderline blood pressure (BP) elevation, and that this enhanced release takes place particularly in the kidney and in the heart, i.e., two organs of key importance in BP homeostatic control (14). Further evidence comes from the direct measurement of sympathetic nerve traffic to the skeletal muscle circulation, a technique which has allowed for documentation of an increase in central sympathetic outflow in young, borderline hypertensives (15). Finally, evidence indicates that, while parasympathetic dysfunction remains stable in the hypertensive state, characterized by more severe increases in BP, sympathetic activation

undergoes a progressive and further potentiation. This has been shown by a study performed by our group (16), in which we quantified sympathetic nerve traffic to the skeletal muscle district in three groups of age-matched subjects: with normal BP, with moderate essential hypertension, and with essential hypertension of a more severe degree. As shown in Figure 13.1, the progressive increase in BP values observed in these three conditions was paralleled by a progressive and marked elevation in sympathetic nerve traffic, suggesting the key role of adrenergic neural factors, not only in the development, but also in the progression, of the hypertensive state. A further demonstration of this phenomenon comes from evidence, collected years ago by our group, that BP variability, i.e., the magnitude of the BP oscillations occurring during the daytime and nighttime, which is largely dependent on adrenergic influences, causes an increase in hypertension, and progresses when hypertension becomes more severe (17).

Three further issues related to the autonomic alterations characterizing essential hypertension deserve to be mentioned. First, a state of sympathetic hyperactivity is not only a feature of young and middle-age hypertensives, but it also occurs in elderly hypertensives, even when the BP elevation selectively affects systolic values. Indeed, when sympathetic nerve traffic was recorded in elderly subjects with systodiastolic or isolated systolic hypertension, a clear-cut sympathetic activation was observed when the values were compared to those found in elderly normotensive controls (18).

Second, the hypertension-related increase in adrenergic outflow appears (*i*) to be specific for some cardiovascular districts, such as the heart, the kidneys, and the skeletal muscle vasculature (14,19), and, more importantly, (*ii*) peculiar to the hypertensive state of essential nature (16,19). This is documented by the evidence that the secondary forms of high BP elevation caused by primary hyperaldosteronism or by renal arterial stenosis appear not to be characterized by an elevated sympathetic cardiovascular outflow (19). It is further documented by the evidence that, in patients with an adrenal phoechromocytoma, central sympathetic outflow is not increased (20). Thus, in sharp contrast with what has been described for essential hypertension, in secondary hypertensive states, the autonomic imbalance is confined to the parasympathetic control of heart rate, which, in these conditions, also appears to be clearly impaired (21). Finally, independently on the "in-office" or "out-of-office" type of BP elevation, sympathetic activity is increased in hypertension. This has been recently shown to occur both in "white-coat" hypertension, i.e., a condition characterized by an elevated clinic but a normal ambulatory BP, and in "masked" hypertension, characterized by normal clinic but elevated ambulatory BP (22).

MECHANISMS RESPONSIBLE FOR AUTONOMIC ALTERATIONS

Although the origin of the autonomic dysfunction occurring in essential hypertension is still undefined, a number of attractive hypotheses have been advanced throughout the years (Figure 13.2). It has been suggested, for example, that these alterations occur because of an excessive number of and/or reactivity to stressful environmental stimuli, which lead, through frequent transient BP elevations, to a stable hypertensive state. To date, however, this hypothesis has been confirmed only in animal studies with controversial or circumstantial support in humans (21). Another hypothe-sis (not exclusive of the previous one) is that the autonomic alterations originate from an impairment of the baroreflex; that is, of a major restraining mechanism of parasympathetic tone (21). This is supported by evidence that, in congestive heart failure and other diseases, the adrenergic hyperactivity is related to a reduced sympathetic modulation by the baroreflex (23). However, in hypertension, a baroreflex impairment has been demonstrated for the parasympathetic, but not for the sympathetic, component of the reflex (16). The impaired parasympathetic modulation of the heart by the arterial baroreceptors occurring in hypertension has been documented by the evidence that the magnitude of the reflex heart rate changes (bradycardia and tachycardia), induced by increasing and reducing BP values via intravenous injection of phenylephrine and nitroprusside, is markedly less in hypertensive patients than in normotensive individuals (16). This heart-rate–baroreflex impairment has been more directly demonstrated by the use of the "spontaneous baroreflex sequence" technique, which allows us to investigate baroreflex control of vagal tone in daily life (24). As

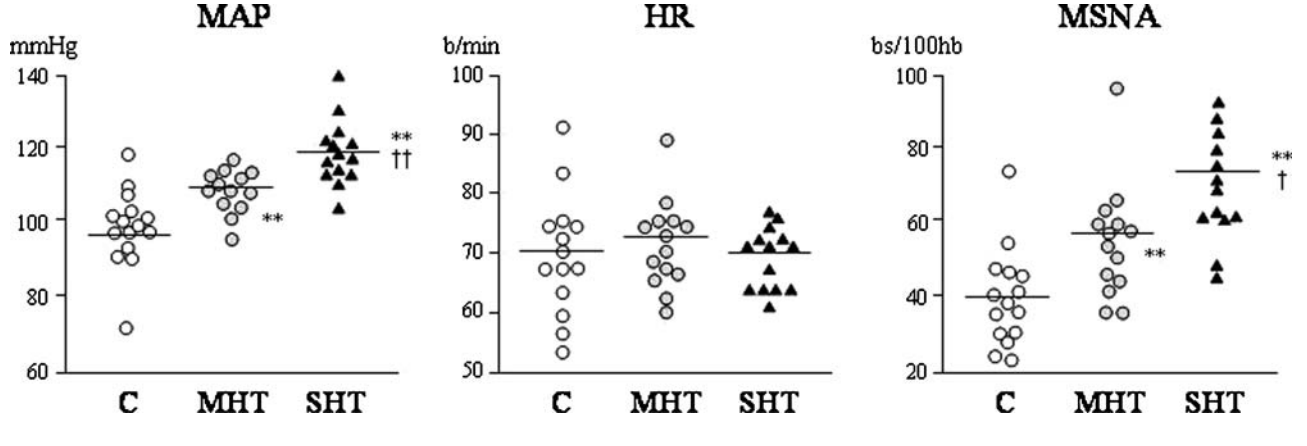

Fig. 13.1 Individual and average values of mean arterial pressure (MAP), heart rate (HR), and muscle sympathetic nerve traffic (MSNA) in normotensives (C), mild hypertensives (MHT), and more severe hypertensives (SHT). Symbols refer to the statistical significance between groups (**$p < 0.01$ vs. C, †$p < 0.02$ vs. MHT, ††$p < 0.01$ vs. C). *Source*: From Ref. 16.

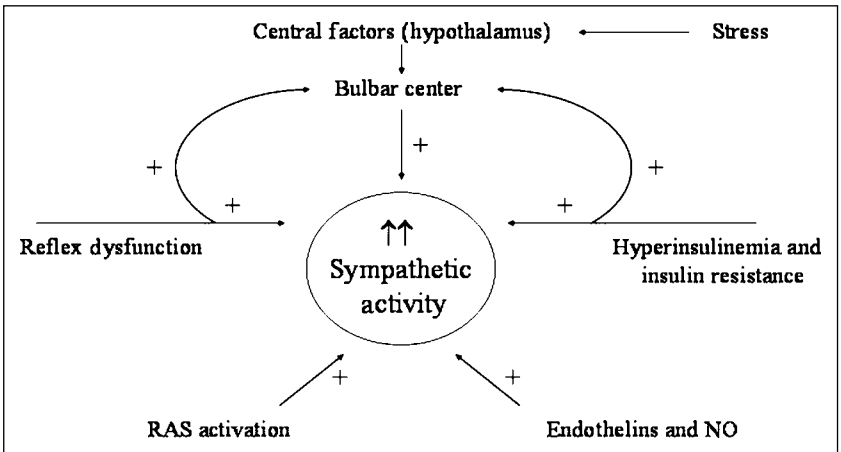

Fig. 13.2 Scheme illustrating the possible mechanisms responsible for the sympathetic overactivity characterizing essential hypertension. *Abbreviations*: RAS, renin–angiotensin system; NO, nitric oxide.

mentioned above, this impairment does not involve the sympathetic component of the baroreflex function, because both the sympathoinhibitory and the sympathoexcitatory responses to intravenous infusions of phenylephrine and nitroprusside are virtually superimposable in essential hypertensive and in normotensive subjects (16). These data, however, do not rule out the possibility that reflex cardiovascular regulation may be involved in the adrenergic overdrive seen in hypertension. First, although unimpaired, the baroreflex is reset toward elevated BP values in hypertension, which means that its influence preserves, rather than suppresses, the increased sympathetic activity. Second, sympathoinhibitory influences, stemming from another reflexogenic area of major importance in controlling circulating blood volume and release of vasoactive substances (such as atrial natriuretic peptides, vasopressin, and renin), the so-called cardiopulmonary receptors (21), appear to be slightly reduced in hypertension, and more so when the hypertensive state is accompanied by cardiac hypertrophy (25). It is, thus, likely that reflex mechanisms contribute to the sympathetic activation and parasympathetic inhibition occurring in hypertension, although their effects on autonomic function (particularly the adrenergic one) appear to be late and nonspecific.

Another hypothesis advanced in recent years claims that the sympathetic activation and the parasympathetic inhibition seen in hypertension depend on a metabolic alteration (i.e., hyperinsulinemia and the related insulin resistance) accompanying the hypertensive condition (4). This hypothesis comes from the evidence that, in experimental animals and in humans, acute infusion of insulin, without altering glycemic levels (the so-called euglycemic clamp infusion technique), markedly stimulates the sympathetic nervous system (26). This finding is of particular relevance when one takes into account that a large proportion of hypertensive patients (>40%) display elevated insulin levels and an insulin-resistance state. This means that hyperinsulinemia and related insulin-resistance conditions may represent one of the mechanisms responsible for the sympathetic activation that characterizes essential hypertension. It should be mentioned, however, that this effect is reciprocal; namely, that a state of sympathetic activation may cause insulin resistance as well (4). This latter hypothesis has recently received further experimental support by the evidence that, when conditions characterized by insulin-resistance, such as obesity and metabolic syndrome, are associated with hypertension, the degree of sympathetic activation is greater than in the uncomplicated high BP state (Figure 13.3) (27,28).

CONSEQUENCES OF AUTONOMIC DYSFUNCTION

Direct and indirect evidence is now available that sympathetic activation promotes cardiac and vascular alterations, thus contributing to the elevated morbidity and mortality rate described in untreated hypertension. In experimental settings, this has been shown to occur for left ventricular hypertrophy, which (*i*) can be induced by suppressor doses of adrenergic agents (29), (*ii*) can be prevented only if the drug-induced BP reduction is not accompanied by excessive reflex cardiac sympathetic stimulation (30), (*iii*) is character-ized by an increased muscle sympathetic neural outflow (31), and (*iv*) is accompanied by an increased cardiac norepinephrine release (32) and by a reduced reuptake of this adrenrgic neurotransmitter from cardiac sympathetic nerve terminals, as directly quantified by sympathoneuronal imaging techniques employing positron emission tomography coupled with 6-[^{18}F]-fluorodopamine (33). Sympathetic acti-vation has also been shown to participate in the development and progression of arteriolar wall hypertrophy and remodeling (34), structural abnormalities that can be found at an early stage of hypertension and help to maintain BP elevation. Recently, the key role exerted by the sympathetic nervous system in the development of cardiac hypertrophy has been confirmed by the prospective evidence (20 years) that, in hypertensive patients, plasma norepineph-rine predicts the development of left ventricular hypertrophy independently of the concomitant presence of hemodynamic (high BP) and antropometric (elevated body mass index) alterations (35). Human evidence has recently been obtained, showing that sympathetic influences also stiffen the large artery walls. This has an unequivocal pathophysiological implication because, in stiffer arteries, the traumatic effect of intravascular pressure is greater and the progression of atherosclerosis probably faster (36). The evidence collected in humans refers to radial artery distensibility (assessed by a beat-to-beat

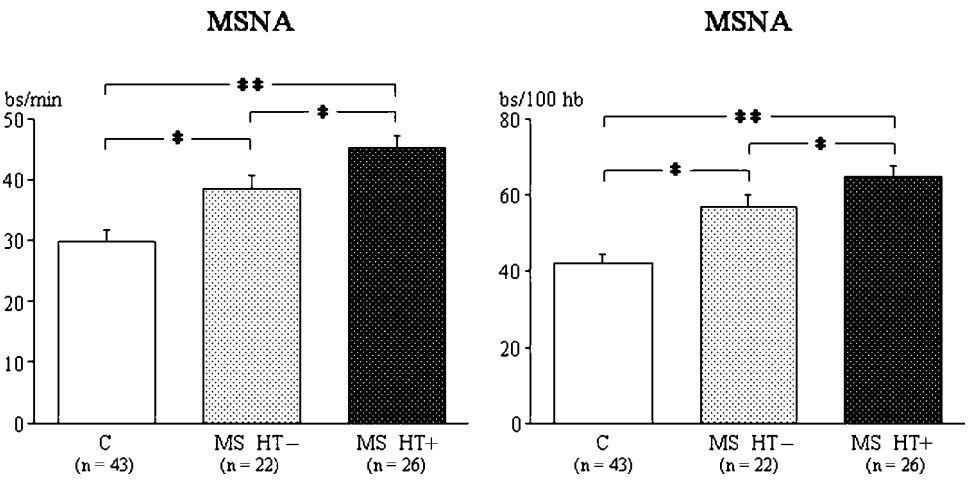

Fig. 13.3 Muscle sympathetic nerve traffic (MSNA), expressed as bursts frequency over time (beats/min; *left panel*) and as bursts frequency corrected for heart rate (beats/100 hb; *right panel*) in healthy subjects (C) and in patients with metabolic syndrome without (MSHT−) and with (MSHT+) hypertension. Data are shown as means ± SEM. *Source*: From Ref. 28.

ultrasonographic device), which appears to be markedly increased following the anesthesia of the brachial plexus (which transiently abolish sympathetic vasoconstrictor drive) in humans undergoing surgery for a Dupuytren's disease (37). Thus, the stiffening influence of the sympathetic nervous system involves the wall of both elastic-type and muscle-type arteries and is visible in both normal and diseased vessels. The mechanism involved is likely to be smooth muscle contraction, because contracting muscle tissue is obviously less distensible than relaxed muscle.

Other adverse consequences of autonomic dysfunction in hypertension should briefly be highlighted. These include an increase in blood viscosity, due to the elevated hematocrit level not infrequently displayed by hypertensive patients, and an alfa-adrenergic-mediated translocation of plasma onto the interstitium (38). As mentioned above, they also include a reduction of the myocardial level of the arrhythmogenic threshold due to the increased heart rate and the reduced coronary perfusion triggered, respectively, by the parasympathetic inhibition and the sympathetic activation characterizing the hypertensive state (1).

THERAPEUTIC IMPLICATIONS AND CONCLUSIONS

The evidence reviewed in this chapter represents the scientific background for considering sympathetic deactivation a goal of the nonpharmacological as well as pharmacological antihypertensive therapeutic intervention. Nonpharmacological interventions trigger, almost univocally (the only exception being the dietary restriction of salt intake), a decrease in sympathetic cardiovascular drive, thus representing an useful approach to be employed in association with pharmacologic treatment (39). In contrast, the effects of antihypertensive drugs on sympathetic function appear to be rather heterogeneous, some compounds eliciting sympathetic activation (diuretics, short-acting calcium antagonists), while others produce sympathoinhibition (Ace-inhibitors, angiotensin II receptor antagonists, beta-blockers, central sympatholitic drugs) (39,40). Interestingly, almost invariably the effects of a given drug on sympathetic function is closely mirrored by its effects on insulin sensitivity (39), underscoring, once again, the close cause–effect relationships between the neural and metabolic alterations characterizing the essential hypertensive state.

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THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM 14

Ulrike M Steckelings, Thomas Unger

INTRODUCTION

The renin–angiotensin–aldosterone system (RAAS) is one of the oldest hormonal systems—no matter if "old" is defined as phylogenetically old, or if it is defined in the sense of being discovered a long time ago (1). The first description of a RAAS component came from Robert Tigerstedt and his student Per Bergman as early as 1897, when they injected a kidney homogenate derived from a healthy rabbit to another healthy rabbit, resulting in a marked elevation in blood pressure (BP) in the recipient (2). Tigerstedt and Bergman termed the BP rising substance "renin." It took decades until, in 1934, the groups by Eduardo Braun-Menendez in Buenos Aires and by Irvine Page in Indianapolis coincidentally, but independently, found that the actual BP rising substance was not renin itself, but a molecule that was cleaved and activated by renin, and which is nowadays termed angiotensin II (Ang II) (3,4).

Today, we know that the RAAS represents a cascade of enzymatic reactions. The huge precursor molecule of Ang II, angiotensinogen, is cleaved by renin, resulting in the still inactive decapeptide angiotensin I (Ang I), which is then further cleaved by the membrane-bound metalloproteinase angiotensin-converting enzyme (ACE) to give the main effector hormone of the RAAS, Ang II (Figure 14.1) (1).

COMPONENTS OF THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

ANGIOTENSINOGEN

Angiotensinogen is a glycosylated α_2-plasmaprotein with a molecular weight of 55 to 65 kDa (5). In situ hybridization studies indicate that the human angiotensinogen gene is located on chromosome 1q42–3. It codes for the angiotensinogen protein, which, in its mature form, is built from 452 amino acids. Renin cleaves the first 10 amino acids, which correspond to Ang I.

There is evidence that a variant of the angiotensinogen gene is associated with increased angiotensinogen plasma levels and hypertension (5).

RENIN

The gene encoding the renin precursor preprorenin is localized on chromosome 1q32. Mature renin contains 340 amino acids and has a mass of 37 kD (6). Renin is primarily released by the juxtaglomerular apparatus of the kidney. Renin secretion is under tight control of several parameters, such as BP and blood volume, plasma sodium content, and sympathetic activation. A tight control of renin release is absolutely necessary, because cleavage of angiotensinogen by renin is the rate-limiting step in the enzymatic cascade leading to Ang II synthesis, i.e., the rate of angiotensinogen cleavage is set by the amount and activity of renin, not by the amount of angiotensinogen, which is always available in abundance in the plasma.

ANGIOTENSIN-CONVERTING ENZYME

The gene for ACE has been mapped to chromosome 17q23 and translates into a 150 kDa protein, which belongs to the family of zinc metallopeptidases (7). ACE cleaves the C-terminal dipeptide His-Leu from Ang I, thus generating Ang II. But Ang I is by far not the only substrate of ACE. ACE also metabolizes bradykinin, substance P, LH-releasing hormone, enkephalines, or the insulin β-chain. In all these latter cases, cleavage by ACE does not elicit an activation of the molecule (as with Ang I), but degradation and inactivation. Thus, inhibition of ACE activity, which is one of the most common pharmacological principles in cardiovascular medicine, not only leads to a decrease in Ang II synthesis, but also to the accumulation of those molecules, which are physiologically degraded by ACE.

A variation in the ACE gene structure was recognized in 1990, consisting of the insertion (I) or deletion (D) of a 250 BP DNA fragment located in intron 16 (8). This so-called "ACE I/D polymorphism" has been suspected to be associated with a variety of cardiovascular and noncardiovascular diseases, but, currently, conclusive data pointing to an association with the I/D polymorphism only exist for diabetic nephropathy and Alzheimer's disease, while reports on most cardiovascular phenotypes are still controversial (9). In recent years,

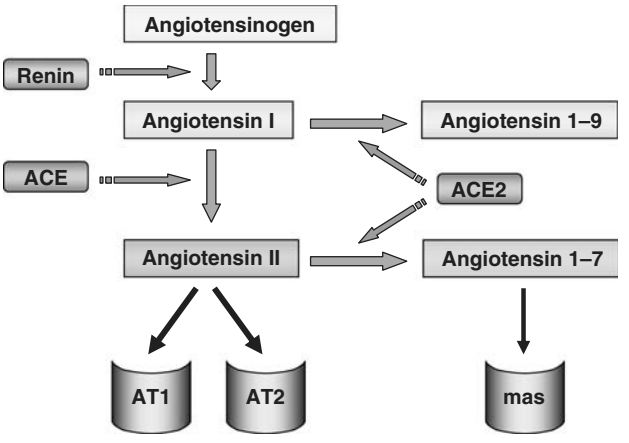

Fig. 14.1 The renin–angiotensin–aldosterone system.

a number of additional ACE polymorphisms have been identified, whose functional significance still has to be clarified.

ANGIOTENSIN-CONVERTING ENZYME 2 (ACE2)

In 2000, the first known homolog of ACE, ACE2, was cloned (10,11). ACE2 catalyzes the generation of Ang 1–9 from Ang I and of Ang 1–7 from Ang II (Figure 14.1). It is insensitive to ACE inhibitors. The fact that ACE2 metabolizes Ang II to give the vasodilator Ang 1–7 has been interpreted to mean that ACE2 provides a counterbalance, preventing the deleterious consequences of the overactivity of the classic RAAS (12).

Interestingly, ACE2 has recently been identified to be a receptor for the SARS virus (13).

ANGIOTENSIN 1–7

Ang 1–7 is cleaved from Ang I by various endopeptidases and from Ang II by ACE2 (14). According to current knowledge there is a specific receptor for Ang 1–7 termed *mas*-receptor, which mediates actions of Ang 1–7 in physiological concentrations. These actions comprise growth inhibition of vascular cells, inhibition of renal tubular Na^+-K^+-ATPase, thus facilitating natriuresis and diuresis, protection from ischemia/reperfusion injury, antiarrhythmic features, inhibition of oxidative stress, and anti-inflammation. Ang 1–7 in pharmacological and suprapharmacological concentrations may also bind to the AT1R and even the AT2R.

ROLE OF RENIN AND ACE BEYOND THE CLASSICAL RAAS CASCADE

In recent years it became clear that the enzymes required for Ang II synthesis, renin and ACE, do not only serve to generate Ang II, but additionally act as ligands or receptors, respectively. Renin (and prorenin) was shown to bind to the renin receptor (RER).

This RER activation causes a nuclear translocation of the transcription factor promyelocytic leukemia zinc finger (PLZF), which acts as a direct adaptor protein of the RER, and an activation of PLZF-regulated genes, such as the phosphatidylinositol-3 kinase (Figure 14.2) (15). In addition, an activation of the MAP kinases ERK1 and ERK2 was reported downstream of RER activation (16). Functionally, renin seems to promote cell proliferation and inhibit apoptosis. Furthermore, a study in rats transgenic for the human RER revealed that it may be involved in the regulation of BP and heart rate (17).

ACE can act as a receptor itself in that the intracellular tail is phosphorylated upon binding of ACE inhibitors and bradykinin (but not Ang I) (18). Ligand binding increases the activity of ACE-associated JNK and elicits the accumulation of phosphorylated *c*-Jun in the nucleus.

The "new" components of the RAAS described in the last two chapters—especially the RER—may offer the opportunity for therapeutical intervention in the future. However, intervention with the "classical" cascade of Ang II synthesis is still the "gold standard" of RAAS-related cardiovascular therapy.

CIRCULATING AND LOCAL RAAS

Originally, the RAAS has been described as a circulating endocrine system, with angiotensinogen being released by the liver, and renin secreted from the juxtaglomerular apparatus of the kidney, both "joining" in the circulation for processing of Ang I (19). Ang I then circulates through the body vasculature, getting almost continuously exposed to and cleaved by ACE, which is predominantly localized on the membranes of vascular endothelial cells. Thus, Ang II is generated within the blood and distributed throughout the body, thereby enabling systemic effects such as vasoconstriction or aldosterone release. These systemic effects mainly purpose to raise BP and minimize loss of body fluids. They represent the body's "emergency kit" in case of a sudden fall in BP, e.g., due to massive bleeding or shock from any cause.

Many years after the detection and characterization of the systemic RAAS, in the early 1990s, the novel concept of so-called local RAASs arose (20). In the meantime, the expression of all RAAS components could be demonstrated in a broad

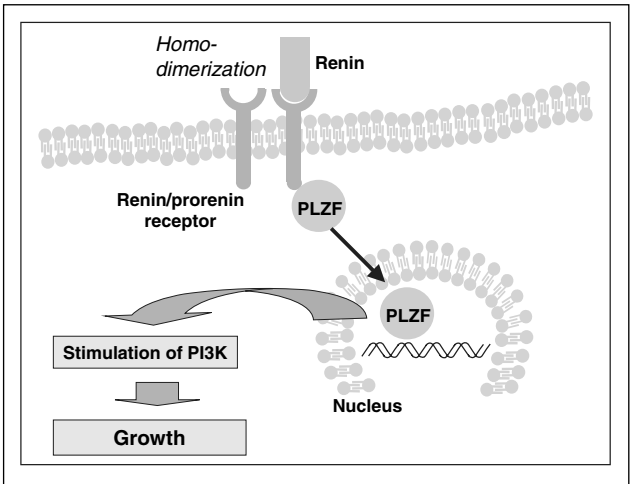

Fig. 14.2 Signaling of the renin/prorenin receptor.

variety of tissues, indicating local Ang II synthesis. Part of these tissues belongs to the cardiovascular system and is involved in "classical" Ang II actions; these are essentially the blood vessels, the kidney, and the heart. However, a complete local RAAS has also been detected in various "unexpected" locations, e.g., in organs which are not—at least not in first line—involved in the regulation of BP and volume homeostasis, among them the central and peripheral nervous tissue, adipose tissue, digestive organs (pancreas, stomach, gut), skin, and reproductive organs.

ANGIOTENSIN RECEPTORS

Ang II exerts its actions primarily via two receptor subtypes termed AT1 and AT2 (1). The existence of more than just one Ang II receptor had long been suspected, but was only proven in 1989 thanks to the development of ligands specific for the AT1- or AT2-receptor, respectively. By the time these receptor subtypes were identified, the scientific community thought of Ang II as a purely cardiovascular hormone responsible for BP regulation as well as volume and electrolyte homeostasis. However, it turned out that all of the well-known cardiovascular actions of Ang II (like, e.g., vasoconstriction, vasopressin release, Na- and water reabsorption directly and by aldosterone release) could be attributed to the AT1R—leaving the AT2Rs physiological role and signaling an enigma over many years. Only in recent years, evidence has accumulated that the AT2R in many aspects opposes AT1R-mediated actions (21). Whether this "ying-yang" between AT1R and AT2R plays an important role for BP regulation has not been decided yet and may be restricted to certain vascular beds or only occur under pathological conditions such as hypertension (22). But the counterplay between the two receptor subtypes seems definitely important in the context of "new" Ang II actions, which have only been detected in recent years, and which comprise, e.g., the modulation of cell proliferation, fibrosis, and inflammation (21).

AT1-RECEPTOR

The genetic message for the human AT1-receptor is located on chromosome 3q22 encoding a 359 amino acid protein (1). In contrast to humans, rodents possess two different AT1-receptors termed $AT1_A$ and $AT1_B$ with the $AT1_A$ receptor predominating in most tissues. The AT1R belongs to the family of G-protein coupled receptors displaying seven transmembrane domains. It is coupled to a great variety of signaling pathways including activation of phospholipase A, C, or D, generation of inositolphosphates, opening of calcium channels or the activation of diverse serine/threonine- and tyrosine-kinases (1).

AT2-RECEPTOR

The AT2R gene is located on the X chromosome and was mapped to the Xq22–q23 region. It is build from three exons, but the region encoding the AT2R protein (a 363 amino acids molecule) is exclusively located on exon 3 (1). Like the AT1R, the AT2R also represents a G-protein-coupled seven-transmembrane glycoprotein. It signals via specific binding proteins (ATIP, PLZF), activation of various phosphatases, activation of the cGMP/nitric oxide (NO) system, and stimulation of phospholipase A2 (23). However, human AT1R and AT2R share only 34% homology, and they differ profoundly with respect to tissue distribution, signaling, and functions.

LOCALIZATION OF ANGIOTENSIN RECEPTORS

Localization and proportion of AT1R and AT2R undergo profound changes in the course of development from early gestation to adulthood. While the AT2R predominates in embryonic and fetal tissues, the AT1R/AT2R ratio changes dramatically after birth in favor of the AT1R (21). Consequently, in the adult organism, the AT1-receptor is abundantly expressed in most tissues, while AT2R expression is restricted to certain locations or only occurs in case of tissue injury or remodeling. In the heart, AT1R and AT2R are localized on cardiomyocytes, while normal cardiac fibroblasts appear to possess AT1R only, but have the ability to recruit AT2R in case of pathological condition, e.g., myocardial infarction or congestive heart failure (1,20). There is still controversy about AT1R and AT2R expression in the blood vessel wall in vivo. While in vitro both receptor subtypes are found in endothelial cells, but only the AT1R in vascular smooth muscle cells (VSMC), VSMC may express both subtypes in vivo. A lower number of AT1R is also found in the adventitia (1,20). In the kidney, the main structures of AT1R expression comprise the interlobular arteries and the surrounding fibrous tissue, the glomeruli, and the cortical tubules, while the AT2R is found in large preglomerular vessels and in the interstitium (1,20). Angiotensin receptor expression in the brain varies substantially between certain nuclei, but, in the vast majority of nuclei, the AT1R predominates. Since the cerebral expression pattern of AT1R and AT2R is very complex, the reader is referred to review articles addressing this topic (24,25). For various structures of the peripheral nervous system, such as ganglia, the vagus nerve, intracardiac conduction systems, enteric nerves, or presynaptic membranes of various locations, the presence of AT1R has been demonstrated. In contrast, AT2R expression in peripheral nerves is only rarely described and seems to be weak or not existent (1,20). However, there is strong evidence for an upregulation and functional role of AT2R in neuronal regeneration (26–28). In adrenals, the AT1R is primarily found in the zona glomerulosa, while the AT2R is preferentially located in the medulla (29). Both angiotensin receptors are also present in female and male reproductive organs, such as the uterus, fallopian tubes, epididymis, testes, and mature or immature spermatic cells (1,20). The uterus represents one of the very few organs in which the AT2R is expressed in much higher density than the AT1R. During pregnancy, AT2R density decreases by more than 90%. Coincidentally, AT1R density is progressively increasing in the trophoblast and placental vasculature with gestational age. In testes, epididymis, and sperm, the AT1R is the dominating receptor or the only subtype described. Various cells and structures of human skin are targets of Ang II actions via both AT1R and AT2R, namely keratinocytes, dermal fibroblasts, dermal microvascular endothelial cells, hair follicles, and sebaceous glands, with the AT1R predominating in all of these locations in healthy skin (30). Most organs of the digestive tract also host AT1R and AT2R,

among them salivary glands, intestine, and pancreas. In both, white and brown adipose tissue, the AT1R is present most abundantly. Interestingly, angiotensin receptors have also been demonstrated on white blood cells (mononuclear leukocytes, macrophages), which can act as a kind of "mobile" RAAS, accumulating at places of injury and inflammation.

Other organs displaying AT1R and AT2R comprise the **lung, retina, spleen, thymus**, and **liver**.

PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL ACTIONS OF ANGIOTENSIN II

PHYSIOLOGICAL ACTIONS

Since angiotensin receptors mediate a wide variety of actions depending on receptor subtype, tissue, or species, we concentrate in this chapter on their cardiovascular actions in health and disease, with an emphasis on hypertension.

One of the major physiological functions of Ang II consists in the control and maintenance of adequate BP. This is achieved by a row of independent mechanisms, one of them the control of vascular tone.

Vascular tone is determined by a counterplay of endothelial cells and VSMC. In this context, the AT1R directly mediates the contractile response of VSMC via activation of phospholipase C and an increase in intracellular Ca-concentrations (31). Endothelial cells are capable of promoting vasodilation by synthesis of NO, which can penetrate into VSMC, where it initiates cGMP generation, thus stimulating protein kinase G, leading to a decrease in cytoplasmatic calcium. Ang II, via the AT2R, has been shown to induce NO synthesis. However, data about whether the AT2R mediates vasodilation are still controversial, and current evidence suggests that it may be restricted to certain vascular beds and/or depend on the BP status (22).

Apart from its direct effect on vascular tone, Ang II also promotes vasoconstriction by facilitating noradrenalin release from vascular nerve endings and by improving the responsiveness of VSMC to noradrenalin (32).

Control and maintenance of adequate BP are furthermore acquired by modulation of extracellular fluid volume. Ang II plays a major role in volume and electrolyte homeostasis by its numerous actions on kidney function. For example, Ang II can directly modify the glomerular filtration rate by constricting efferent and afferent arterioles (33). In addition, Ang II is able to facilitate sodium retention by direct effects in the proximal tubule or by indirect effects such as decreased medullary blood flow or an enhanced filtration fraction. Ang II induced aldosterone release from the adrenal represents another mechanism contributing to sodium and water retention. All these renal effects are mediated via the AT1R (1,20). Data about AT2R actions in the kidney are still rare. There is some recent evidence that it may inhibit prorenin processing in the juxtaglomerular apparatus, thus counteracting the short-loop negative-feedback inhibition of renin secretion via the AT1R (34).

Central actions of Ang II, such as vasopressin release or stimulation of thirst, and sodium intake additionally contribute to the maintenance of extracellular fluid volume.

PATHOPHYSIOLOGICAL ACTIONS IN HYPERTENSION AND RELATED END-ORGAN DAMAGE

While the above-stated actions of Ang II on blood vessels, kidneys, and the brain serve to maintain adequate BP and extracellular fluid in times of sodium depletion (a problem our early ancestors were more confronted with than present-day populations) or fluid (blood) loss, an excess of circulating or local Ang II or an overreactivity of the RAAS have deleterious effects and contribute to hypertension and related end-organ damage.

For some forms of secondary hypertension, the activation of the RAAS is an obvious and well-examined pathophysiological mechanism (35). For instance, in case of reduced renal perfusion pressure as a result of renal artery stenosis or parenchymal disease (e.g., chronic glomerulonephritis or pyelonephritis, polycystic renal disease, connective tissue disorders), renin secretion from the juxtaglomerular apparatus is increased, resulting in elevated plasma Ang II levels. The pathophysiological role of the RAAS in essential hypertension is less obvious (19). The most prominent hint toward a dysregulation of the RAAS in essential hypertension comes from the observation that, in the majority of hypertensive patients, renin levels are either normal or upregulated, and, although reduced renin levels would be expected as a reaction to increased renal perfusion pressure, only about one third of patients display low renin levels (36). Several suggestions have been made to explain what causes these "inappropriately" high levels of renin: (a) increased sympathetic drive, (b) nephron heterogeneity with a subpopulation of ischemic nephrons responsible for increased tonic renin release, and (c) defective feedback regulation of RAAS activity in kidneys and adrenals in response to varying levels of sodium intake.

Hypertension is one of the most relevant risk factors for cardiovascular morbidity and mortality due to its deleterious effects on end-organ structure and function (37). It is well established for most affected tissues that an activated RAAS contributes to hypertension-related end-organ damage (38). The vasculature reacts to chronically elevated BP levels with remodeling of the vascular wall, leading to an increased media-to-lumen ratio (38). This growth-promoting effect of Ang II can be largely attributed to the activation of growth factors such as PDGF, VEGF, or bFGF by Ang II (37). However, there is more to vascular end-organ damage than just hypertrophy. Ang II via the AT1-receptor stimulates NAD(P)H oxidases, resulting in the production of reactive oxygen species (ROS) and increased oxidative stress (39). NO, a major vasodilator and vasoprotective agent, reacts strongly with the superoxide anion O_2^-, thus loosing bioactivity (40). Furthermore, the powerful oxidant $ONOO^-$ emanates from this reaction. Oxidative stress and ROS production is nowadays considered to be a stimulus for local inflammation and fibrosis via activation of key transcription factors, such as NF-kappaB and AP-1, followed by an enhanced transcriptional rate of various cytokines, chemokines, adhesion factors, and—again—growth factors (41). Direct stimulation of NF-kappaB and AP-1 by Ang II itself may further add to this effect (42). While the arising inflammatory response contributes to the higher susceptibility of hypertensive patients for developing atherosclerosis and cardiovascular disease, vascular fibrosis is the major determinant of arterial stiffness.

Regarding Ang II actions in the heart, it is well documented that Ang II via the AT1R promotes cardiac hypertrophy, which is mainly due to cardiomyocyte hypertrophy (43). Cardiac hypertrophy develops as a reaction to chronically elevated intracardiac pressure (due to hypertension, or as a result of stenosis of the cardiac valves or the big, afferent blood vessels). Cardiac hypertrophy is a compensatory mechanism, which in earlier stages preserves cardiac function. However, an excess of hypertrophy leads to decompensation, resulting in cardiac failure and increased mortality (44). Several mechanisms lead to a deterioration of cardiac function due to enhanced Ang II production, among them impaired diastolic calcium handling (45), cardiac fibrosis (46), impaired diastolic relaxation due to disturbed sarcoplasmic reticulum calcium pump activity (47), and also arrhythmias (48).

The role of the AT2R in cardiac hypertrophy is a current matter of intense debate, and it has not been decided yet whether it inhibits or promotes hypertrophy, or which specific conditions make it act in one or the other way (49).

Renal damage is a frequent long-term consequence of hypertension (50). It is characterized by renal arteriolar thickening, fibrinoid deposition into the glomeruli, and accompanied by an inflammatory response and proteinuria (51). Ang II is involved in the pathogenetic mechanisms by its growth-promoting, proinflammatory, and profibrotic features as discussed above. Furthermore, fibrinoid deposition is facilitated by leakage of renal microvessels (52). Ang II seems to promote leakage of microvessels in the kidney and other organs (e.g., in retina or heart) via increased VEGF expression (53).

Stroke represents the most frequent cardiovascular event caused by hypertension. It is either caused by intracranial haemorrhage or by cerebral infarction, the latter being a consequence of atherosclerotic plaque formation in arteries nourishing the brain or of embolism of cardiac origin (54).

THERAPEUTICAL INTERVENTION WITH THE RAAS

Therapeutical intervention with the RAAS is discussed in detail in the following chapters of this book. In brief, there are two main mechanisms by which the RAAS can be inhibited: either by inactivation of the enzymes responsible for Ang II generation, or by blockade of the angiotensin AT1-receptor (Figure 14.3) (55). ACE inhibitors have been the first development in this row of RAAS interfering drugs (56). Originally, they were thought of as therapeutics for hypertensive patients with an activated RAAS and high renin plasma levels. However, it soon turned out that they were also effective in essential hypertension. Moreover, in parallel with growing scientific knowledge about Ang II actions beyond BP regulation—in this context, those actions involved in the development of end-organ damage, such as inflammation, cell proliferation, or fibrosis, have to be stressed—clinical data revealed that ACE inhibitors have the potential to prevent end-organ damage by mechanisms exceeding the reduction of BP (57). The same additional effectiveness was found to be a feature of one of the more recent developments among RAAS interfering drugs: AT1R-blockers (ARBs) (57). Both drugs, ACE inhibitors and ARBs, act by diminishing Ang II actions mediated by the AT1 receptor—ACE inhibitors by reducing the amount of stimulating Ang II, ARBs by direct receptor blockade. Furthermore, both drugs display additional mechanisms of action: ACE inhibitors by accumulation of bradykinin, thus stimulating bradykinin actions such as increased NO synthesis, ARBs by facilitating the activation of unblocked AT2-receptors by Ang II.

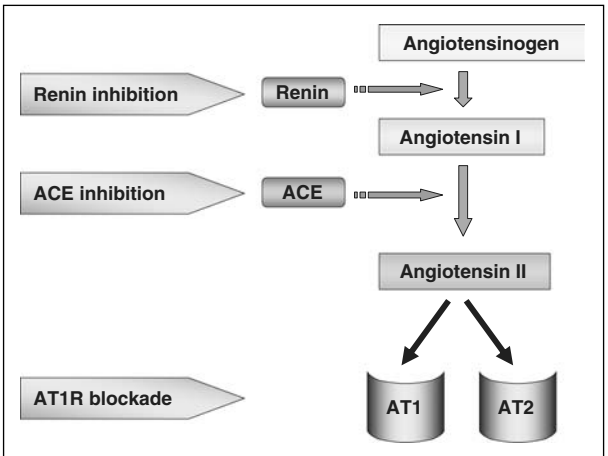

Fig. 14.3 Therapeutic intervention with the renin–angiotensin–aldosterone system.

Another way to prevent Ang II synthesis would be to inhibit renin activity. A respective drug termed Aliskiren was approved by the FDA in March of 2007 (58). Whether renin inhibition holds advantages over the current concepts of RAAS inhibition will have to be decided in future clinical trials.

Last but not least, there is a current renaissance of the aldosterone antagonists spironolactone and the more recently developed eplerenone, the latter having higher specificity for the mineralocorticoid receptor, resulting in less side effects (59). Two recent large clinical studies provided evidence that both drugs are capable of reducing mortality in heart failure patients (60,61).

Taken together, the RAAS is one of the major determinants in the pathogenesis of hypertension and related end-organ damage. Consequently, several current and future therapeutic approaches aim to inhibit the synthesis of the main effector hormone, Ang II, or they prevent the stimulation of AT1R. However, the RAAS also harbors its own opponents, which in many cases apparently counteract the detrimental actions mediated via the AT1R; the main opponents being the AT2-receptor, ACE2 and Ang 1–7. Whether stimulation of this integrated counteracting system may be a novel therapeutic option will have to be clarified in the future.

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15 ETIOLOGICAL AND PATHOPHYSIOLOGICAL ASPECTS OF HYPERTENSION: OTHER HUMORAL-ENDOCRINE FACTORS

Michel Burnier

INTRODUCTION

The physiological regulation of blood pressure (BP) is a very complex interplay between cardiac, vascular, renal, neural, and endocrine factors modulated by genetic and environmental factors. Thus, hypertension which, is a disorder characterized by a sustained increase in BP above a predefined normal range of values, can result from any imbalance between these regulatory mechanisms. Numerous humoral and endocrine factors have an impact on BP and, hence, have been considered as potential pathophysiological causes of hypertension. Among them, the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS), which are discussed in the two preceding chapters, play a pivotal role in the regulation of vascular tone, and an inappropriate activity of these systems definitively contributes to the development and maintenance of secondary forms of hypertension, such as renovascular hypertension, primary hyperaldosteronism, or hypertension secondary to a pheochromocytoma. However, besides these two major systems, several other hormones and vasoactive substances affect BP control and may lead to hypertension either through a direct effect on the vasculature or by interfering with the renal handling of sodium. In many cases, these hormones also interact with the RAAS and the sympathetic nervous systems. As an increase in BP can result from an increased activity of vasoconstrictor systems, as well as from a decreased activity of vasodilating factors, this chapter discusses the humoral and endocrine factors, which promote or prevent sustained increases in BP, and thereby may contribute to the etiology of hypertension.

ENDOTHELIN

Endothelin (ET) is a very potent endogenous vasoconstrictor produced by the endothelium and identified by Yanagisawa et al. in 1988 (1). There are three isoforms of ET (i.e., ET-1, -2, and -3) but ET-1 is the only relevant peptide in humans. ET is derived from proendothelin, which is cleaved into a big-ET, and then converted to the active ET-1 by an ET-converting enzyme. Several stimuli induce ET release by endothelial cells, including shear stress, thrombin, angiotensin II, vasopressin, catecholamines, and hypoxia. (Figure 15.1) (2). The effects of ET are mediated by two receptors, i.e., the ET-A and ET-B receptors. The ET-A receptor is widely distributed and is the principal receptor located on vascular smooth muscle cells and cardiomyocytes. In these cells, activation of ET-A receptors leads to an activation of phospholipase C, an increase in intracellular calcium, and, hence, to cell contraction. The ET-B receptor is located on both vascular smooth muscle and endothelial cells. In endothelium cells, activation of ET-B receptors releases vasodilating substances, such as nitric oxide (NO), prostacyclin (PGI_2), and adrenomedullin. In the vasculature, activation of the ET-B receptor induces vasoconstriction.

If vasoconstriction is the hallmark of ETs action, several other biological properties of ET have been described. Thus, renal function appears to be particularly responsive to the effects of ET (3). Administration of low doses of ET-1 in animals and humans has been shown to decrease glomerular filtration rate (GFR) and renal blood flow (RBF) through the stimulation of vascular smooth muscle cells and contraction of mesangial cells and to reduce urinary sodium excretion. Similarly, overexpression of ET in the mice kidney has been associated with the development of glomerulosclerosis, interstitial fibrosis and the development of renal cysts but not hypertension suggesting a role of ET in the development of some renal diseases independently of the hypertensive effect (4). These effects appear to be mediated by the activation of ET-A receptors. However, ET-1 can also lower BP and produce a natriuretic response through the activation of ET-B receptors, which have been localized on renal tubular epithelial cells (5). ET has also been found to have a vasodilatory effect on the renal medulla mostly evident on a high sodium intake (6). Recent data suggest that the renal medullary ET system is

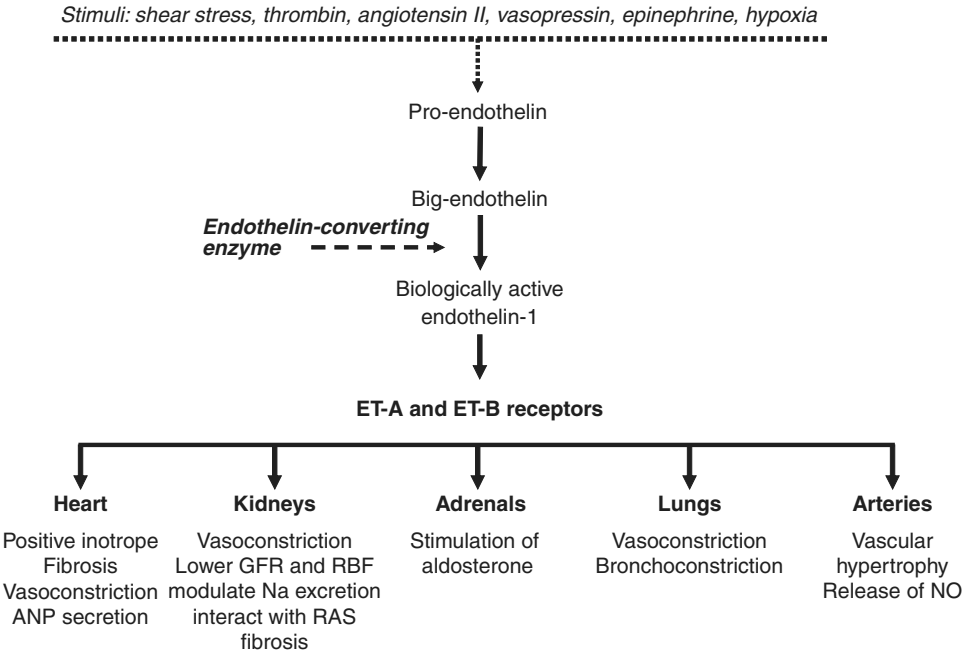

Fig. 15.1 The endothelin system and its multiple effects. *Abbreviations*: ANP, atrial natriuretic peptide; ET, endothelin; GFR, glomerular filtration rate; Na, sodium; NO, nitric oxide; RAAS, renin–angiotensin–aldosterone system; RBF, renal blood flow.

important for BP regulation. Interestingly, in line with this observation, transgenic rats deficient in ET-1, specifically in the collecting duct, develop hypertension (7). In the normal heart and in isolated cardiomyocytes, ET-1 had positive inotropic and growth-promoting effects (8). At the vascular level, ET may contribute to the remodeling of small and large arteries (9).

Experimental data have demonstrated that ET-1 interacts very closely with NO via activation of ET-B receptors on endothelial cells. Indeed, ET-1 promotes the release of NO and thereby maintains a balance between the vasodilatory effect of NO and the vasoconstrictor effect of ET-1 itself (10). Thus, in all tissues, the vasoconstrictor effects of exogenous ET-1 are significantly enhanced when NO production is inhibited. There is also a close interaction between ET and the RAAS (11,12). Angiotensin II enhances the vascular responsiveness to exogenous ET-1 and increases the release of ET-1 and the expression of preproendothelin in endothelial cells. Some of the effects of angiotensin II on cardiac tissue may actually be mediated by ET-1. In the heart, ET-1 has been found to stimulate aldosterone synthesis (13).

The role of ET as a potential pathophysiological cause of hypertension has been suggested using several experimental and clinical approaches. In rats, knockout of the ET-B receptor is associated with the development of severe salt-sensitive hypertension (14). In humans with essential hypertension, plasma ET levels are usually not elevated except in Afro–Americans (15). However, circulating concentrations of ET may not necessarily reflect the tissue concentrations because ET acts as an paracrine/autocrine system. Nonetheless, elevated circulating concentrations of ET have been reported in some human and experimental forms of hypertension, such as the mineralocorticoid-induced and renovascular hypertension in the rat and hypertension in renal transplant patients and patients with diabetes or chronic renal failure (16). There is increasing evidence that ET may play a role in the development of hypertension in eclampsia (17).

The best demonstration of the role of ET in hypertension in humans has come from the use of selective ET antagonists. Indeed, in recent years, several selective and nonselective nonpeptide antagonists of ET-A and ET-B receptors have been developed and investigated. In mild to moderate hypertensive patients, the dual ET-A and ET-B receptor antagonist bosentan (500 to 2000 mg) lowered BP as effectively as the angiotensin-converting enzyme inhibitor (ACEI) enalapril (20 mg) (18). Similarly, a significant decrease in BP was found with a selective ET-A ET receptor antagonist (19).

NITRIC OXIDE

Besides ET, endothelial cells are also producing NO, a potent vasorelaxant factor, which contributes to the local regulation of vascular tone. NO is formed by the enzyme nitric oxide synthase (NOS) from the amino acid L-arginine (20). Once formed, NO diffuses to the underlying vascular smooth muscle cells, activates soluble guanylate cyclase (SCG) and produces a vasorelaxation. Three forms of NOS have been described: a neuronal NOS present in neural cells, an inducible NOS (iNOS), and an endothelial NOS (eNOS). In the vessels, NO is released from endothelial cells in response to physical stimuli (shear stress and hypoxia) and by the stimulation of endothelial receptors, such as bradykinin and muscarinic receptors (Figure 15.2). NOS activity can be inhibited using endogenous analogs of L-arginine, such as asymmetric dimethylarginine or *N*-monomethyl-L-arginine (L-NMMA). Some of these analogs are increased in disease states; for example, in patients with chronic renal failure.

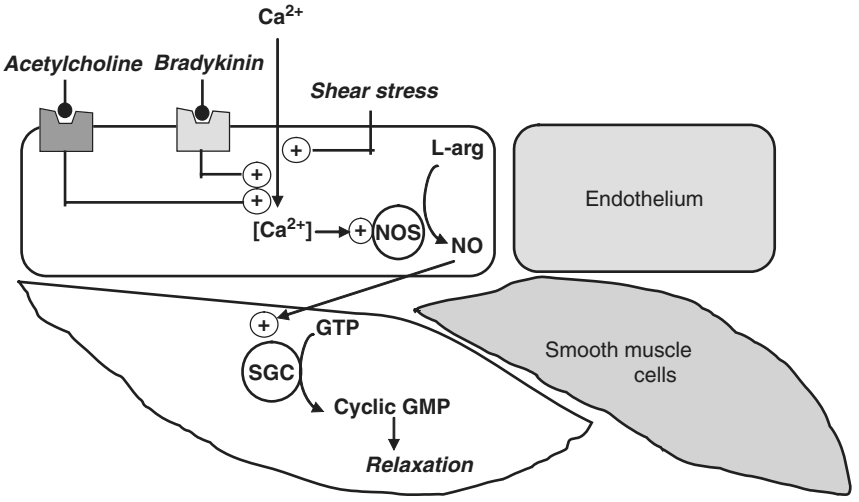

Fig. 15.2 The NO pathway and its ability to induce vasorelaxation. *Abbreviations*: NO, nitric oxide; NOS, nitric oxide synthase; SCG, soluble guanylate cyclase.

The potential role of NO in the pathophysiology of cardiovascular diseases including hypertension has first been evoked with the demonstration that acetylcholine, in the absence of endothelium, is a vasoconstrictor rather than a vasodilator (21). Following this seminal observation, numerous studies have demonstrated the crucial role of the endothelium in the regulation of cardiovascular homeostasis and have led to the concept of endothelial dysfunction. Thus, endothelial dysfunction of large and small arteries has been described in animal models of hypertension as well as in patients with essential hypertension (22–25). Several mechanisms are discussed whereby endothelial dysfunction develops in hypertension. Studies have suggested an impaired NO synthesis and release, but endothelial dysfunction may also be consecutive to an increased breakdown of NO, as the vasorelaxing properties of NO are counteracted by oxidative processes in the tissues (26,27). Superoxide anions are potent scavengers of endothelial-derived NO (28). Whether endothelial dysfunction is a primary or secondary event in hypertension has been discussed because an elevation of BP per se can cause endothelial dysfunction (29). However, a blunted endothelium-dependent vasodilatation has been observed in offspring of hypertensive parents, suggesting thereby that endothelial dysfunction can precede the development of hypertension and may play a primary role in the genesis of the disease (30). Of note, transgenic mice deficient for the eNOS develop a systemic hypertension associated with an increased peripheral vascular resistance (31,32).

NO can contribute to the etiology of hypertension by various other mechanisms (33,34). One of them is the development of atherosclerosis (34). Indeed, NO has been reported to decrease monocyte and leukocyte adhesion to endothelial cells, to inhibit platelet aggregability and platelet–vessel wall interaction, to decrease the transport of lipoproteins into the vessel wall, and to inhibit vascular smooth muscle cell proliferation as well as some components of the vascular inflammation (34). Another pathway whereby NO can affect BP is the interaction with the RAAS. NO has indeed been found to suppress renin release by juxtaglomerular cells and, hence, to reduce the activity of the RAAS and to participate in the regulation of renal hemodynamics (35,36). As discussed previously, NO also interacts closely at the vascular level with ET. Some of these interactions may actually lead to an increased vasoconstrictor tone. At last, the activity of NO has been found to be related to other vasoactive compounds, such as prostanoids and bradykinins.

NATRIURETIC PEPTIDES

In the 1980s, DeBold and collaborators discovered that rat atrial extracts had potent natriuretic and vasodilatory properties (37). This original finding led to the identification of the atrial natriuretic peptide (ANP) and subsequently to the recognition of a family of four distinct natriuretic peptides: ANP (17 amino acids), BNP (32 amino acids), CNP (22 amino acids), and urodilatin (32 amino acids). ANP is synthesized and secreted predominantly by the atria. BNP was initially isolated from pig's and dog's brains but it is produced essentially by cardiomyocytes (38). CNP has been localized in the brain and in the heart but also in several other peripheral tissues, including the kidney, the adrenal glands, and the endothelium. Urodilatin has been isolated from human urine and has been found only in the kidney (39).

ANP and BNP are released from the heart in response to changes in atrial or ventricular stretch (Figure 15.3). Plasma levels of natriuretic peptides are also influenced by the body position and the salt intake. Natriuretic peptides act by stimulating specific receptors (natriuretic peptide receptor A, B, and C). These receptors are widely distributed throughout the body, including the endothelium, smooth muscle cells, heart, adrenal gland, lung, brain, adipose tissue, and in the kidney (40). Natriuretic peptides are degraded by the neutral endopeptidase 24.11 and by a receptor-mediated clearance via the C receptor.

ANP and BNP possess diuretic, natriuretic, vasodilatory, and antiproliferative properties. ANP also causes intravascular volume contraction as documented by increases in hematocrit and serum albumin when administered to binephrectomized

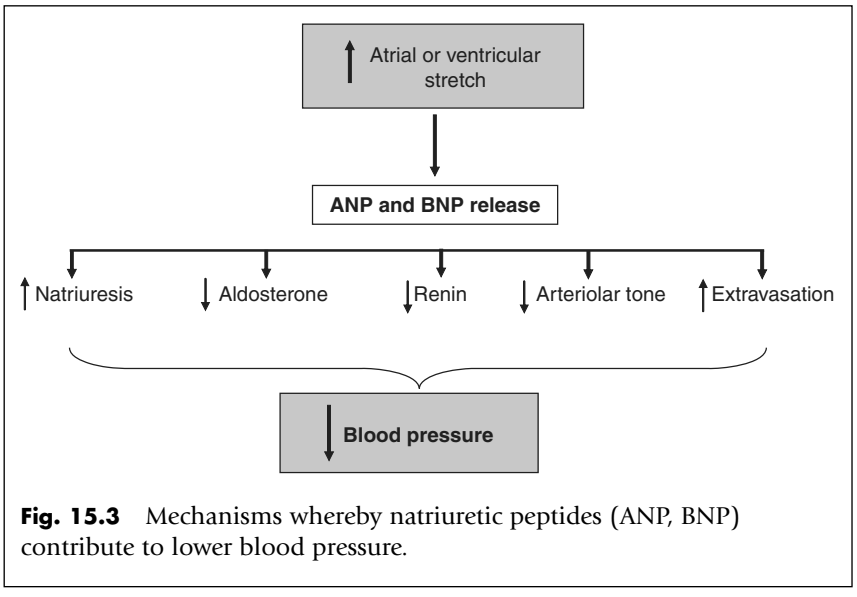

Fig. 15.3 Mechanisms whereby natriuretic peptides (ANP, BNP) contribute to lower blood pressure.

rats (41). ANP has an inhibitory action on aldosterone and renin secretion (42). ANP and BNP antagonize the vasoconstriction induced by the infusion of norepinephrine or angiotensin II (43). There is also some evidence that the central effects of ANP contribute to fluid and electrolyte balance and to the regulation of systemic hemodynamics (44). These central effects of ANP are mediated by an interaction between ANP and sympathetic tone in the brain stem.

Whether natriuretic peptides participate in the pathogenesis of hypertension is still debated. Experimentally, mice in which either the Pro-ANP or the ANP-A receptor genes have been deleted develop hypertension (45,46). In contrast, mice overexpressing the ANP and BNP genes have a lower BP than controls (47). In rat models of hypertension, an altered ANP secretion in response to salt loading or to an increased atrial pressure has been observed, suggesting a role of these peptides in hypertension (48,49). In humans, low to normal plasma ANP levels have been measured in hypertensive patients (50,51). However, some investigators found raised plasma ANP levels in patients with essential hypertension, even though blood volume is generally not expanded in these patients. This observation may be explained by an increased central venous pressure, owing to a greater venous return or to atrial distension in some hypertensive subjects (52,53). In offspring of hypertensive parents, Ferrari et al. have reported a reduced ANP response to salt loading, indicating that ANP deficiency may be a predisposing factor to the development of hypertension (54). A similar impaired ANP response to salt loading has been reported in Afro–Americans and in patients with salt-sensitive hypertension (55).

PROSTAGLANDINS

Prostaglandins are the product of arachidonic acid metabolism (56). Their production involved several steps: firstly, the release of arachidonic acid from membrane phospholipids under the action of phospholipase A_2; secondly, the catalysis of arachidonic acid by cyclooxygenases (COX 1, 2, or 3) to generate PGH_2; and thirdly, the generation of specific prostaglandins under the effect of prostaglandin synthases, such as prostacyclin synthase, leading to the formation of PGI_2 or thromboxane synthase, which generates thromboxane A_2. This cascade leads to the synthesis of several prostaglandins with multiple biological properties, including vascular, renal, and inflammatory effects (Figure 15.4). Phospholipase A_2 is activated by a variety of stimuli, including angiotensin II, norepinephrine, and bradykinin.

Prostaglandins act mainly near their sites of release because they are degraded rapidly by local metabolism into inactive products. At the vascular level, prostaglandins can produce either a vasoconstriction (thromboxane A_2, $PGF_{2\alpha}$) or a vasodilatation (PGE_2, PGI_2). One important property of vasodilatory prostaglandins is their ability to modulate the vasoconstriction induced by potent vasoactive substances such as angiotensin II (57). In the normal adult kidney, both COX-1 and COX-2 are constitutively expressed: COX-1 is present in the glomerulus, the afferent arteriole, and in tubular cells, and COX-2 has been located in the afferent and efferent arterioles, the podocytes, the macula densa, and some tubular and interstitial cells (58). Intrarenal prostaglandins participate actively in the regulation of renal perfusion and GFR (59). They are also implicated in the maintenance of sodium, potassium, and chloride homeostasis and in the regulation of renin secretion (59,60). The impact of prostaglandins on renin secretion may be of particular relevance to the genesis of hypertension (61). Indeed, recent data have demonstrated that mice deficient in the PGI_2 receptor are resistant to the development of renovascular hypertension, a renin-dependent form of hypertension (62).

In hypertensive patients, a deficiency in vasodilatory prostaglandins has been reported (63). Similarly, an increase in thromboxane A_2 has been measured in essential hypertension (64). These observations lead to the hypothesis that there is an imbalance between anti- and prohypertensive prostaglandins in hypertension. The potential role of prostaglandins in hypertension is further emphasized by the observation that selective as well as nonselective COX-1 and COX-2 inhibitors increase BP, favor sodium retention, and may induce hypertension in some patients (65–67). However, the hypertensive effect of nonsteroidal anti-inflammatory drugs is more frequent among hypertensive than normotensive patients. This finding would indicate that prostaglandins act as a counter-regulatory mechanism to limit the increase in BP in hypertension rather than a primary hypertensive mechanism.

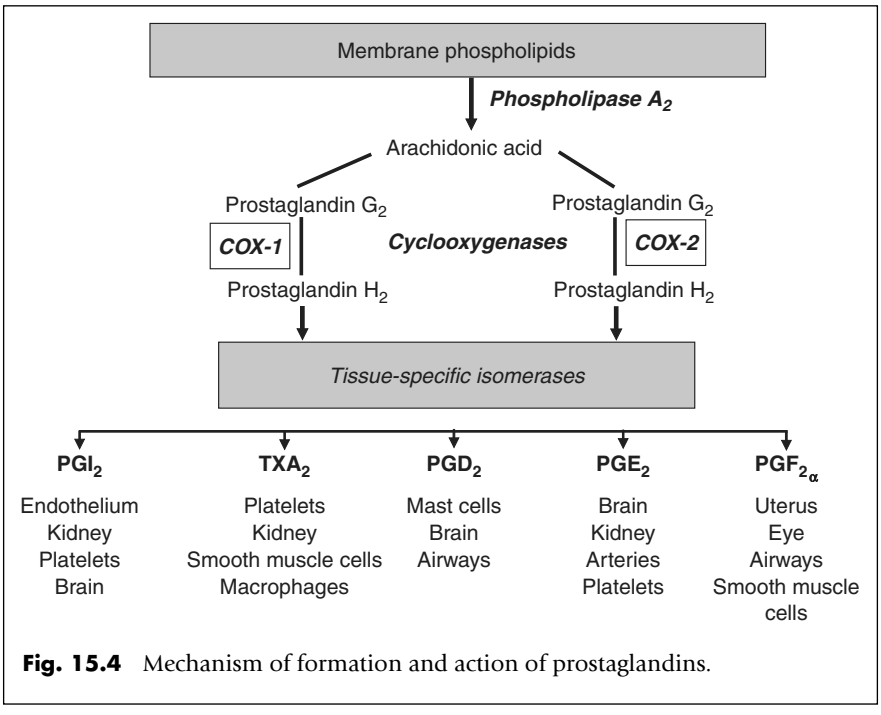

Fig. 15.4 Mechanism of formation and action of prostaglandins.

KALLIKREIN–KININ SYSTEM

The interest for bradykinin as an effective mediator in cardiovascular control has been revived by the development of ACEI, which interfere with the degradation of bradykinin. The kallikrein–kinin system consists of proteases (kallikreins) that release kinins for kininogen, the precursor protein (68). Kininogen is synthesized primarily by the liver, but mRNA for the high molecular weight (HMW) kininogen has been identified in endothelial cells. Kallikreins are present in plasma, where they generate bradykinin from the HMW kininogen, and in tissues, particularly in the kidney. Tissue kallikrein cleaves a low molecular weight kininogen to release lys-bradykinin (kallidin). Kallidin is then metabolized through an aminopeptidase into bradykinin. Kinins act by stimulating specific receptors (kinin B1, B2, and B3 receptors). The B1 receptor is involved in the chronic inflammatory and pain-producing response to kinins. The B2 receptor mediates most of the other actions of kinins. In the circulation and tissues, kinins are destroyed by aminopeptidases and carboxypeptidases. The dipeptidase kininase II [angiotensin-converting enzyme (ACE)] is the most important metabolizing enzyme within the cardiovascular and renal systems. The synthesis, activity, and release of renal kallikrein mRNA and protein levels are influenced by several hormonal systems, including mineralocorticoids, glucocorticoids, testosterone, thyroxine, insulin, vasopressin, cathecholamines, and angiotensin II. Of note, renal kallikrein mRNA of females is twice that of males.

The very first suspicion that kinins could play a role in hypertension was published in 1934 when a reduction in urinary kallikrein excretion was found in hypertensive patients (69). Thereafter, little attention has been given to this system. Later on, a similar observation was made in various groups of hypertensive patients, including black people and patients with a low renin hypertension and in rats with hypertension (70–72). All genetic models of hypertension in the rat show abnormalities in the kallikrein–kinin system. With time, increasing evidence for a role of kinins in BP have been gathered (73). Mutant mice, animals in which the B2 receptor has been knocked out, display a significantly higher BP, reduced RBF, and an increased renal vascular resistance when receiving a high sodium diet (74). Similarly, selective B2 receptor blockade has been shown to cause a rise in BP in various experimental models of hypertension in rats (75,76). Conversely, overexpression of human tissue kallikrein lowers BP in mice (77). More recent family studies have suggested that individuals with a greater urinary kallikrein excretion genotype were less likely to have one or two hypertensive parents, and urinary kallikrein was recognized as a strong marker of a genetic component of essential hypertension (78,79). Finally, studies using bradykinin antagonists have suggested that bradykinin contributes to the BP lowering effect of ACEIs (80).

ANDROGENS AND FEMALE SEX HORMONES

Gender-associated differences in BP have been clearly demonstrated in animals as well as in humans (81). Thus, men have a higher BP than age-matched premenopausal women, and are at greater risk for cardiovascular and renal diseases. In male spontaneously hypertensive rats (SHR), the pressure–natriuresis relationship is shifted to the right, and castration of male SHR has been found to restore it, suggesting that androgens contribute to the higher BP measured in males (82). Androgen receptor blockade lowers BP in male SHR to the level of female SHR (83), and the administration of testosterone to ovariectomized female SHR increases BP (82). This latter finding would indicate that androgens play a role in the pathogenesis of hypertension that occurs after menopause in some women (Figure 15.5) (84). Thus, at the time of menopause, not only the loss of female hormones, but also the relative change in estrogens/androgens ratio may affect BP. Androgen receptors have also been localized in different parts of the renal tubule, such as the proximal tubule in

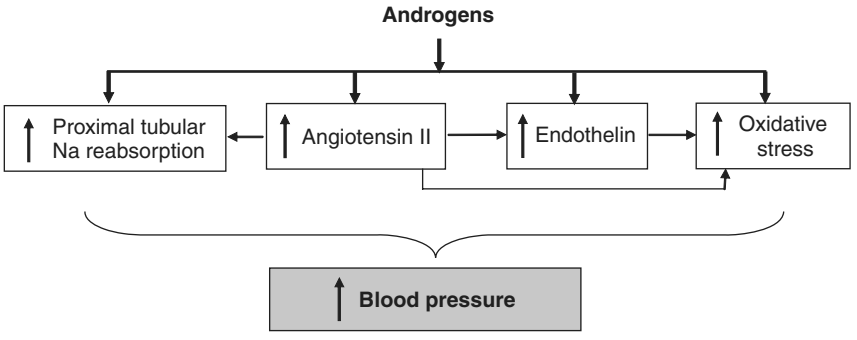

Fig. 15.5 Effects of androgens leading to an increase in blood pressure.

human kidneys (85) and the collecting tubule in the rat (86). When injected to rats, dihydrotestosterone, the main metabolite of testosterone, has been found to directly stimulate the proximal volume reabsorptive rate and, hence, to increase extracellular volume and BP (85).

There is also some evidence suggesting that female sex hormones (estrogens and progesterone) participate in the regulation of BP and may protect against salt-induced changes in BP. When Dahl salt-sensitive rats (DS) receive a high sodium diet, females become less hypertensive than male rats (87). In this animal model, ovariectomy results in an accelerated development of salt-sensitive hypertension in females (87). Interestingly, reversal of the diet to a low salt intake reverses the hypertension in intact male and female DS rats, but this is not the case in ovariectomized female DS rats. The interpretation of this finding is that female sex hormones act to suppress sodium-dependent as well as -independent increases in BP (88). A greater rise in BP has also been reported in female SHR rats after ovariectomy (89,90). More recent experimental data suggest that a loss of female hormones decreases the threshold of the hypertensive effect of salt (91).

Several studies have reported gender differences in various components of the RAAS that could partially explain the gender differences in BP (92). In a normotensive population, a higher plasma renin activity (PRA) has been measured in men than in women, regardless of age and ethnic heritage (93). Exogenous female sex hormones administered for oral contraception have also been shown to stimulate angiotensinogen production, which may lead to a increase in BP in some women (94). Other studies have reported that PRA is higher in postmenopausal than in premenopausal women, although PRA remains higher in men than in women for the same age (92). In animals significant differences have also been observed between males and females. The administration of testosterone to ovariectomized female rats increases PRA, and PRA is lower in males after castration (95,96). Finally, in Sprague–Dawley rats, a linear correlation between the levels of testosterone and PRA levels has been reported (3,17), suggesting that testosterone stimulates the RAAS. In accordance with this observation, several studies have found that androgens, like estrogens, enhance renal angiotensinogen mRNA (95,97). Androgens also upregulate the expression as well as the affinity of AT_1 receptors in male tissues (98).

Sexual hormones affect also the response to a stimulation of the RAAS. Thus, Miller et al. have compared the renal hemodynamic response to the infusion of exogenous angiotensin II in young normotensive premenopausal women and in age-matched men and found striking differences (99). Both groups exhibited an increase in BP and a decrease in effective renal plasma flow with angiotensin II, but only men maintained their GFR, resulting in an increased filtration fraction. In women, the administration of angiotensin II decreased GFR leading to a reduction in filtration fraction.

At last, endogenous as well as exogenous female sex hormones have been found to influence systemic and renal responses to salt in women (100). In young normotensive women, whether under contraceptives or not, BP is rather insensitive to salt, with a normal pattern of adaptation of renal proximal and distal reabsorption to changing salt intake (100). In contrast, women become salt-sensitive after menopause, an observation which may explain the increase in BP occurring at menopause in some women. The renal hemodynamic response to salt and the regulation of sodium excretion is also modulated by female sex hormones.

VASOPRESSIN

Arginine–vasopressin (AVP) has been recognized as one of the most potent vasoconstrictor peptides through the activation of V_1 vascular receptors. Moreover, vasopressin is a crucial determinant of fluid balance, mediated by its activity on renal V_2 receptors. Vasopressin has been shown to play a role in BP homeostasis in several physiological and pathological clinical conditions, such as changes in posture, dehydration, hemorrhage, adrenal insufficiency, and heart failure (101). Thus, vasopressin could potentially participate in the pathogenesis of some forms of hypertension.

When administered directly in the brain (in the lateral or third ventricle), small doses of vasopressin V1 agonist induce a sudden rise in BP, which is not observed with a V2 agonist, and this effect may be due to an activation of sympathetic nervous system (44). Elevated levels of vasopressin have been documented in several experimental rat models of hypertension, including in the DOCA-salt hypertensive rat, the SHR, and the Dahl salt-sensitive rat (102–104). In humans, however, the evidence for a role of vasopressin in the pathogenesis of essential hypertension is rather weak. Administration of an effective and selective V1 antagonist did not lower BP in normotensive subjects and in hypertensive patients on a regular sodium diet (105,106). However, the administration of a vasopressin receptor blocker has been associated with a moderate decrease in BP in patients with severe hypertension or malignant hypertension (107,108).

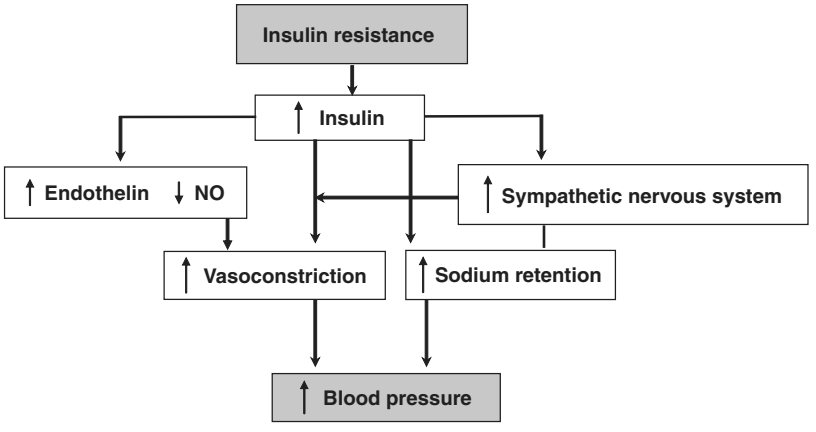

Fig. 15.6 Mechanisms whereby insulin resistance leads to an increase in blood pressure.

OTHER ENDOCRINE FACTORS

Besides the above-mentioned humoro-endocrine factors involved in the regulation of BP, several other endocrine factors can contribute to the development hypertension. Thus, glucocorticoid excess due to an adrenocorticotropic hormone (ACTH) excess or Cushing's disease is characterized by hypertension, truncal obesity, glucose intolerance, hirsutism, and osteoporosis (109). The increase in BP is linked to the fact that cortisol has some mineralocorticoid activity and may lead to sodium retention at high concentrations. Glucocorticoids also increase the synthesis of angiotensinogen and may reduce the synthesis of PGI_2, resulting in a greater vascular reactivity to angiotensin II and catecholamines.

Insulin is another hormone that is increasingly considered in the genesis of hypertension (110). Hypertension, obesity, dyslipidemia, and glucose intolerance represent a cluster of risk factors, which constitute the metabolic syndrome. Insulin resistance in some peripheral tissues appears to be the main feature of metabolic syndrome. This peripheral insulin resistance is associated with an increased activity of the sympathetic nervous system, an increase in ET, and a decrease in NO production. Moreover, insulin causes sodium retention, an effect which may further increase BP (Figure 15.6).

Thyroid hormones are also implicated in cardiovascular regulation, and both patients with hyperthyroidism and hypothyroidism may develop hypertension in the course of their disease (111). The increase in BP associated with an excess of thyroid hormones is due to an increase in cardiac output with an increased heart rate and pulse pressure. Blood volume is often increased and peripheral resistances are low in hyperthyroidism, whereas blood volume is low in hypothyroidism. In addition, thyroid hormones have a major impact on renal function, including on sodium and water excretion. Thyroid hormones have been shown to be essential for the function of the Na/K-ATPase in the kidney (112). They interact closely with the RAAS as well as with NO and ET. An increased activity of the sympathetic nervous system appears to be responsible for the rise in BP observed in hypothyroidism.

Hypertension is a clinical characteristic of acromegaly (113) and hyperparathyroidism (114). In the former, hypertension is due to the excess of growth hormones, which leads to vascular hypertrophy, but also to an hyperdynamic state, due to an activation of the sympathetic nervous system, and renal sodium retention. In the latter, hypertension is associated with several factors, including hypercalcemia, an activated RAAS, and a generalized hyperresponsiveness to vasoconstrictors. The release of a parathyroid hypertensive factor has also been evoked in patients with primary hyperparathyroidism.

CONCLUSIONS

The mechanisms by which the set point of BP regulation is altered in hypertension are extremely complex. For a comprehensive understanding of the humoral and endocrine factors involved in the genesis of hypertension, one should not forget that there are multiple interactions between the systems, that each of these factors is influenced by genetic and environmental components, and that there is likely a hierarchy of function and control systems. Another important aspect to consider is the timing at which these neurohormonal alterations happen. Indeed, there is increasing evidence that changes occurring during the fetal period and the early years of development determine the BP at a later stage in life. Therefore, the respective role of each neurohormonal component of BP control will probably differ, depending on when hypertension begins.

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WHERE IS HYPERTENSION RESEARCH GOING? 16

Alberto Zanchetti

INTRODUCTION

From time to time, repeated concerns are expressed about the state of hypertension research (1). It is often felt that the field is ripe, major fruits have already been harvested, new advances in drug research are not foreseen, and recent emphasis in considering hypertension in the context of total cardiovascular risk (2) has watered down its pathophysiological role and its research appeal. Furthermore, with the disappearance of severe hypertension and infrequent interest in secondary forms, hypertension is being pulled out of hospitals, and research possibilities are shrinking.

I have recently commented on this matter in an editorial on the *Journal of Hypertension* (3). Although there is some ground for each of these arguments, these predictions are contradicted by the reality of a growing body of excellent and innovative research approaching different aspects of hypertension.

It is certainly true that the modern concept of evaluating total cardiovascular risk may give the impression that hypertension is no longer exerting the dominating or unique role in cardiovascular prevention it used to exert several years ago. Nonetheless, recent data from a World Health Organization survey (4) indicates that high blood pressure (BP) is on the very top of the list of leading global risk factors responsible for mortality worldwide (Figure 16.1). Furthermore, BP is a risk factor that can be easily measured by doctors and nurses, as well as by the patients themselves, and can be measured repeatedly both as a marker of risk and as a target of treatment. Finally, at variance with other risk factors, high BP is in a positive feedback, vicious circle relationship with induced cardiovascular damage, which, as illustrated in the scheme of Figure 16.2, contributes by its development to further rises in BP.

Several areas of hypertension research may provide new opportunities. The advent of cheap compounds within almost every one of the several classes of antihypertensive agents available now makes a call to a more intensive approach to the diagnosis and treatment of hypertension a feasible task without the obstacle of unbearable costs for public or private healthcare in several parts of the world. As illustrated in Figure 16.3, two thirds of the approximately one billion people with hypertension worldwide are in countries with developing economies, and by 2025 they will amount to a billion out of a total of 1.5 billion (5). Developing countries will become more and more involved in research on the prevention and treatment of hypertension, and a positive trend to this direction is already witnessed by an increasing number of publications from authors belonging to developing economies. Because of cheaper agents, earlier treatment, well before the risk factors turn into producing subclinical organ damage, can be implemented, treatment with the goal of achieving BPs lower than 140/90 mmHg can be thought of, and suitable investigations can be planned.

BLOOD PRESSURE CONTROL

At the same time, a major remaining problem is the wide gap between expert recommendations and practice in effectively controlling elevated BP (Figure 16.4). The often expressed belief that this gap is entirely due to poor compliance of physicians and patients, is rather naïve. Even in interventional trials, where stepwise treatment schedules are enforced by wilful investigators according to strict protocols, BP goals are rarely achieved in more than 50–60% of patients, particularly of the complicated ones (7). Likewise the recommendation to bring BP below 130/80 mmHg in diabetic and renal patients (2) remains little more than wishful thinking (7), unless this is translated into the recommendation that, in these patients, antihypertensive treatment should already be initiated when BP is in the high-normal range (130–139/88–90 mmHg) (8).

The real difficulties in bringing BP to the recommended goals may lie in the fact that antihypertensive treatment is often started, or intensified, too late, when organ damage has already developed to a point that it is not easy to regress and, at most, its progress can only be slowed down. This calls for earlier intervention in the natural history of hypertension, a solution which has perhaps been delayed by the emphasis given to the evaluation of the absolute risk of cardiovascular disease (9,10). This has been a legitimate scientific approach, which, however, has largely been used by health providers to establish prescriptive rules and arbitrary cutoffs based on short-time perspectives (5–10 years) and on purely economic calculations (11,12). Important information has been neglected, if not completely ignored, such as

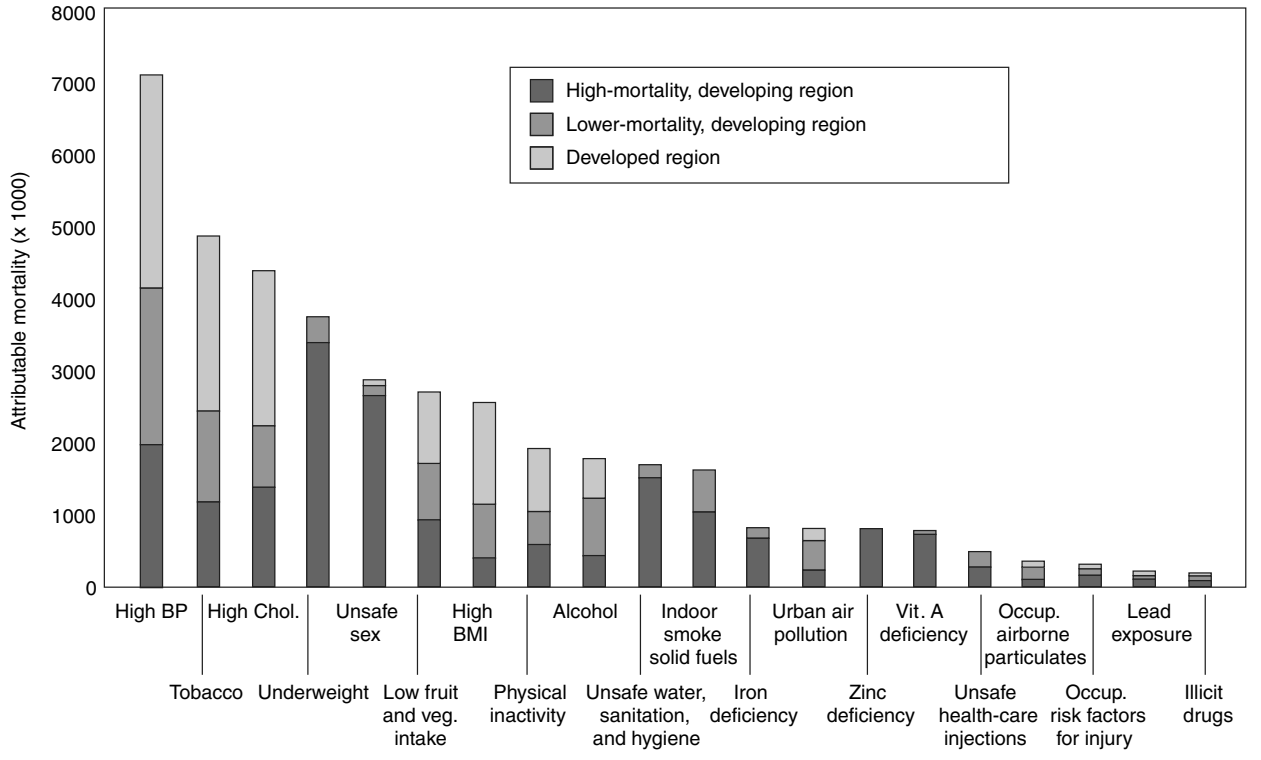

Fig. 16.1 Mortality due to leading global risk factors (WHO World Health Report 2002). *Abbreviations*: BMI, body mass index; BP, blood pressure; WHO, World Health Organization. *Source*: From Ref. 4.

that already provided by the Hypertension Detection Follow-up Program (13) in 1982 (information upon which attention was soon called up) (14,15). In that trial, treatment of hypertension in "complicated" hypertensive patients was found to be accompanied by a much greater absolute benefit than in "uncomplicated" patients, but the absolute risk of treated "complicated" hypertensives remained four times greater than that of similarly treated "uncomplicated" ones. Similar observations have later been made in the context of the Hypertension Optimal Treatment (HOT) study (16), as illustrated in Figure 16.5. Likewise, the common observation that treated (and commonly "high-risk") hypertensives remain at a higher risk than untreated (and commonly "lower risk") hypertensives (13–15) has often been misinterpreted, to the point that some have introduced antihypertensive treatment as a "risk factor."

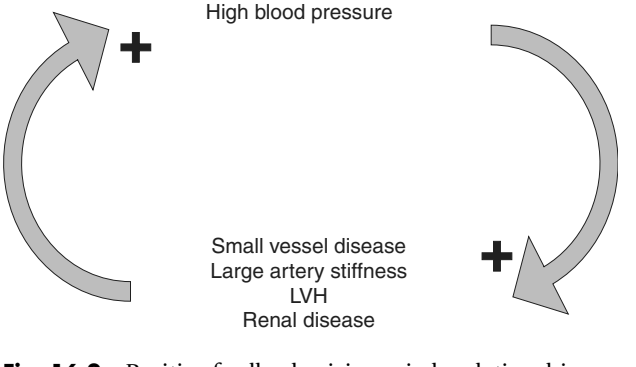

Fig. 16.2 Positive feedback, vicious circle relationship between high blood pressure and blood pressure dependent cardiovascular and renal damage. *Abbreviation*: LVH, left ventricular hypertrophy.

CURRENT RESEARCH OPPORTUNITIES

These considerations are made as an illustration of current research opportunities. First, some rethinking of the exclusive emphasis given to calculation of "absolute" risk may be welcomed. The 2003 European Society of Hypertension–European Society of Cardiology (ESH–ESC) guidelines (2) openly mentioned that strict use of common cutoffs of absolute risk to initiate antihypertensive treatment would lead to the recommendation to treat, almost exclusively, elderly patients; younger hypertensives, especially women, would never deserve treatment, unless after a cardiovascular event. Consequently, these guidelines shared a previous suggestion to base decisions on absolute risk for elderly patients, and on relative risk for younger and middle-aged subjects (17). This approach has been reconfirmed in the most recent 2007 ESH–ESC guidelines (18) and also shared by the Fourth European guidelines on cardiovascular disease prevention (19).

Second, it has been mentioned that the introduction of low-cost medications through a growing number of generic compounds should make widespread treatment of BP economically feasible. This is an opportunity for research, concerning both health control and intervention trials. For instance, a recent trial in China has used low-cost out-of-patent medications to show the benefits of reducing systolic BP to just below, rather than just above, 140 mmHg (20).

Third, if subclinical organ damage is a paramount factor in determining overall cardiovascular risk and limiting the possibility of a fully successful treatment, then there is a wide

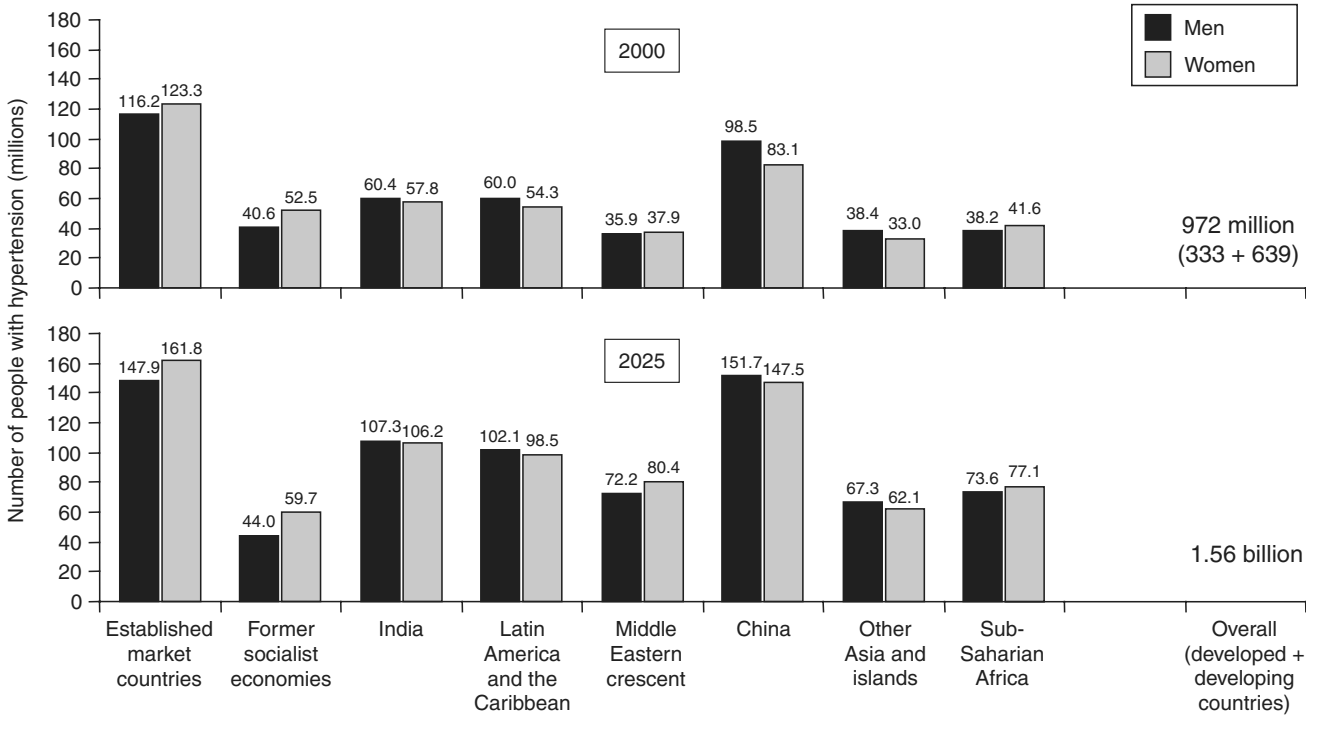

Fig. 16.3 Number of people with hypertension aged 20 years and older by world region and sex in 2000 and 2025. *Source*: From Ref. 5.

and productive area for intensive research on the nature and determinants of hypertension-associated organ damage. This is an area where research has been active but, so to say, hindered by excessive worship of the cardiovascular "event" (12), which is considered by many as the only meaningful outcome. However, as illustrated in Figure 16.6, most of intervention trials comparing treatment regimens based on different antihypertensive agents may have failed to show differences in outcomes because the patients were chosen in a too late stage of the cardiovascular disease continuum when organ damage was scarcely reversible and the ancillary specific properties of some compounds could hardly exert their action (12).

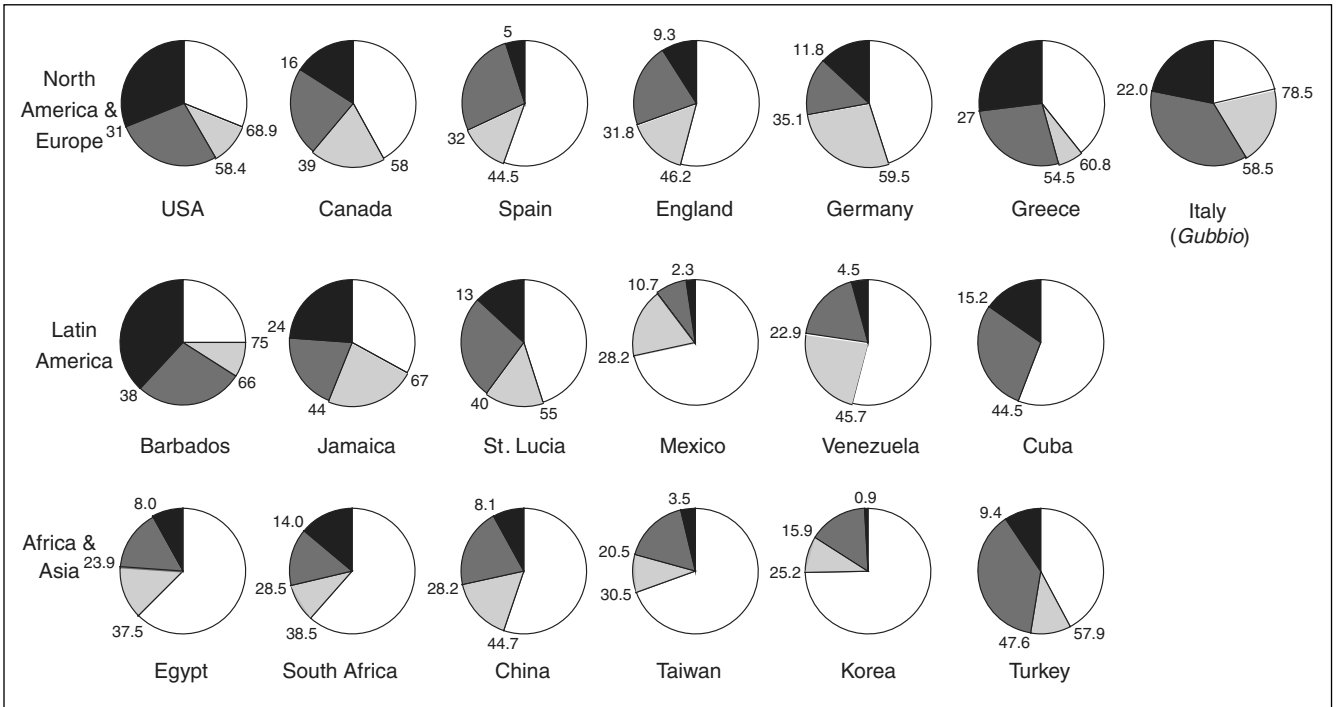

Fig. 16.4 Awareness, treatment, and control of hypertension by world region. Numbers in a counterclockwise direction indicate percentages of controlled, treated, and aware hypertensives. *Source*: From Ref. 6.

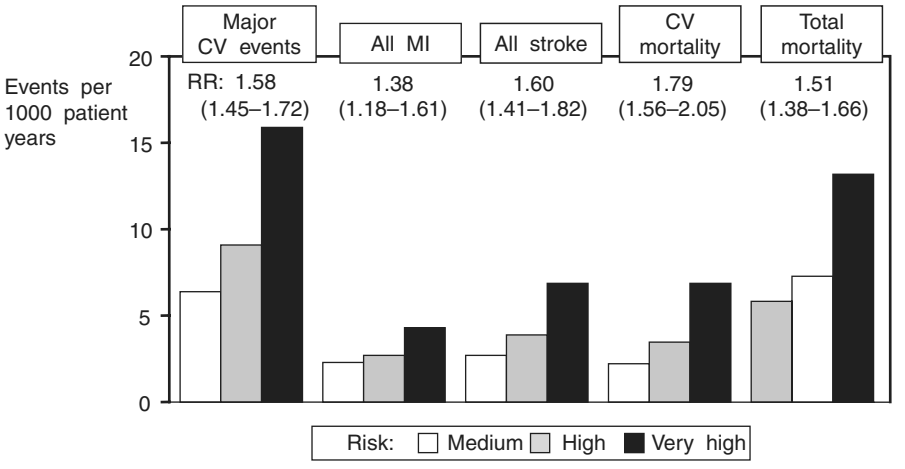

Fig. 16.5 Events in treated hypertensives from the Hypertension Optimal Treatment (HOT) study, stratified according to WHO-ISH risk strata (left columns: medium risk; central columns: high risk; right columns: very high risk). *Abbreviations*: CV, cardiovascular; MI, myocardial infarction; RR, mean trend relative risk (of very high to high, and high to medium risk). *Source*: From Ref. 16.

Along this line of thought, research opportunities are quite wide. Not only is there a need of new intervention trials exploring the benefits of antihypertensive therapy in subjects at a much earlier stage of the cardiovascular continuum; but further pharmacological research on differential actions of existing compounds on development, progression, and regression of subclinical organ damage should be done. Finally, there is new research on new compounds that may more directly interfere with one or another mechanism of organ dam-age (e.g., myocardial or renal fibrosis), even independently of BP lowering, compounds that might be associated to cheap antihypertensive agents and potentiate their actions on organ damage and, later on, events. Suffice it to mention here that, although hypertension in the elderly and particularly isolated systolic hypertension are considered high risk conditions, not one of the antihypertensive agents that have been shown to effectively and beneficially lower BP in the elderly directly influence large artery stiffness, which is

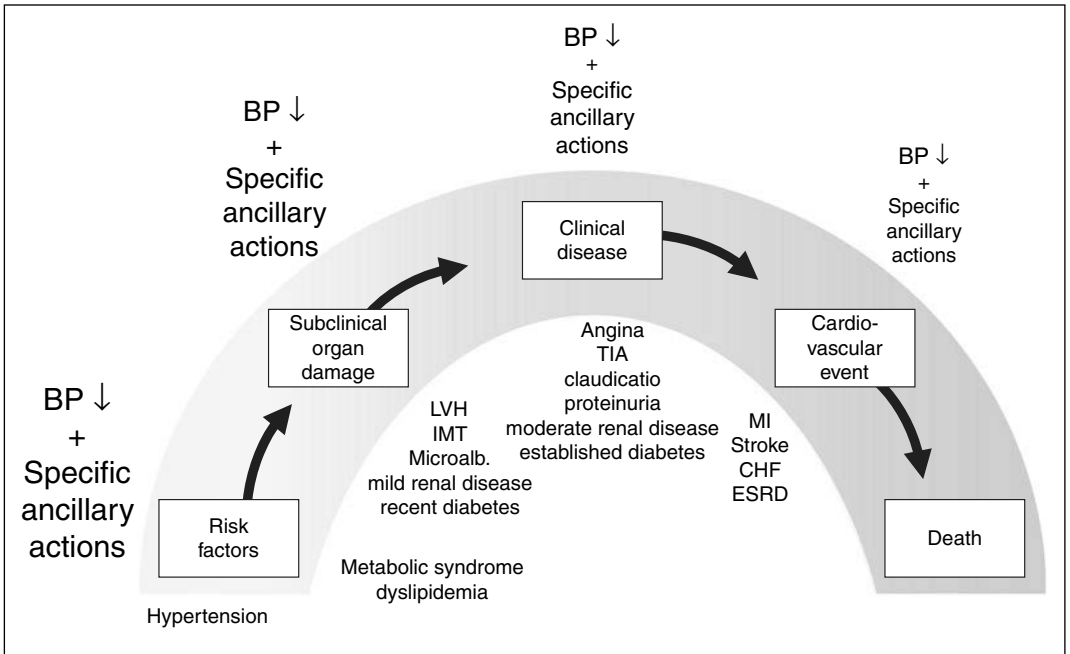

Fig. 16.6 The cardiovascular continuum in hypertension and the relative preventive effect of blood pressure lowering and ancillary actions of antihypertensive agents. BP↓: blood pressure lowering. The size of the characters used for BP↓ and specific ancillary actions is proportional to the presumed size of the beneficial action. *Abbreviations*: CHF, chronic heart failure; ESRD, end stage renal failure; IMT, vascular intima-media thickness; LVH, left ventricular hypertrophy; MI, myocardial infarction; TIA, transient ischemic attack. *Source*: From Ref. 12.

known to be at the basis of systolic hypertension in the elderly. This is an area for bold, farsighted research.

GENETIC RESEARCH

Finally, active and stimulating research is growing in the area of genetics of hypertension. Although this research has produced great advances in understanding the genetic basis of some rare forms of secondary hypertension, the results of the studies on essential hypertension have given only few substantial results, while many of the studies have been frustrating, being negative or producing results that were subsequently not reproduced by other investigators.

Despite these frustrations, it must be recognized that the current strategies to give nonpharmacological recommendations to large strata of the population (e.g., those defined as "prehypertensives" by the 7th report of the Joint National Committee) (21) or pharmacological measures to all "hypertensive" patients without being able to identify those individuals genetically predisposed either to hypertension or to the consequences of hypertension, appear to have achieved less than the expected protection, both for reasons of adherence to intervention and for reasons of acceptable cost. Here, genetic research is promising, if the limitations of many of previous investigations are understood: too fragmented research, insufficient number of subjects included, incomplete phenotyping, limited number of genes and polymorphisms explored, insufficient matching of phenotypes and of genes potentially involved. The potentialities of genetic research, however, are growing at an unbelievable rate. What is required is concerted, rather than fragmented, research. An encouraging example has recently come from the European Community that has financed a project of a Network of Excellence, InGenious HyperCare (Integrating Genomics, Clinical Research, and Care in Hypertension), which also has the collaboration of the European Society of Hypertension.

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SECTION 4

Target organ damage: measurement and clinical importance

CARDIAC DAMAGE AND PROGRESSION TO HEART FAILURE 17

Enrico Agabiti Rosei, Roland E Schmieder

INTRODUCTION

During the last 30 years, left ventricular hypertrophy (LVH), defined as an abnormal increase in the left ventricular mass (LVM), detected either by an electrocardiogram (ECG) or by the more sensitive echocardiographic technique, has been recognized as an important and independent risk factor in hypertension for predicting several cardiovascular events, including myocardial infarction, congestive heart failure (CHF), sudden cardiac death, and stroke. Classification into concentric or eccentric (nondilated) hypertrophy and concentric remodeling, by using the echocardiographic measured left ventricle (LV) wall to radius ratio (values ≥ 0.42 define concentric patterns), has been shown also to have risk-predicting value, concentric geometry being related to more evident vascular alterations and worse prognosis.

FROM LVH TO CHF

From the earliest Framingham Heart Study report (1) on the prevalence of heart failure, to the more recent demonstration of Vasan and Levy (2), hypertension remains one of the most common causes of cardiac failure. In the presence of a chronic pressure overload, such as in arterial hypertension, a parallel addition of sarcomeres takes place, with an increase in myocyte width, which in turn increases wall thickness. In the development of hypertensive heart disease, myocyte hypertrophy is also associated with apoptosis, collagen deposition, and ventricular fibrosis, with an impairment of coronary hemodynamics as well, thus profoundly influencing functional properties of the left (and right) ventricle.

Most of the earlier randomized clinical trials evaluating the efficacy of antihypertensive drugs have demonstrated a significant change in hypertensive disease evolution. In fact, antihypertensive treatment induced a significant prevention of systolic cardiac failure, thereby increasing patients' survival. Clinical manifestations of atherosclerotic disease, such as stroke and coronary artery disease, became more prominent causes of cardiovascular morbidity and mortality in hypertensive patients (3).

However, at present time, with increased aging of the general population, a persistent increase in morbidity and mortality associated with CHF has been observed, and about 75% of patients with CHF have a history of arterial hypertension (4,5).

In more recent years, it has been well recognized that approximately half of the patients with overt CHF may display normal ejection fraction and marked impairment in diastolic function (6). Diastolic dysfunction may be defined as impairment in ventricular relaxation and filling during diastole, which are often present before alterations in systolic function are detectable. This phenomenon is particularly evident in elderly hypertensive patients in the presence of a reduced coronary flow reserve, with or without associated epicardial coronary artery disease (Table 17.1).

The fundamental mechanisms contributing to the progression from compensatory LVH to heart failure in hypertension are still largely undefined (Figure 17.1).

In spontaneously hypertensive rats (SHR) and renal hypertensive rats (RHR), the response of ventricular dP/dt to stimulation of beta-adrenergic receptors was found reduced as a

Table 17.1 Main characteristics of patients with diastolic heart failure and of patients with systolic heart failure

Characteristic	Diastolic heart failure	Systolic heart failure
Age	Frequently elderly	All ages (typically 50–70 years)
Sex	More often females	More often males
LV cavity dimensions	Usually normal, concentric LVH	Usually LV dilatation
LV ejection fraction	Normal	Depressed, usually 40% or lower

Abbreviations: LV, left ventricle; LVH, left ventricular hypertrophy.

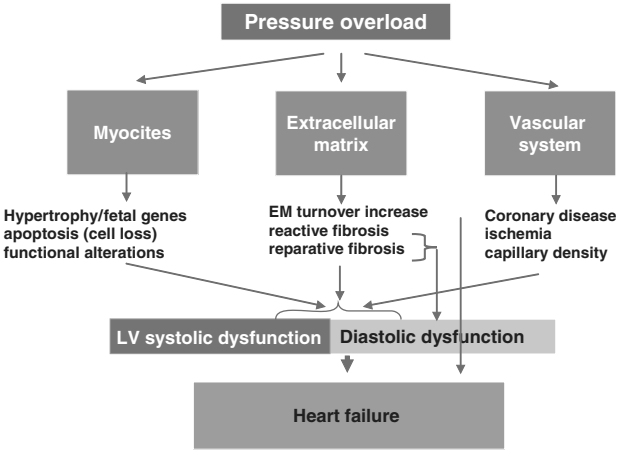

Fig. 17.1 Pathophysiological changes in the transition from pressure overload to heart failure.

consequence of decreases in both their number and density, in comparison with responses in age-matched normotensive control animals (6).

Experimental studies have pointed to alterations in a guanine nucleotide-binding protein subunit (Gsa) as one of the possible mechanisms responsible for the pathogenesis of hypertension and the development of LVH (7).

Other biochemical alterations are represented by the increased expression of slow myosin ATPase isoform [beta-myosin heavy chain (beta-MHC)] relative to the fast myosin ATPase isoform [alfa-myosin heavy chain (alfa-MHC)]; this change should be interpreted as adaptive, promoting a more favorable energetic economy (8,9).

Cardiac hypertrophy involves a structural remodeling of cardiomyocytes and nonmyocytes, and fibroblasts contribute to perivascular fibrosis that initially surrounds intramural coronary arteries and thereafter moves into the interstitial space (10,11).

The initiation of reactive fibrosis is triggered, at least in part, by the local activation of trophic peptides and, in particular, of the renin–angiotensin–aldosterone systems (RAAS), which results in the expression of transforming growth factor-β1 (TGFβ1), fibronectin, and a relative increase in collagen I (12,13).

Angiotensin II may also regulate collagen degradation by reducing the activity of interstitial matrix metalloproteinase-1 (MMP-1) activity and by enhancing the production of tissue inhibitor of metalloproteinase-1 (TIMP-1) in endothelial cells.

In conclusion, molecular mechanisms have recently been proposed to explain how hemodynamic and neurohumoral factors could induce the transition from hypertension to LVH and then to CHF. Although some of these mechanisms could become new targets for pharmacological interventions, their importance has not yet been completely established (14).

The postulated mechanisms that underlie cardiac dysfunction, alone or in combination, are hemodynamic load, decreased intrinsic myocardial contractility, adverse chamber remodeling, impaired coronary hemodynamics, and ventricular fibrosis.

The progressive increase in LV dimensions in patients with LVH is aimed to achieve a contractile reserve under conditions of stress. The adaptation of LV geometry to maintain cardiac output, however, increases wall stress, which further influences cardiac dilatation, and this has been considered the first step in the transition from cardiac hypertrophy to cardiac failure (15).

PATHOGENESIS OF CARDIAC STRUCTURE ADAPTATION

In arterial hypertension, elevated blood pressure (BP) is the fundamental trigger to the sequence of biological events that lead to development of LVH. Statistically, only 10% of the variation in LVM could be accounted for based on office systolic BPs averaged over a 30-year period (16). LVM is more closely related to average 24-h BP (17,18), and even highly sophisticated measurements of BP can not fully account for the variance in LVM (19); the circardian pattern of BP appeared to be of further importance. Despite similar mean ambulatory BP values, "nondippers" have increased left ventricular mass compared with individual displaying the usual circardian pattern (20). Overall, 24-h mean BP and average daytime systolic BP—in most studies the best statistical correlates of LVM—account for about 25% of observed variance in LVM (21,22), and the simplistic view that only BP is a culprit of LVM has to be revised.

Nonhemodynamic factors other than BP, such as age, sex, ethnicity, body mass index, stiffness of large arteries, diabetes, and dietary salt intake, are operative in determining who among the hypertensive patients develop LVH and to what degree LVM is increased (Figure 17.2). Obesity is a major risk factor for LVH development: A 2 kg/m^2 increase in body mass index correlated with a 50% risk of increased LVM in a cohort of elderly men and women (23). Hemodynamically obese hypertensive patients are usually characterized by expanded plasma volume and increased cardiac output, both imposing an additional hemodynamic load on the left (and right) ventricle (24,25).

Epidemiological data clearly indicate that dietary salt intake modifies the process of LVH in hypertensive subjects as well (26,27). This has been reported irrespective of whether dietary salt intake has been assessed by measuring 24-h urine sodium excretion in clinical stable conditions or by

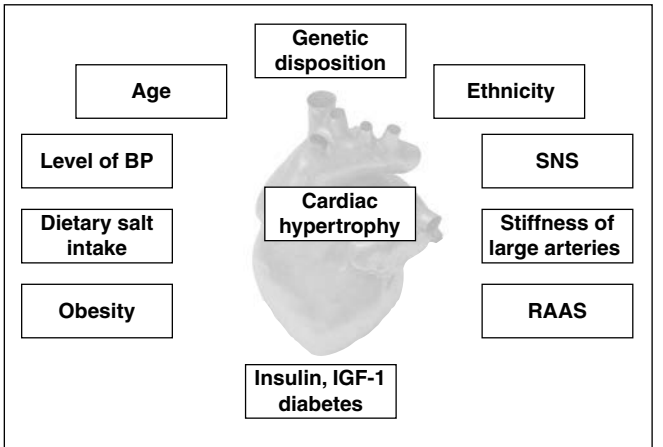

Fig. 17.2 Pathogenesis of cardiac hypertrophy in hypertension. *Abbreviations*: BP, blood pressure; IGF-1, insulin-like growth factor 1; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system.

directly measuring the salt ingested with food (12). Of note, this relationship has been found to be independent of 24-h-BP, body weight, and other clinical determinants of LVH (27,28). In normotensive and hypertensive rats, high salt intake induced myocardial hypertrophy and fibrosis that was found to be related to increased activity of the aldosterone synthase activity and production of aldosterone in the myocardium, despite decreased plasma renin activity and lowered plasma aldosterone concentration in the systemic circulation (29). Most recent trials have indicated that increase in intracellular sodium leads to an upregulation of growth-stimulating genes, thereby directly inducing growth-stimulating signals.

Gender, ethnicity, and genetic factors are also well established as nonhemodynamic factors that contribute to the development of LVH. In the Framingham study, LVM increase was documented in a higher percentage of hypertensive women than men—70% compared with 31%, a difference that parallels the higher contribution of hypertension to the risk of CHF in women (30). In African Americans, the prevalence of LVH increases compared to whites at similar BP evaluations (31). Several studies have further suggested that approximately 30% of the LVM variance is genetically determined (32). Studies of genetic influence of LVM have focussed mainly on candidates' genes that are related to the RAAS, to the sympathetic nervous system (SNS) or its receptors, and on components of the signal transduction mechanisms involved in cardiac hypertrophy.

The effect of SNS is evident in experimental models and in human studies. Although in pheochromocytoma LVH prevalence is relatively low, new studies applying the cardiac spillover methodology, and thereby assessing the direct effect of the sympathetic drive to the heart, have found a close correlation between the cardiac noradrenaline spillover and LVM (33). These findings are in accordance with previous data, which demonstrated that increased peripheral muscle sympathetic nerve activity as measured by microneurography is elevated in hypertensive patients with LVH (33,34).

Experimental and clinical trials highlight the role of RAAS in mediating LVH (35,36). In particular, inadequate suppression of the RAAS in relation to the dietary salt intake is related to an accelerated LVH (37). Angiotensin II acts primarily via the angiotensin type 1 receptor in myocytes, induces hypertrophy and hyperplasia, and regulates collagen synthesis. Angiotensin II production further upregulates expression of the fibrogenic cytokine TGFβ1, thereby inducing perivascular and interstitial fibrosis. The specific role of the angiotensin type 2 receptor is less clear, although its modulating effect on LVM has been pointed out by experimental and clinical data (38).

The coexistence of hypertension and diabetes increases the prevalence of LVM. Moreover, insulin resistance and high insulin levels are associated with the development of LVH in hypertensive patients (39). Other major metabolic cardiac risk factors, notably hypercholesterolemia and hyperglycemia, may also modify the extent of LVM and the prevalence of LVH in the hypertensive population.

Both hemodynamic and nonhemodynamic factors are of pathogenetic prevalence for the development of LVH. Most evidence stems from experimental data, but several clinical trials clearly indicate that the variety of nonhemodynamic factors, including dietary salt intake or neuroendocrine stimulation (SNS, RAAS), modify the adaptive response of the myocardium to increased cardiac workload in hypertension.

LVH AND ISCHEMIA

LVH and failure are frequently associated with coronary artery disease. Hypertension is one of the major risk factors for coronary atherosclerosis.

In the assessment of LVH by electrocardiographic criteria, the use of the pattern of "definite LVH," including S–T segment and T wave abnormalities, was strongly associated with an increase of the incidence in acute myocardial infarction and sudden death (1,40,41). When using the voltage criteria for LVH, a less strong association with myocardial infarction was observed, suggesting that alterations in the repolarization could reflect the presence of reduced coronary perfusion.

It has been shown that the presence of LVH is associated to structural and functional alterations in both large (42–44) and small arteries (45–47). Vascular structural changes were particularly evident in patients with concentric LVH (48–51).

The presence of vascular alterations is in large part responsible for reduced coronary reserve, consistently observed in patients with LVH (52).

The concomitant atherosclerotic process of epicardial coronary vessels (53) and the structural alterations (54) and rarefaction of small coronary vessels limit blood supply in a situation where oxygen request is increased due to the greater mass of tissue. An insufficient compensatory angiogenesis has also been demonstrated during the development of adult LVH (55).

In the presence of LVH, the decrease of coronary perfusion in subendocardial layers may yield to myocyte necrosis and reparative fibrosis (56), favoring the progression toward heart failure.

Other extravascular mechanisms potentially responsible for impaired coronary reserve include changes in wall tension, heart rate, and contractility. In fact, oxygen requirements, as measured by the triple product (heart rate × LV mass × end-systolic stress) are progressively increased in patients with LVH in respect to patients with normal LV mass and geometry (57).

The reduction of the regulatory capacity of coronary flow is greater during exercise, when oxygen demand increases. In fact, in resting conditions, the reduction in coronary flow reserve may not have important consequences, but during exercise-induced increase in oxygen requirement it may become clinically relevant, producing the clinical manifestations and favoring the progression of LV dysfunction (58).

Functional alterations may occur and further deteriorate the vasodilator response of coronary microcirculation. Functional alterations related to endothelial dysfunction have been shown to precede morphological changes in the vascular wall and may trigger the development of vascular remodeling (Table 17.2) (59,60).

All these observations suggest that LVH represents a state of potential or actual myocardial ischemia.

LVH AND SYSTOLIC PERFORMANCE

In both normotensives and hypertensives, LV systolic function seems to be closely dependent on myocardial afterload, as indicated by the linear relationship between LV endocardial fractional shortening (FS) and end-systolic stress (61). In most patients with mild to moderate hypertension, left ventricular systolic function is well preserved.

Table 17.2 Mechanisms for coronary flow reserve reduction in the presence of left ventricular hypertrophy

Myocardium
Myocite hypertrophy
Perivascular and interstitial fibrosis
Extravascular compression (wall stress increase and abnormal diastolic filling)
Oxygen requirements increase
Coronary vasculature
Atherosclerosis of coronary epicardial vessels
Structural alterations of small vessels (media thickening)
Arteriolar rarefaction (or insufficient compensatory angiogenesis)
Endothelial dysfunction

A few years ago, supernormal LV ejection fraction or FS in limited subgroups of hypertensive patients with mild LVH were found, possibly reflecting enhanced myocardial contractility (62,63). In fact, marked concentric LVH in patients with severe hypertension improves LV chamber contraction by reducing LV wall stress (63).

However, these findings seem to be in contrast with data from experimental studies, which have shown a progressive impairment of contractile state of cardiac muscle during gradual onset of hypertension (64,65).

The apparent paradox has been cleared by the evidence that left ventricular FS or ejection fraction, measured at the endocardium, reflect chamber dynamics, but they do not necessarily provide a direct measure of myocardial fiber shortening. In fact, the circumferential fibers responsible for shortening of the left ventricular short axis are located in the mid portion of the left ventricular walls, between two longitudinal shells responsible for long axis shortening and twisting. Experimental data have also shown that myocardial shortening in subendocardial layers exceeds that seen in the outer (subepicardial layers) and the effect of nonuniform wall thickening is greater in the presence of cardiac hypertrophy (66,67). The use of a more physiological midwall mechanics index, related to circumferential end-systolic stress, has shown that myocardial chamber function may be often overestimated in hypertensive patients, particularly when left ventricular wall thickness is increased. Several studies have demonstrated that LV midwall function is commonly reduced in hypertensive patients (around 15–20%) (68–73). The subgroup of patients with a depressed LV midwall function present other features associated with an elevated cardiovascular risk profile, such as concentric geometry, elevated peripheral resistances and heart rate, overweight, or obesity (72). Higher midwall FS values have been associated to female gender, both in hypertensive patients and in a general population (74,75).

In three prospective studies, the prognostic significance of midwall systolic performance was evaluated, and the presence of a reduced midwall FS measured at baseline resulted as an independent predictor of cardiovascular morbidity and mortality (76–78).

The regression of LVH in patients with reduced midwall systolic performance is associated with a significant improvement of midwall FS (79–81).

Despite the fact that LV chamber performance is often found normal in resting conditions in many hypertensive patients, abnormal ejection fraction response to exercise may be observed. This seems to be particularly evident in patients with concentric hypertrophy, or in those with eccentric hypertrophy and obesity, which is often associated with a volume overload condition.

On the basis of all these considerations it appears reasonable that patients at high risk of developing asymptomatic systolic dysfunction or heart failure, such as hypertensives with LVH, should periodically undergo an echocardiographic study for evaluation of LV mass and function.

LVH AND DIASTOLIC PERFORMANCE

For many years, the occurrence of heart failure has been attributed to a progressive impairment of systolic function. However, more recently, it has been observed that a large number of cases with typical symptoms of CHF present a normal or only mildly impaired systolic function (82–86). In hypertensive patients with LVH, abnormalities in both myocardial relaxation and passive filling have been detected (86).

These aspects have become even more relevant, owing to the increase of the elderly population in Western countries. Diastolic dysfunction can be observed in a greater percentage of patients with LVH. Increasing age, higher heart rate, and obesity may worsen diastolic filling. Gender-related difference has been observed in the impact of impaired diastolic relaxation on exercise capacity in hypertensives with LVH, and females could be more likely to have an altered cardiac adaptation to physical activity than men. Recent reports identify elderly women as the most likely candidates for diastolic heart failure.

Diastolic heart failure may be observed in approximately one-third or more of all heart failure cases. Whether it may be associated with a lower mortality rate compared to other forms of heart failure is still controversial; however, it is associated with a high morbidity. It is conceivable that early recognition and appropriate therapy of diastolic dysfunction can prevent further progression to diastolic heart failure and death (Figure 17.3).

Myocardial relaxation reflects the time course and extent of cross-bridge dissociation after systolic contraction. The load

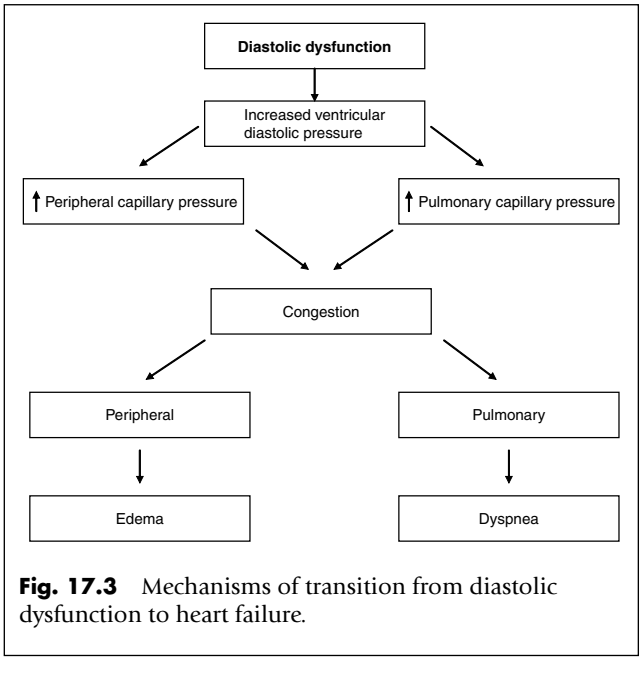

Fig. 17.3 Mechanisms of transition from diastolic dysfunction to heart failure.

imposed on the muscle, the rapid reduction of cytosolic calcium to baseline levels, and alterations in sensitivity of myofilaments to calcium may profoundly modify myocardial relaxation. Myocardial relaxation alterations may be related to the downregulation and reductions in protein levels of sarcoplasmic ATP-dependent reticulum pumps, influencing the course time of transient calcium, and the frequency– force response. In addition, the increase of beta-myosin ATPase activity and the changes in troponin subunit isoform expression and phosphorylation represent other molecular adaptations affecting myocardial relaxation. The increase of isovolumic relaxation time, due to a slower and delayed relaxation, is frequently observed in hypertensive patients. Invasive techniques, with cardiac catheterization and simultaneous pressure and volume measurements, represent the gold standard to assess left ventricular diastolic function, with measurements of the rate of left ventricular relaxation, the rate and timing of diastolic filling, as well as myocardial stiffness; however, they are clearly unpractical for routine diagnostic evaluation, which is relevant in the large population of hypertensive patients (87).

Passive filling dynamics are influenced also by alterations of passive deformation properties of the myocardium, interestingly, not only related to the wall thickness, but also, most importantly, to its composition. The increase in extracellular matrix collagen tissue may be promoted by the stimulation of the RAAS. Subendocardial ischemia, typically seen in patients with LVH, even in the presence of normal epicardial arteries, can deteriorate diastolic filling. Conversely, since most of the coronary flow occurs in diastole, alterations of myocardial relaxation or compliance may affect blood supply (Table 17.3). Diastolic abnormalities may be observed early in the natural history of hypertension and may also be demonstrated in normotensive subjects with parental hypertension (88,89).

The evaluation of LV diastolic function in asymptomatic patients with hypertension has been made possible by the wide use of echocardiography, first with the measurements of M-mode tracings (90), and thereafter with the assessment of Doppler transmitral flow velocities (91–94). The influence of several factors, such as age, gender, heart rate, and BP values, have been extensively evaluated in order to assess the technical variability of Doppler flow velocity changes.

Transmitral flow velocities, evaluated by Doppler echocardiography, reflect left ventricular early filling (E wave velocity) as well as atrial contraction and emptying (A wave velocity). Three patterns of transmitral flow velocities can be recognized, representing progressive worsening of diastolic LV filling: (a) "slowed relaxation," with a reversed early to late velocity (E/A) ratio, slowed deceleration time and increased isovolumic relaxation time; (b) "pseudonormalization," with a preserved ratio E/A, but a shortened deceleration time due to abnormalities of both relaxation and compliance; (c) "restrictive pattern" with an increase of E/A ratio (>1.5–2), associated with a very abrupt deceleration time, suggestive of an elevated atrial pressure with an abnormal rise in pressure in a stiff left ventricle. For the diagnosis of diastolic dysfunction, analysis of the pulmonary venous filling patterns and/or Doppler analysis of myocardial velocities at the level of the mitral annulus is indicated (Figure 17.4) (94,95).

It is believed that diastolic abnormalities may precede systolic chamber dysfunction, though no longitudinal studies have clarified this aspect. A few studies, using different techniques, showed that diastolic left ventricular performance significantly influences exercise capacity in hypertensive patients with LVH (96–99).

Brogan et al. (84) and Fagard et al. (100), who defined diastolic dysfunction on the basis of left ventricular end diastolic pressure and pulmonary wedge pressure, respectively, found an association between diastolic dysfunction and subsequent incidence of heart failure or cardiovascular events. Three studies, performed in large population samples of middle aged and elderly adults and a large cohort of hypertensive patients (101–103), have indicated that the presence of alterations of E/A ratio are associated with a significant increase in incident heart failure, cardiac mortality, and in subsequent cardiovascular morbidity and mortality, respectively (Table 17.3). More recent information has been derived from a community survey, examining 2,042 subjects aged 45 years or older. In this study, diastolic dysfunction evaluated by Doppler technique, comprehensive of transmitral, outflow tract, and pulmonary flow examination, was observed in 47% of hypertensives and in 25.5% of patients with normal ejection fraction (>50%). The frequency of CHF increased dramatically with higher severity of diastolic function (104).

LVH AND ARRHYTHMIAS

VENTRICULAR ARRHYTHMIAS

The clinical spectrum of hypertensive heart disease ranges from impaired coronary reserve, impaired filling and

Table 17.3 Prognostic significance of diastolic dysfunction (evaluated by transmitral Doppler echocardiography)

Reference	No. of patients	Follow-up (years)	Diastolic dysfunction	Relative risk	Events
101	2,671 (CHS)	5.2	E/A <0.7	1.88 (95% CI, 1.33–2.68)	CHF
			or >1.5	3.5 (95% CI, 1.8−6.8)	
102	3,008 (SHS)	3	E/A <0.6	1.18 (95% CI, 0.7–2.1, $p = 0.31$)	Cardiac death
			E/A >1.5	2.8 (95% CI, 1.196.75, $p < 0.05$)	
103	1,839 (PIUMA study)	4.4	E/A <median value, adjusted for age and HR	1.57 (95% CI, 1.11−2.18, $p < 0.01$)	Nonfatal CV events

Abbreviations: CHF, congestive heart failure; CHS, Cardiovascular Health Study; CV, cardiovascular; HR, heart rate; PIUMA, Progetto Ipertensione Umbria Monitoraggio Ambulatoriale; E/A, early peak to late peak velocity ratio; SHS, Strong Heart Study.

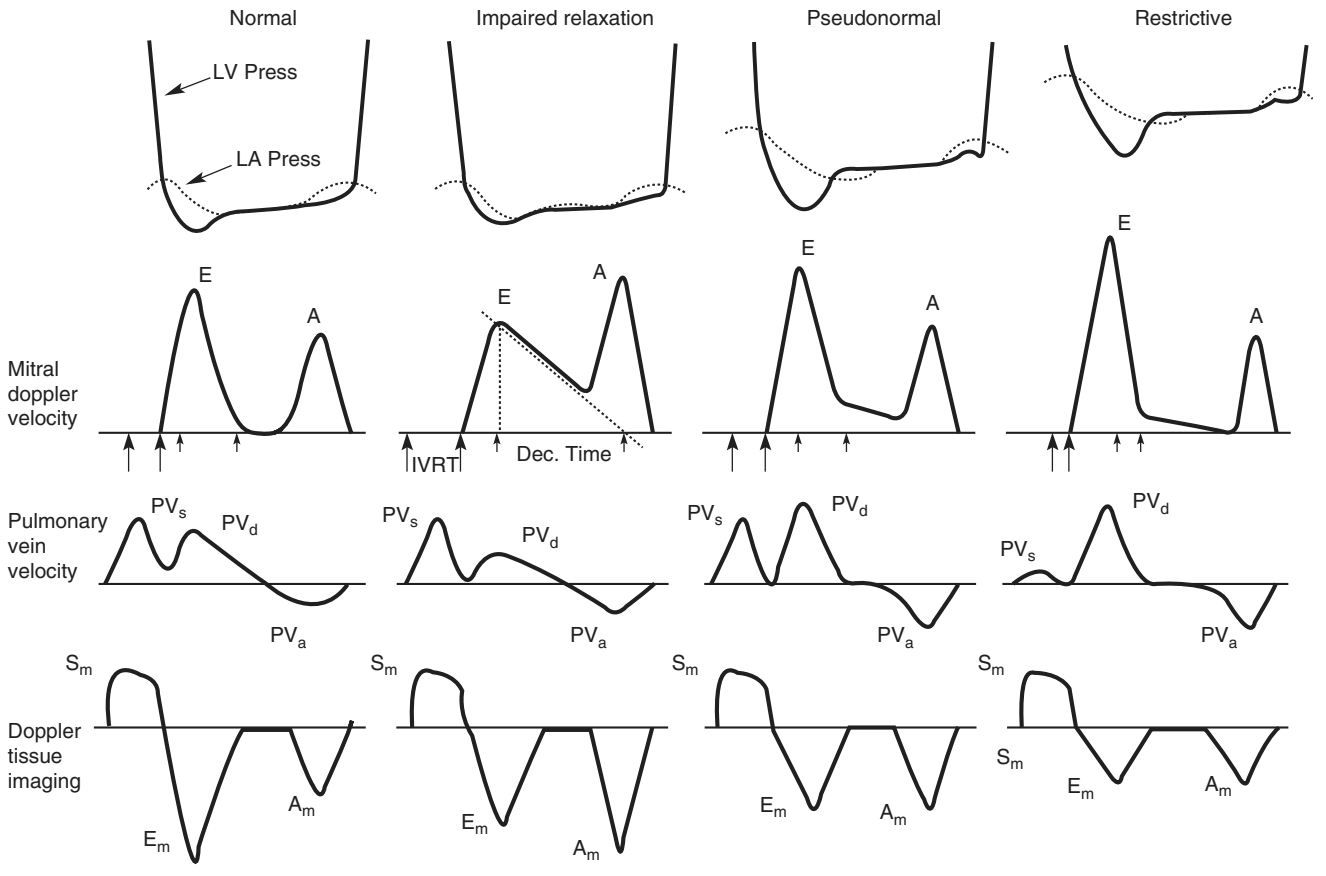

Fig. 17.4 Diastolic filling patterns by Doppler echocardiography. *Abbreviations*: LA, left arterial; LV, left ventricular.

pumping function and ventricular remodeling, to cardiac arrhythmias, such as ventricular ectopy and atrial fibrillation. As early as 1984, Messerli reported that hypertensive patients with LVH have a significantly greater prevalence of premature ventricular contractions and complex ventricular arrhythmias than patients without LVH or normotensive subjects (105). This finding was confirmed later in large population-based studies (106,107). Hence, the presence of ECG criteria of LVH represents a risk of higher incidence of sudden death that is most prominent in women (108). On the basis of epidemiological observations, a pathophysiological chain of evidence linking hypertension, LVH, and sudden death has been proposed (109–111). Furthermore, the Framingham cohort indicated that, in patients with LVH, the presence of symptomatic ventricular arrhythmias was associated with a nearly twofold increase in mortality (111). Hypertensive patients with LVH also have more ventricular arrhythmias during the interval from 6:00 a.m. to noon, an interval when cardiac death is most frequent (112). This observation and the evidence of increased ventricular vulnerability detected by different techniques (late potentials, ST depression on Holter recording, programmed ventricular stimulation, changes in the fibrillation threshold) support the link between ventricular ectopy and cardiac sudden death in hypertensive patients (108).

However, the mechanism by which LVH leads to increased arrhythmogenicity and, ultimately, to increased mortality still remains to be elucidated. In a follow-up trial of a geriatric population, hypertensive patients without documented coronary artery disease but with echocardiographic LVH were more likely to experience ventricular fibrillation or sudden death than the counterparts without LVH (31% versus 10%) (113). Potential mechanisms are subendocardial ischemia, cardiac hypertrophy, high BP by itself, irregular hypertrophic pattern, fibrosis within the myocardium (interstitial as well as perivascular), and the hypertrophic cardiac myocyte, per se (Figure 17.5). Furthermore, excessive activity of the SNS and the RAAS exert indirectly or directly arrhythmogenic effects (109). However, it remains unproven whether individuals with the greater degree of electric instability are likely to be at high risk for sudden death.

Since numerous studies have documented that LVH, per se, is associated with ventricular arrhythmias (109), one would expect that these ventricular arrhythmias would disappear with reduction of LVH. In a double-blind study, the use of

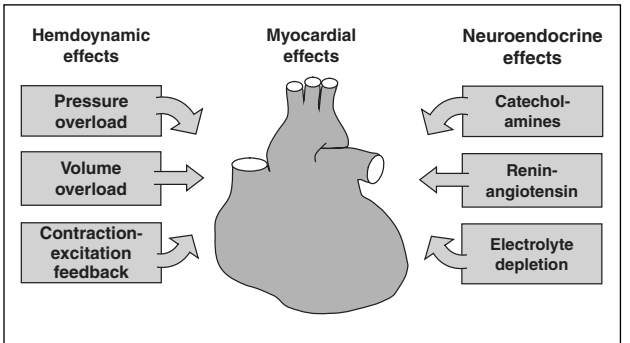

Fig. 17.5 Electrogenesis of ventricular arrhythmias in left ventricular hypertrophy (LVH).

angiotensin-converting enzyme inhibitors (ACEIs) lead to a marked reduction in LVH and, at the same time, to a marked reduction in ventricular ectopy, whereas, in the placebo group, LVH progressed, and no changes in ventricular ectopy occurred (114). Overall, reduction in ventricular ectopy has been found with the use of calcium antagonists, ACEIs and beta-blockers (108,109). The fact that ventricular ectopy disappeared with three different drug classes makes it unlikely that the underlying mechanism is a direct antiarrhythmic effect of any drug on the ectopically firing myocardium. The potential proarrhythmogenetic effects of diuretics are matter of concern, since diuretics have been shown to increase ventricular ectopy both at rest and during exercise (115). This proarrhythmogenic effect may result from an intracellular electrolyte shift. Whether the reduced ventricular ectopy transfers into improved cardiovascular prognosis and less cardiac sudden death remains to be documented.

ATRIAL FIBRILLATION

Data from the Framingham study also support evidence of an increased prevalence of atrial fibrillation among patients with hypertensive cardiovascular disease as compared with control subjects, both in men (risk ratio 2.1) and in women (risk ratio 1.9) (116). Among different cardiovascular risk factors, LVH was found to be a better predictor of atrial fibrillation than smoking, hypertension, or diabetes (116). Subsequent studies showed that both the left atrial chamber diameter and LVM independently predicted the development of atrial fibrillation (117). Hypertensive heart disease is therefore the most prevalent and potentially modifiable independent risk factor for the development of atrial fibrillation and its complications, including thromboembolism.

As a consequence, BP control may be a common opportune strategy for the prevention of atrial fibrillation. If LVH coexists, treatment should aim at not only controlling BP but also reducing LVH. At a first glance, beta-blockers may be considered first-line treatment to maintain sinus rhythms in patients with myocardial infarction, heart failure, and hypertensive heart disease. However, in hypertensive patients with LVH diagnosed by ECG (LIFE study), angiotensin receptor blocker (losartan)-based therapy is more effective than beta-blocker (atenolol)-based therapy in reducing the development of atrial fibrillation and the associated cardiovascular morbidity and mortality including stroke (118). New onset of atrial fibrillation occurred in 150 patients randomized to losartan versus 221 to atenolol (6.8 versus 10.1 per 1000 person-years: relative risk 0.67), despite similar BP reduction (118). A smaller trial indicated that beta-blockers might prevent the reoccurrence of atrial fibrillation after successful cardioversion within the first 3 months of follow-up, but this study is inconsistent with respect to the result that hypertensive patients had decreased atrial fibrillation than normotensive subjects—a finding that clearly contradicts all other studies (119).

In accordance with the LIFE-trial, in hypertensive patients with high cardiovascular risk, angiotensin receptor blocker (valsartan)-based treatment prevented new onset of atrial fibrillation to a greater extent than calcium antagonist (amlodipine)-based treatment. Throughout the follow-up period, atrial fibrillation was newly observed in 252/6,278 hypertensive patients on valsartan (3.67%) as opposed to 299/6,888 hypertensive patients on amlodipine (4.37%). The corresponding hazard ratio for at least one occurrence of atrial fibrillation was 0.84 ($p < 0.045$) and of persistent atrial fibrillation 0.68 ($p < 0.005$) in the VALUE trial, which remained significant even after adjusting for LVH at baseline, age, and history of coronary heart disease (120).

Treatment with ACEIs do not have such strong evidence that they reduce the incidence of new onset of atrial fibrillation in hypertensive patients. In the only two available prospective trials with ACEIs, no such effect was observed (121,122), whereas, according to a retroprospective longitudinal cohort analysis from a database of 8 million patients in a managed care setting, ACEIs were associated with lower incidence of atrial fibrillation than calcium antagonists (123). Also the combination of amiodarone with angiotensin receptor blocker or ACEI is more able to maintain sinus rhythm than amiodarone therapy alone (124,125).

In the largest trials with hypertensive patients (LIFE-trial, VALUE-trial) the difference in favor of the angiotensin receptor blockers remained significant even after adjusting for in-treatment BP and LVH (118,120). This points the fact, that in addition to BP control and effective reduction of LVH other factors might be of pathogenetic importance. Indeed, the RAAS blockade has been found to prevent left atrial dilatation and atrial fibrosis, to slow conduction velocity, and to exert direct antiarrhythmogenic effects (121,126). Beyond that, there is increasing evidence that inflammation in the left atrium is of pathogenetic relevance for the development of atrial fibrillation, and, consequently, drugs with anti-inflammatory potential, such as angiotensin receptor blockers or statins, facilitate the prevention of atrial fibrillation (127,128).

Thus, RAAS blockade emerged as a new preventive strategy of atrial fibrillation. The incidence of new development of atrial fibrillation could be reduced with angiotensin receptor blockers and ACEIs in patients with systolic left ventricular dysfunction and with angiotensin receptor blockers and, though less certain, with ACEIs in hypertensive patients. The use of the RAAS blockade following cardioversion appears promising but requires further studies.

REGRESSION OF LVH

A large number of clinical and experimental studies have shown that long-term antihypertensive treatment may be associated with a regression of LVH.

The development and the regression of LVH in hypertension do not depend exclusively on the level of BP, but may also be modulated by several neurohumoral factors and by the aortic properties.

Nonpharmacological intervention may be useful in inducing LV mass decrease; in particular, body weight reduction in hypertensive obese patients was found associated with a reduction of LV mass, even independent from BP changes. On the opposite end of the spectrum, insufficient results support the direct effect of dietary sodium or alcohol restriction on LV mass, independent from BP reduction (129).

A large number of clinical trials have established that BP reduction may reverse LVH. Important determinants of LVH reduction are represented by the extent of BP decrease and by the duration of treatment.

The results of the SAMPLE study (21) have demonstrated that changes in LV mass during antihypertensive treatment

with an ACEI are not significantly related with changes of office measurements of BP, while the results are significantly associated with the degree of mean 24 h BP change. More recently, it has been shown that, not only the extent of 24 h BP reduction, but also the homogeneity, i.e., less variability in daily BP fluctuations (as evaluated by the so-called smoothness index), may be important for LVH reversal (130).

However, as anticipated, hypertensive cardiac hypertrophy and fibrosis are determined not only by BP levels, and it has been suggested that different classes of antihypertensive drugs do not have the same effect in reducing LV mass, probably because, beyond BP control, they may differently interfere with several nonhemodynamic factors, including the RAAS and the SNS. In order to extract the maximal amount of information from previous studies, several meta-analyses of demonstrable echo reversal of LVH obtained with the use of different antihypertensive drugs have been performed. Dahlöf et al. (131) have calculated that LV mass reduction for the same decrease of BP is greater during antihypertensive treatment with ACEIs, in comparison with all other classes of antihypertensive drugs, and similar conclusions have been reached by Cruickshank et al. (132). In 1995, Fagard (133) reviewed the prospective randomized comparative studies performed at that time, in order to assess whether some classes of drugs would be more effective than others in reducing LV mass. The meta-analysis of such studies, comparing diuretics, beta-blockers, calcium channel blockers, and/or ACEIs, showed that the reduction of LV mass with each of these classes was similar to the reduction obtained with the other three classes statistically combined, and, in addition, that the effect was similar for the direct comparison of converting enzyme inhibitors and calcium channel blockers. Two more recent meta-analyses by Jennings (134) and by Schmieder (135) have included only randomized, double-blind, parallel group comparisons and have indicated that the degree of BP reduction and the baseline value of LV mass represent the main determinants of LVH regression; however, they have also observed that ACEIs, angiotensin II receptor blockers, and calcium-antagonists may be more effective than beta-blockers and diuretics in reducing LV mass, with similar BP reduction.

Most of the studies included in the meta-analyses were relatively small and of short duration, (usually 6 months or less), often noncomparative, and without a reliable quality control of echocardiograms.

Further information has been obtained by some large, randomized, blinded studies comparing the effect of two or more different antihypertensive drugs. Furthermore, it has been thought that the length of antihypertensive treatment is associated with a progressive decrease of LV mass, thereby potentially reducing possible differences among classes of drugs. However, according to the most recent analysis of the LIFE trial, the significant difference found after 6 months between angiotensin receptor blocker-based therapy and beta-blocker-based therapy was maintained throughout the whole follow-up period (up to 6 years), with differences of similar magnitude at yearly examinations (Figure 17.6) (136). Of note, BP was similarly reduced throughout the whole follow-up period, hereby suggesting that antihypertensive agents have long-lasting disparate effects on LVM reduction.

In addition, BP control may be difficult in hypertensive patients with target organ damage and requires the use of combinations of antihypertensive agents. To this regard, it should be emphasized that major intervention trials comparing the effects of single antihypertensive drugs on left ventricular mass were, actually in large part, comparisons of different combination therapies, since the majority of patients in the study took more than one drug. In the SAMPLE study (21), more than 50% of patients were treated with the combination of lisinopril plus a diuretic. The same remark applies to the LIFE study, where the beta-blocker or the angiotensin II blocker was associated with diuretics in 90% of patients.

In the RACE study (137), patients enrolled were also subdivided according to addition or no addition of a diuretic to the baseline therapy. The extent of the reduction in left ventricular mass was similar in the two subgroups, and the advantage of ramipril over atenolol was evident also in patients who were in combination therapy.

The evaluation of the effect of antihypertensive treatment on the myocardial tissue composition seems particularly interesting, possibly affecting the fibrous perivascular and interstitial tissue. This hypothesis has been recently addressed in a study in human beings by Brilla and coworkers (138); in fact, they have demonstrated that treatment for 6 months with the ACEI lisinopril or with the diuretic hydrochlorothiazide induced a similar reduction of BP; however, lisinopril

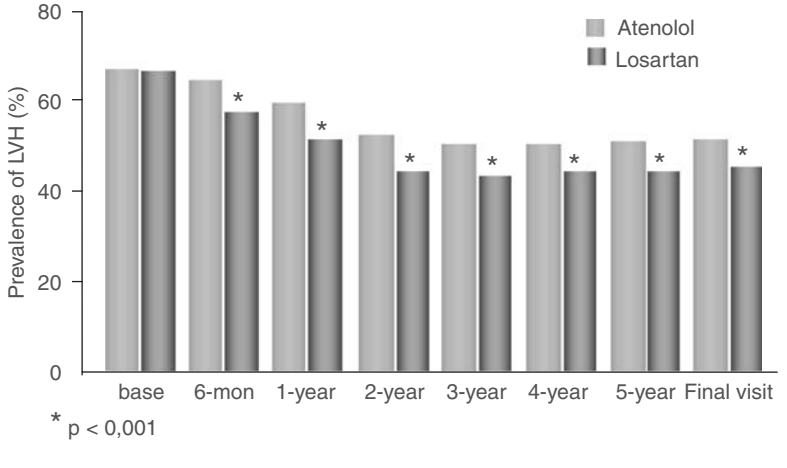

Fig. 17.6 Prevalence of left ventricular hypertrophy (LVH) by echo throughout the LIFE trial.

caused a decrease in collagen content of the myocardium, in association with an improvement of some diastolic function parameters, while the diuretic had no effect on these parameters and only reduced myocyte diameter. Recent experimental and human studies have shown that angiotensin II antagonists may also exert a favorable effect on regression of myocardial fibrosis (139). Future studies will give further useful information on this point.

In conclusion, recent longer term studies indicate that all classes of antihypertensive drugs can induce regression of LVH along with the decrease of BP. Differences on reduction of LV mass for the same decrease of BP are usually of lower magnitude than these achieved by effective BP control, but the effect on LV and RV structure and composition may not be the same with different antihypertensive drugs.

CLINICAL AND PROGNOSTIC SIGNIFICANCE OF LVH REGRESSION

Several studies have demonstrated that, in patients with LVH at baseline, the decrease of LV mass is associated with a number of pathophysiological changes, such as: (a) improved systolic performance at the midwall, (b) possible improvement of diastolic filling, (c) autonomic nervous system changes toward normalization, (d) possible reduction or ventricular arrhythmias and prevention of atrial fibrillation, and (e) coronary reserve improvement. All these changes might explain an improvement of clinical prognosis in hypertensive patients (Table 17.4) and have also been observed after treatment withdrawal with redevelopment of hypertension, thus eliminating any possible doubt on supposed adverse consequences of LVH regression (140). Over the years, evidence has accumulated from several studies, using not only electrocardiography, but also echocardiographic measurement of LV mass, that a reduction in LVH with antihypertensive treatment is associated with an improvement in outcome and with a decrease of the risk of cardiovascular morbidity and mortality.

Levy et al. (141) observed that the changes toward normal ECG features of LVH in 524 subjects in the Framingham Heart Study, over a mean follow-up of 5 years, were associated with a reduction in cardiovascular risk. More recently, the results of the HOPE study (142) have confirmed that regression of the Sokolow criteria for LVH was associated with a lower number of cardiovascular events, while no change or a worsening of this ECG index of LVH implied a less favorable outcome. Also, the large and long-term LIFE study has shown that the greater regression of LVH with losartan was accompanied by a reduced incidence of cardiovascular events (143).

Other studies have measured LVM changes using echocardiography, and again it was observed that subjects who failed to achieve LVH regression or in whom LVH developed during follow-up were much more likely to suffer morbid events than those in whom LVH regressed or never developed (144–147). The results have been evaluated separately and in a meta-analysis (Figure 17.7) (148). Accordingly, in the echocardiographic substudy of the LIFE-trial (149), including about 960 patients followed for more than 4 years, there was a decrease of about 20% of the primary endpoint (death, nonfatal myocardial infarction, and stroke) for one standard deviation of reduction of LV mass (i.e., 25 g/m^2).

The meta-analysis has analyzed younger patients, with and without LVH, followed by their family doctors, according to a prospective design, while, in the LIFE study, all patients had LVH, were older, at higher cardiovascular risk, were randomized to receive antihypertensive treatment, and were followed according to a clinical protocol. Therefore, the informations obtained in the meta-analysis and in the LIFE study should be considered complemental.

Left ventricular geometric adaptation, evaluated at baseline, implies a different risk for cardiovascular events in hypertension, with concentric hypertrophy representing the most adverse situation. Muiesan et al. have evaluated the relation between changes in LV geometry during antihypertensive treatment and subsequent prognosis in 436 consecutively seen uncomplicated hypertensives (249 M, 187 F, age range 18–71 years) followed for a mean period of 6.4 years. Persistence of LVH from baseline to follow-up was confirmed as an independent predictor of cardiovascular events. Cardiovascular morbidity and mortality were significantly greater in patients with concentric than in those with eccentric geometry both in presence ($p = 0.04$) or absence of LVH ($p = 0.02$) at follow-up. This study (with the longest follow-up among those published so far) strongly indicates that changes of LV geometry during treatment may have additional prognostic significance in patients with and without LVH (Figure 17.8) (150). Similar results have been obtained from a further analysis of data obtained in the LIFE study (151).

All these results, taken together, strongly indicate that LV mass during treatment has an important prognostic value.

Table 17.4 Pathophysiological and clinical consequences of LVH regression

	Presence of LVH	Reversal of LVH
Systolic dysfunction	Depressed at the midwall	Unchanged (or improved at the midwall)
Diastolic filling and relaxation abnormalities	Present	Unchanged or improved
Autonomic nervous system function	Present	Changes toward normalization
Ventricular arrhythmias	Frequently present	Reduced number
Coronary reserve	Reduced	Improved
Associated vascular structural changes	Present	Improved

Abbreviation: LVH, left ventricular hypertrophy.

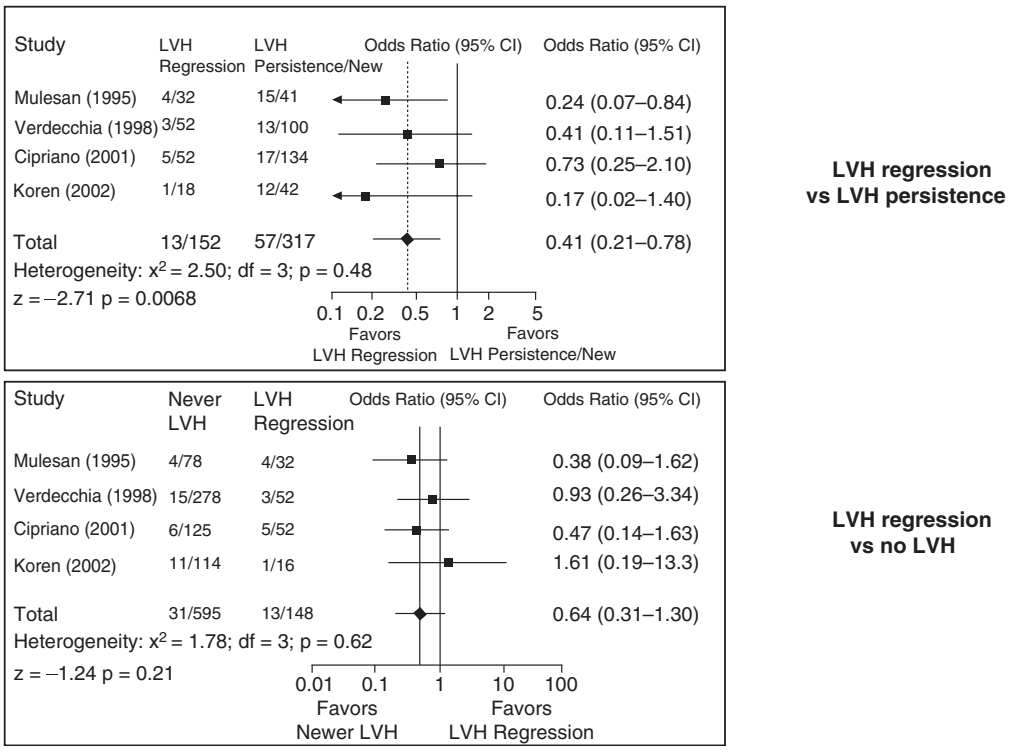

Fig. 17.7 Prognostic values of left ventricular hypertrophy (LVH) regression. *Source*: From Ref. 148.

In all these studies, BP values did not have results associated with cardiovascular risk, although it cannot be excluded that the observed changes of LV mass index may reflect, at least in part, pressure control.

In conclusion, the lack of decrease, or the increase, of echocardiographically determined LV mass in treated hypertensive patients is associated with a worse prognosis, while, on the contrary, the risk for cardiovascular events is significantly reduced and almost normalized by complete regression of LVH.

CONCLUSIONS

At present time, LVH should be considered both a risk factor and a marker of risk, which may also be detectable using

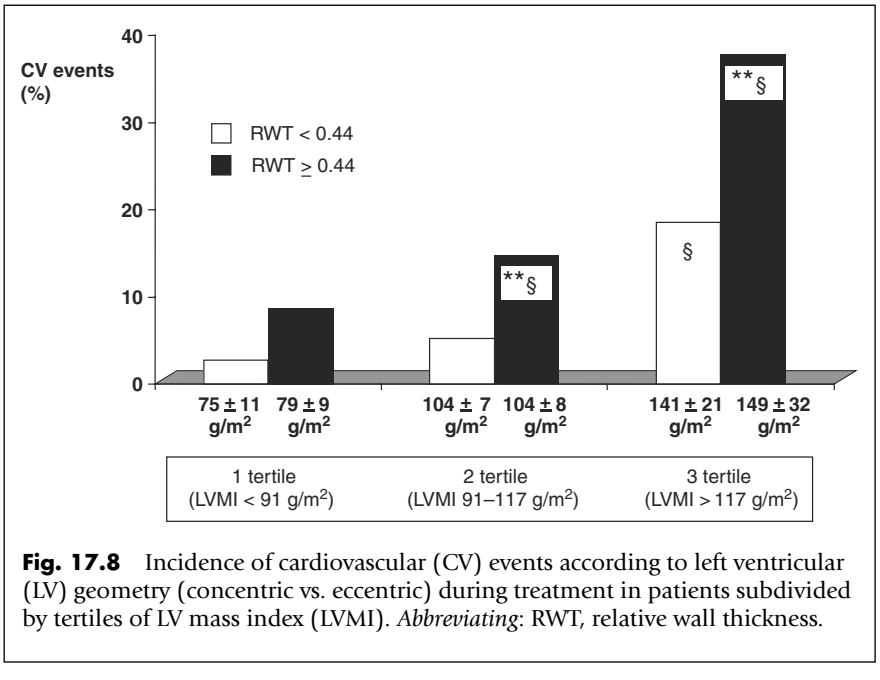

Fig. 17.8 Incidence of cardiovascular (CV) events according to left ventricular (LV) geometry (concentric vs. eccentric) during treatment in patients subdivided by tertiles of LV mass index (LVMI). *Abbreviating*: RWT, relative wall thickness.

echocardiography in asymptomatic patients with moderate hypertension. The incidence of cardiovascular events in hypertensive patients is clearly related to LV mass during treatment, and regression of LVH is associated with a better prognosis, even independently from changes of other risk factors, including BP. However, in some cases, LVH is difficult to regress or remains unaffected by treatment. Probably not only the quantity of left ventricular mass, but also its quality (i.e., collagen content, contractile machinery), should be evaluated. LVH clearly predisposes to cardiac ischemia and to CHF, but the incidence of stroke is also higher in the presence of increased LV mass.

Ongoing studies will more precisely assess the quantitative relation between development or regression of LV mass and incidence of cardiovascular events.

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BRAIN DAMAGE 18

Cristina Sierra, Antonio Coca

INTRODUCTION

Stroke is the third most frequent cause of death after cancer and heart disease in developed countries and one of the most common reasons for developing cognitive impairment and vascular dementia (VD) (1). High blood pressure (BP) is a major risk factor for stroke, and a continuous relationship between BP and the occurrence of stroke has been well established (2,3). On the other hand, evidence from hypertension treatment trials has shown that relatively small reductions in BP [5–6 mmHg in diastolic BP (DBP), 10–12 mmHg in systolic BP (SBP) over 3–5 years] reduce the risk of stroke by more than one third (4). The primary prevention of stroke through antihypertensive therapy and BP control is well established. Likewise, higher BP levels after stroke increase the risk of recurrent stroke (5), and recent trials indicate that BP reduction with combined antihypertensive therapy is beneficial in reducing stroke recurrence (6).

Hypertension is known to be the most important factor for developing macrovascular cerebral complications such as stroke and, consequently, VD (2,3,7). Hypertension may also predispose to the development of more subtle cerebral processes based on arteriolar narrowing or pathological microvascular changes. It has been suggested that cerebral microvascular disease contributes to the development of vascular cognitive impairment (8). The mechanisms underlying hypertension-related cognitive changes are complex and not yet fully understood (Figure 18.1). Correlations between cerebral white matter lesions (WML) and elevated BP provide indirect evidence that structural and functional changes in the brain over time may lead to reduced cognitive functioning when BP control is poor or lacking. In addition, there is some evidence that antihypertensive drug treatment may play a role in the prevention of cognitive impairment (9) or VD (10) through BP control.

The presence of cerebral WML is an important prognostic factor for the development of stroke (11,12), cognitive impairment (13), and dementia (14). Older age and hypertension are constantly reported to be the main risk factors for cerebral WML (15). Hypertensive patients have a higher rate and extent of areas of cerebral WML compared with normotensives (15,16). In addition, it has been shown that treated, controlled, hypertensive patients have a lower prevalence of WML than both untreated and treated but not controlled hypertensive patients (16). Recent evidence strongly supports the idea that the presence of cerebral WML in hypertensive patients should be considered a silent early marker of brain damage.

PATHOPHYSIOLOGY OF VASCULAR CEREBRAL DAMAGE IN ESSENTIAL HYPERTENSION

The brain is highly vulnerable to the deleterious effects of elevated BP. Systolic and diastolic hypertension in both men and women are well-established risk factors for the development of ischemic and hemorrhagic stroke. Hypertension is a major risk factor for two distinct kinds of vascular problems: the complications of atherosclerosis, including cerebral infarction, on the one hand, and the complications of hypertensive small vessel disease, including intracerebral hemorrhage and lacunar infarctions, and cerebral WML, on the other hand. In some cases, some of these lesions, such as lacunar infarcts and cerebral WML, may be silent and only detectable by radiological findings.

Stroke may be classified based mainly on clinical grounds, clinicoradiological correlates, or purely radiological findings. Briefly, with respect to infarct topography, infarcts can be divided into cortical (anterior cerebral artery, divisions of the middle cerebral artery or posterior cerebral artery territory, together with external watershed infarcts) or subcortical (lacunar, striatocapsular, anterior choroidal artery territory, white matter medullary, or internal watershed infarcts). In general, hypertension is more likely to be implicated in subcortical infarcts (lacunar infarcts, WML).

In the development and progression of chronic high BP, hypertensive cerebral angiopathy occurs, as do secondary reparative changes and adaptive processes, at all structural and functional levels of the cerebral vascular system (Table 18.1). Hypertension causes marked adaptive changes in the cerebral circulation, including increased brain vessel resistance and loss of the physiological mechanism of autoregulation. Hypertensive encephalopathy results from a sudden, sustained rise in BP sufficient to exceed the upper limit of cerebral blood flow autoregulation. The cerebral circulation adapts

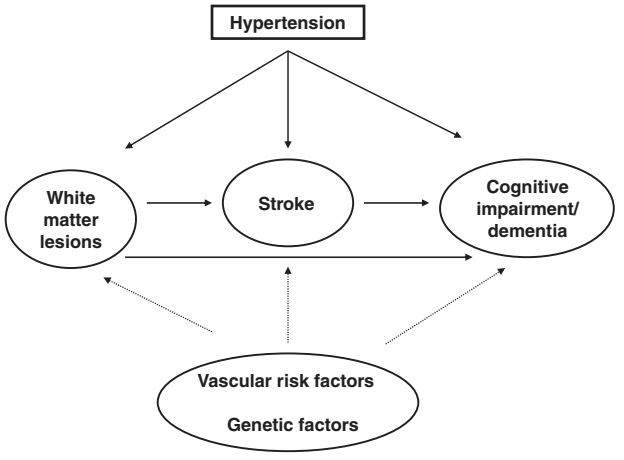

Fig. 18.1 Associations between hypertension, white matter lesions, stroke, and cognitive impairment.

to less severe chronic hypertension at the expense of changes that predispose to stroke due to arterial occlusion or rupture.

Stroke is a generic term for a clinical syndrome that includes focal infarction or hemorrhage in the brain, or subarachnoid hemorrhage. Atherothromboembolism and thrombotic occlusion of lipohyalinotic small-diameter end arteries are the principal causes of cerebral infarction. Microaneurysm rupture is the usual cause of hypertension-associated intracerebral hemorrhage. Rupture of aneurysms on the circle of Willis is the most common cause of nontraumatic subarachnoid hemorrhage.

Lacunar infarction is the infarct subtype most closely and directly associated with hypertension because of its high prevalence among clinical lacunar syndromes and the hypertensive lipohyalinotic changes seen in small penetrating vessels at necropsy (17). In other types of infarct the effect of hypertension is less direct and is mediated by its effects on atherogenesis

Table 18.1 Main physiopathological cerebrovascular changes associated with high blood pressure

Mechanical stress (endothelial lesion)
Endothelial dysfunction (loss of vasodilatory capacity)
Increased vascular permeability
Opened ionic channels
Hypertrophy of smooth muscle vascular vessels (reduced lumen)
Contraction of smooth muscle vascular vessels (increased vascular resistance)
Synthesis of collagen fibre (vascular stiffness)
Transudation of plasmatic products to the arterial wall

in large extracranial or intracranial vessels. Lacunae are small infarcts or occasionally hemorrhages related to Charcot–Bouchard microaneurysms.

SILENT CEREBROVASCULAR DISEASE

Since the introduction of brain magnetic resonance imaging (MRI) more than 25 years ago, with its high sensitivity and resolution capacity, there is increasing evidence that "asymptomatic" hypertensive brain damage, mainly WML (Figure 18.2), is fairly common in apparently normal middle-aged and elderly people. Tables 18.1 and 18.2 summarize possible underlying pathological processes of early cerebrovascular damage and their association with functional changes.

CEREBRAL BLOOD FLOW AUTOREGULATION

High BP influences the cerebral circulation, causing adaptive vascular changes. Thus, hypertension influences the autoregulation of cerebral blood flow by shifting both the lower and upper limits of autoregulatory capacity toward higher BP, while hypertensive patients may be especially vulnerable

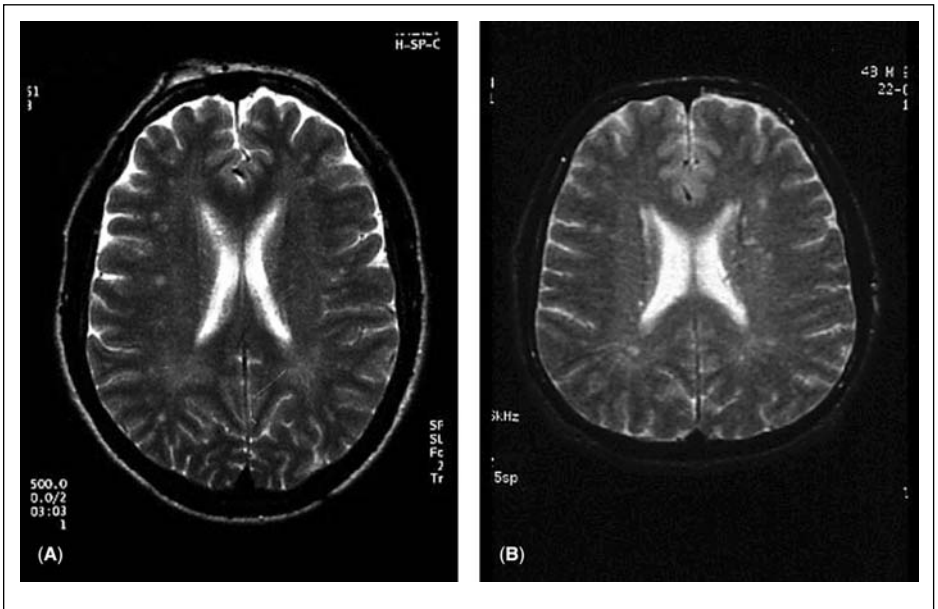

Fig. 18.2 Brain magnetic resonance imaging in axial plane T2-weighted images: presence of white mater lesions. (**A**) Periventricular hyperintensities. (**B**) Confluent lesions at subcortical and periventricular levels.

Table 18.2 Early cerebrovascular damage associated with hypertension

Functional abnormalities
Reduced cerebral blood flow
Increased cerebrovascular resistance
Reduced cerebral vasomotor reactivity
Incipient cognitive impairment
Structural abnormalities
Vascular remodelling
Lacunar infarct: small deep infarcts caused by penetrating arteriolar occlusive disease
White matter lesions: periventricular white matter lesions caused by subcortical hypertensive small vessel disease

to episodes of hypotension (15,18), which may play a role in the development of silent cerebrovascular damage, such as WML. Increased cerebral vascular resistance could be due to narrowing of the small vessels by lipohyalinosis and microatherosclerosis. The effect of high BP on small vessels is well known, with vascular remodeling occurring in cerebral blood vessels during chronic hypertension. It has been suggested that this structural alteration impairs autoregulation, exposing the white matter to fluctuations in BP. For this reason it has been hypothesized that changes in cerebral hemodynamics may play a role in the development of WML (18).

However, most studies have found no significant changes in resting cerebral blood flow in either normotensive and hypertensive individuals with silent WML, and, in fact, there are contradictory findings on the relationship between vasomotor reactivity (or vasodilatory capacity) and WML. Kuwabara et al. (19) reported a close relationship between cerebral hemodynamic reserve capacity, measured by positron emission tomography, and the severity of WML in hypertensive patients. Bakker et al. (20) confirmed the association between decreased vasomotor reactivity and WML, measured by transcranial Doppler in 73 elderly individuals, of whom 56% were hypertensives. Conversely, Chamorro et al. (21) showed preserved vasomotor reactivity in 41 patients (71% hypertensives) with silent WML and first-ever lacunar infarction, although they had increased cerebrovascular tone measured by transcranial Doppler. We recently found an association between silent cerebral WML and increased cerebrovascular tone in middle-aged, never-treated, essential hypertensive patients, without affecting either cerebral blood flow velocity or the vasodilatory capacity of cerebral vessels (22). Using exogenous contrast-based perfusion MRI, O'Sullivan et al. (23) have recently shown that elderly hypertensive patients with WML have a significant reduction in the cerebral blood flow of normal-appearing white matter compared with hypertensives without WML, suggesting that hypoperfusion may be an early feature of the development of WML. Nevertheless, it remains unclear whether hypoperfusion is a primary pathogenic mechanism or simply a secondary effect of damaged tissue.

CEREBRAL ARTERIOSCLEROSIS

The main current hypothesis concerning the association between high BP and ischemic WML is that long-standing hypertension causes lipohyalinosis of the media and thickening of the vessel walls, with narrowing of the lumen of the small perforating arteries and arterioles that nourish the deep white matter (15). The perforating vessels, which originate in the cortical and leptomeningeal arteries, have a relatively poor anastomotic system, which makes the white matter vulnerable to cerebral ischemia. Low BP has also been reported to be a risk factor for WML (15). Hypertension may also cause disturbances in the blood–brain barrier, leading to lesions in the white matter due to cerebral edema, the activation of astrocytes, and the effects of destructive enzymes or other poisons, which pass through the damaged vessel walls (15).

Postmortem studies show that WML seen on MRI scans are associated with degenerative changes in arterioles related to atherosclerosis, suggesting that cerebral arteriosclerosis of the penetrating vessels is the main factor in the pathogenesis of ischemic WML (15). Bots et al. (24) reported that WML were related to atherosclerosis, indicated by increased common carotid intima-media thickness and carotid plaques, while de Leeuw et al. (25) showed that aortic atherosclerosis during midlife, assessed on abdominal radiographs, was significantly associated with periventricular WML 20 years later.

Several vascular risk factors have been linked with WML, and it seems that the greater the number of vascular risk factors for cerebrovascular disease, the greater the extent and severity of WML. Pantoni and Garcia (15), in a review of more than 160 studies on WML, found that in studies with a multivariate analysis, diabetes mellitus and hypertension were associated with WML, although the association with lipid abnormalities and smoking was not so clear. WML have also been reported to be associated with a history of stroke, lacunar infarcts, heart disease, and atrial fibrillation, which are frequently associated with both hypertension and other vascular risk factors (15).

ROLE OF GENETIC FACTORS IN THE PATHOGENESIS OF VASCULAR CEREBRAL DAMAGE

A family history of cerebrovascular disease and stroke is often perceived as a risk factor for stroke. The Framingham Heart Study found a positive association between a verified paternal or maternal history of stroke and an increased risk of stroke in offspring (26). Concordance rates in twin studies have shown an almost fivefold increase in stroke prevalence among monozygotic twins compared with dizygotic twins (27). However, the identification of individual causative mutations remains unanswered. The inheritance is complex, multigenic, and heterogeneous. Associations with polymorphisms have been investigated in a variety of candidate genes, including hemostatic genes, genes controlling homocysteine metabolism and lipid metabolism, the angiotensin-converting enzyme (ACE) gene, and the endothelial nitric oxide synthase gene, with conflicting results (28), which may reflect methodological difficulties, since many studies were small and underpowered or required careful case-control matching.

The ACE gene is probably the most extensively investigated candidate gene in ischemic stroke. A number of studies have reported an association between an intron 16 insertion (I)/deletion (D) polymorphism of the ACE gene and stroke, with a relative risk of the order of 1.5–2.5, but other studies have found no significant association (28). A meta-analysis has evaluated the risk of stroke in 1918 subjects versus 722 controls from seven studies and concluded that the ACE

genotype conferred a small but modest effect, with an odds ratio of 1.31 [95% confidence interval (95% CI: 1.06–1.62)], according to a dominant model of inheritance (29). A variant of the angiotensinogen gene (M235T) has also been implicated in vascular disease, but so far its evaluation in stroke suggests that it is not an important risk factor. However, it has been proposed that an epistatic interaction with the ACE gene may exist (30).

Genetic risk factors have been implicated in the presence and severity of cerebral WML but remain undetermined. A recent genetic study of elderly twins indicated that susceptibility to white matter hyperintensity on brain MRI was largely determined by genetic factors (31). As mentioned above, genes contributing to interindividual variation in BP levels and essential hypertension may play a role in the etiology of WML or stroke, either through their effects on BP levels or through separate pathways. The renin–angiotensin system is an example of a system that may be involved in the pathogenesis of both hypertension and arteriosclerosis. Kario et al. (32) found a positive association between the ACE D allele and the presence of both silent and clinically overt stroke in Japanese hypertensives. Sierra et al. (33) reported an association between the DD genotype or the D allele of the ACE gene and WML in asymptomatic middle-aged hypertensive patients.

Of the genes thought to potentially predispose to WML in the presence of arterial hypertension, the apolipoprotein E (apoE) gene is one of the best candidates. This is because apoE, which is encoded by the apoE gene, plays a crucial role in lipid metabolism and neuronal repair after injury of any type. On the other hand, the apoE $\varepsilon 4$ allele (1 of the 3 polymorphic forms of the apoE gene) is associated not only with the vascular risk factors for WML (34) but also with its consequences, particularly cognitive impairment and dementia (35). A recent study confirmed that apoE $\varepsilon 4$ carriers with hypertension are suffering more cognitive impairment (36). De Leeuw et al. (37) studying 971 subjects aged 60–90 years (>50% of whom were hypertensives), recently found that the coexistence of an $\varepsilon 4$ allele and arterial hypertension is strongly associated with the presence of subcortical WML, but that hypertension alone or the presence of an $\varepsilon 4$ allele alone are not. This interaction may reflect a decreased capacity for neuronal repair in the presence of 1 or 2 $\varepsilon 4$ alleles. The results of this study support the hypothesis that the effect of arterial hypertension on cerebral white matter is enhanced in $\varepsilon 4$ carriers.

EPIDEMIOLOGY OF VASCULAR CEREBRAL DAMAGE

Hypertension represents a relative risk of stroke up to 6 times (38), while stroke is the most frequent complication in hypertensives (Figure 18.3) (39). As mentioned above, stroke is one of the leading causes of death worldwide and of disability in developed countries, and also a major economic burden with a considerable public health impact. In Western countries, ischemic stroke accounts for approximately 80% of all stroke and hemorrhagic stroke for the remaining 20%. Incidence rates, commonly quoted at 2 per 1,000 population, rise steeply from less than 1 per 1000 among people aged under 45, to more than 15 per 1,000 among those aged 85 or more, but vary widely (40). In industrialized countries, approximately 75% of all strokes occur in people aged over 65 years. Around 80% of people survive the first 4 weeks following stroke and 70% survive for a year or more. Prevalence rates exceed 8 per 1,000 adults with a similarly marked age gradient (40) suggesting future pressure on health services. Disabilities are common and sometimes severe among stroke survivors, requiring increased formal and informal care.

Cognitive impairment and dementia represent one of the principal neurological disorders in the elderly. Aging is associated with a large increase in the prevalence and incidence of degenerative and VD. The prevalence of dementia is estimated at around 8% in people aged 65 years and over and 15–20% in those older than 80 years (41). Alzheimer's disease is the most common form of dementia (responsible for 50–60% of cases), followed by VD (responsible for 30% of cases). Hypertension is a major risk for cerebrovascular disease and thereby for VD. Traditionally, Alzheimer's disease has been thought to be a primary neurodegenerative disorder and not of vascular origin. However, evidence has emerged to support the view that vascular risk factors and disorders may be involved in Alzheimer's disease (42).

PREVALENCE OF CEREBRAL WHITE MATTER LESIONS

Various studies have examined the prevalence of WML in both normotensive and hypertensive subjects. The ARIC study (16) reported a prevalence of WML of 24.6% in individuals aged

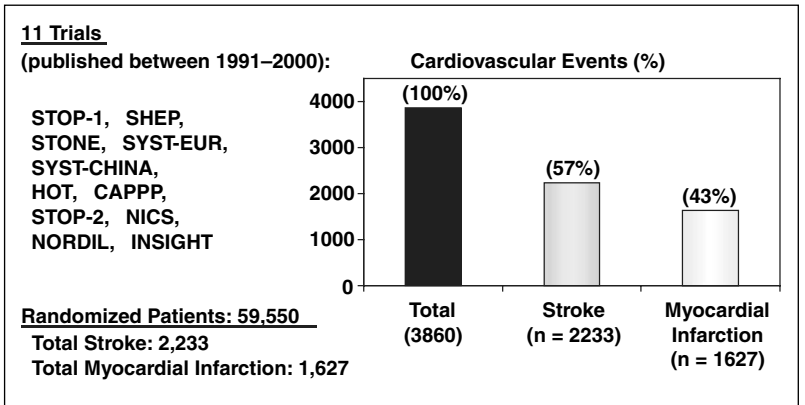

Fig. 18.3 Number of fatal and nonfatal cerebral strokes and fatal and nonfatal myocardial infarctions reported in large prospective hypertension trials published after 1990. *Source*: From Ref. 39.

55–72 years, 49% of whom were hypertensive. The Cardiovascular Health Study (43) found a prevalence of 33.3% in individuals aged 65 years or older, 44% of whom were hypertensive. The prevalence was 27% in the Rotterdam Study (44), which included individuals aged 65–84 years, 39% of whom were hypertensive. Shimada et al. (45) studied 28 normotensives and 20 hypertensives aged 59–83 years and found a prevalence of advanced WML of 25% and 40%, respectively. Goldstein et al. (46) found a prevalence of WML of 54.9% in 144 normotensive individuals aged 55 to 79 years (10% with casual BP elevations). The differences in prevalence between studies may be due to subtle variations in WML assessment, but especially to the impact of risk factors, such as age and hypertension, which are influenced by study selection criteria. Most studies included both normotensive and hypertensive patients (untreated and treated), or subjects with a wide range of ages or only elderly people. Our group found a prevalence of WML of 40.9% in a cohort of 66 untreated hypertensives aged 50–60 years (47).

EVIDENCE OF THE RELATIONSHIP BETWEEN HIGH BP AND VASCULAR CEREBRAL DAMAGE

HIGH BP AND RISK OF STROKE

Overviews of large-scale observational studies have demonstrated that usual levels of BP are positively and continuously associated with the risk of stroke in a log-linear fashion (48). This relationship between BP and stroke holds over a wide BP range, from systolic levels as low as 115 mmHg and diastolic levels as low as 70 mmHg (48). Data from prospective observational studies indicate that usual levels of BP are directly and continuously related to the risk of initial stroke and a prolonged difference in usual BP levels of just 9/5 mmHg is associated with an approximately one-third difference in stroke risk, with similar proportional effects in hypertensives and normotensives (3,4). Each 5–6 mmHg reduction in usual DBP is associated with a 38% lower risk of stroke (4). Elevated BP is positively associated with both ischemic and hemorrhagic stroke, but the association appears to be steeper for hemorrhagic stroke. The relationship between BP and stroke risk remains virtually unchanged after adjustment for serum cholesterol levels, smoking, alcohol, or a history of previous cardiovascular disease (48). Similar associations appear to exist between BP and the risk of recurrent stroke although much of the evidence on recurrent stroke comes from smaller cohort and observational studies (48). Data from the United Kingdom Transient Ischemic Attack (UK TIA) Collaborative Group showed that a 10 mmHg reduction in usual SBP was associated with a 28% reduction in the risk of recurrent stroke (49).

Although a continuous relationship between both SBP and DBP and the occurrence of stroke has been well established, there is epidemiological evidence from the Multiple Risk Factor Intervention Trial (MRFIT) study that the systolic component of BP may exert a strong deleterious effect on cerebrovascular disease (Figure 18.4) (50). It is known that increased arterial stiffness results in increased characteristic impedance of the aorta and increased pulse wave velocity, which increases systolic and pulse pressures. Large-artery stiffness is the main determinant of pulse pressure. Data from the Systolic Hypertension in the Elderly Program (SHEP) study show an 11% increase in stroke risk and a 16% increase in the risk of all-cause mortality for each 10 mmHg increase in pulse pressure (51). Laurent et al. (52), in a longitudinal study, found that aortic stiffness, assessed by carotid-femoral pulse wave velocity, is an independent predictor of fatal stroke in patients with essential hypertension.

HIGH BP AND RISK OF COGNITIVE IMPAIRMENT/DEMENTIA

As mentioned before, hypertension is known to be the most important factor for developing macrovascular cerebral complications such as stroke (7) and, consequently, VD (7). Hypertension may also predispose to the development of more subtle cerebral processes based on arteriolar narrowing or pathological microvascular changes. It has been suggested that cerebral microvascular disease contributes to the development of vascular cognitive impairment (8). Results from cross-sectional (53) and longitudinal (54–57) studies have shown a correlation between BP and cognitive function in

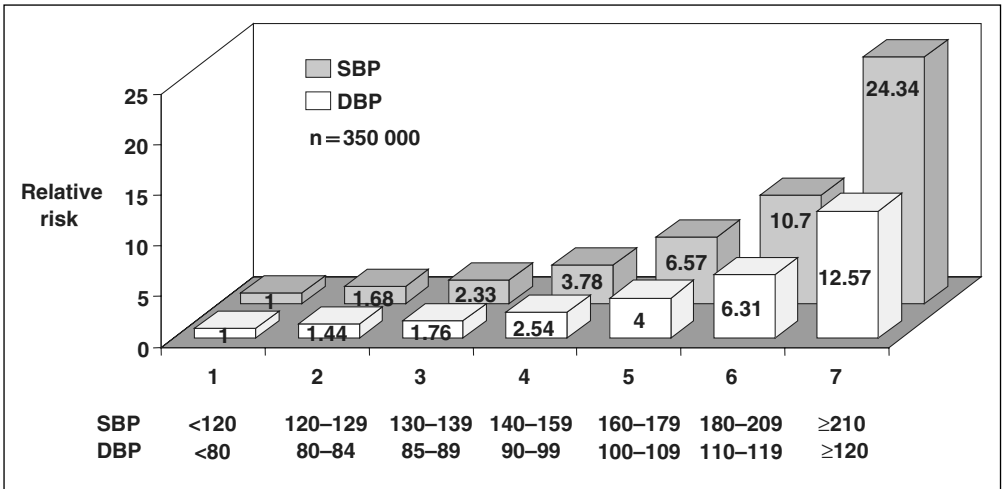

Fig. 18.4 Relationship between cerebrovascular mortality and systolic (SBP) and diastolic blood pressure (DBP) values. *Source*: From Ref. 50.

elderly people. These studies have reported an association between high SBP (the Honolulu-Asia Aging Study) (55), high DBP (the Uppsala Study) (56), elevated SBP and DBP (the Framingham Study) (54), and hypertension (National Heart, Lung, and Blood Institute Twin Study) (57) at midlife and impaired cognitive performance in late life. In addition, there is some evidence that antihypertensive drug treatment could play a role in the prevention of cognitive impairment (9) or VD (10) through BP control.

The mechanisms underlying hypertension-related cognitive changes are complex and not yet fully understood. It is unclear whether the impact of elevated BP on cognitive decline in late-life is mediated through its chronic, negative effect on the structural characteristics of the brain. Recent data have stressed that high pulse pressure is associated with an increased risk of Alzheimer's disease (41). Because increased pulse pressure is a clinical indicator of arterial stiffness, it could be postulated that functional arterial changes are involved in the pathogenesis of dementia. A recent study has shown a relationship between arterial stiffness, evaluated by carotid-femoral pulse wave velocity, and cognitive impairment in 308 elderly subjects attending a geriatric outpatient clinic reporting memory impairment (58).

Conversely, some studies have reported an increased incidence of dementia and Alzheimer's disease in individuals with low DBP or SBP, especially in very elderly people (≥80 years) (41). The severity of atherosclerosis increases with age, resulting in high SBP and low DBP in later life. Severe atherosclerosis in very elderly people combined with episodic or sustained hypotension and possibly excessive treatment of hypertension may induce cerebral hypoperfusion, ischemia, and hypoxia in this group of patients.

The presence of cerebral WML is an important prognostic factor for the development of stroke (11,12), stroke recurrence (59–61), cognitive impairment (13,43,44), and dementia (14). Various studies have shown an association between the presence of cerebral WML and cognitive function in both normotensive and hypertensive elderly populations (13,43,62–65). In a longitudinal study, de Groot et al. (13) examined the relationship between severity of WML and cognitive decline over a 10-year period in 563 elderly subjects (60–90 years) and found that subjects with severe periventricular WML had more rapid cognitive decline. An association between the presence of WML in brain-MRI and the poorer performance on neuropsychological tests were found in middle-aged, asymptomatic, never treated essential hypertensive patients (65). In this study, hypertensive patients with WML had a significantly poorer digit span forward performance, a standardized measure of attention, and slightly lower scores on visual memory test than hypertensives without WML (65). In addition, a longitudinal study of 1,077 people aged 60–90 years undergoing a brain-MRI at baseline and followed-up for a mean of 5.2 years found that WML, especially in the periventricular region, increased the risk of dementia (76%: Alzheimer's disease; 13%: VD; 11%: other types of dementia) (14). Likewise, in the Cardiovascular Health Study, individuals with more severe WML had a twofold increase in the risk of dementia (66). In this study, 3,608 participants undergoing a brain-MRI at baseline in 1991 were followed to 1998–1999. There were 480 incident cases of dementia, of which 330 (69%) were classified as Alzheimer's disease. apoE $\varepsilon 4$ genotype was also a powerful predictor of dementia.

Correlations between cerebral WML and elevated BP provide indirect evidence that structural and functional changes in the brain over time may lead to reduced cognitive functioning when BP control is poor or lacking. Skoog et al. (67) reported an association between elevated BP at age 70 and the development of dementia 10–15 years later, while patients with WML at age 85 had a higher BP at age 70, suggesting that previously increased BP may increase the risk of dementia by inducing small-vessel disease and WML. Likewise, Swan et al. (68) showed that midlife SBP is a significant predictor of WML and decline in cognitive function.

In summary, there are various relationships connecting hypertension with WML, stroke, cognitive impairment, and dementia, and also relationships between these factors, as shown in Figure 18.1. However, the mechanism that would explain all these relationships remains to be fully elucidated.

HIGH BP AND WML

The association between hypertension and WML has been established in cross-sectional (15,16,43–45) and longitudinal studies (69–71). However, some reports have suggested that this relationship is only evident when 24-h ambulatory BP monitoring (ABPM) is used to assess BP. Goldstein et al. (46) found a correlation between WML and office SBP, but not DBP, in a group of elderly normotensive subjects. Conversely, the severity of WML correlated with both SBP and DBP, measured by ABPM. In a group of mixed normotensives, "white coat" hypertensives, and sustained hypertensives, Shimada et al. (45) also found a correlation between the number of lacunae and periventricular hyperintensities with 24-h BP, but not with office BP. Sierra et al. (47) found a correlation between WML and both clinic and 24-h ABPM in 66 untreated middle-aged hypertensive patients. This study also showed higher BP values (including office, 24-h, daytime and nighttime estimates) in hypertensive patients with WML, compared with those without (47).

With respect to the circadian pattern of BP, Kario et al. (72) reported that both nondippers and extreme dippers had significantly more silent cerebrovascular damage (measuring both lacunae and WML) than dippers. Although BP variability has been related to target organ damage in hypertension, its relationship with cerebral alterations has not been established. A report by Goldstein et al. (46) suggested a higher standard deviation of waking SBP in patients with more severe WML. In contrast, neither the circadian rhythm nor the long-term variability of BP were related to WML in a group of 66 middle-aged never treated hypertensive patients (47).

CONNECTING LEFT VENTRICULAR HYPERTROPHY AND WHITE MATTER LESIONS AS TARGET ORGAN DAMAGE

A number of studies have reported that echocardiographically determined left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular morbidity and mortality in essential hypertensive patients (73,74). In addition, Bikkina et al. (75) demonstrated that left ventricular mass (LVM) is associated with an increased risk of cerebrovascular events, such as stroke and transient ischemic attack, in an elderly cohort from the Framingham Heart Study. It has also been proposed that left ventricular geometric patterns add prognostic information to both the development of cardiovascular disease (76) and the presence of extracardiac target organ damage in essential hypertension (77,78). Hypertensive

patients with concentric LVH have more advanced target organ damage, including renal (77,78) and retinal (78) involvement, than those with other patterns of left ventricular geometry. With respect to WML, several studies have shown an association between LVH and cerebral WML (43,78–81), whereas others have not (45). With respect to geometric patterns, a study found a close relationship between the presence of silent WML and concentric LVH in middle-aged, untreated, essential hypertensive patients, with WML being more common among patients with concentric LVH (81). This association was independent of the degree of BP elevation. Another study has recently shown that the presence of LVH in middle-aged essential hypertensives is associated with a reduction of regional cerebral blood flow in the area of the cerebral striatum (82).

The mechanisms connecting LVH to cerebrovascular damage are still unclear and might reflect long-term exposure to genetic, hormonal, or metabolic factors in addition to BP. It is difficult to differentiate the relative role of elevated BP from the direct contribution of LVH to the increased risk of developing cerebrovascular disorders, and longitudinal studies are necessary.

EVIDENCE OF THE RELATIONSHIP BETWEEN ANTIHYPERTENSIVE THERAPY AND THE PREVENTION OF VASCULAR CEREBRAL DAMAGE

Epidemiological studies have shown that each 5–6 mmHg reduction in usual DBP is associated with a 38% lower risk of stroke (4). Clinical trials have also shown that a 10 mmHg reduction in usual SBP was associated with a 28% reduction in the risk of recurrent stroke (49). In addition, there is some evidence that antihypertensive drug treatment could play a role in the prevention of cognitive impairment (9) or VD (10) through BP control.

PRIMARY PREVENTION OF STROKE

In the review by MacMahon (83) in 1996 of 17 randomized trials of antihypertensive treatment, a net BP reduction of 10–12 mmHg systolic and 5–6 mmHg diastolic conferred a reduction in stroke incidence of 38% (SD 4), with similar reductions in fatal and nonfatal stroke. Because the proportional effects of treatment were similar in higher and lower risk patient groups, the absolute effects of treatment on stroke varied in direct proportion to the background risk of stroke. The greatest potential benefits were observed among those with a history of cerebrovascular disease. In the overviews of randomized trials performed by the BP Lowering Treatment Trialists' Collaboration (84) in 2000, the data showed that placebo-controlled trials of calcium antagonists reduced the risk of stroke by 39% (95% CI: 15–56) and that placebo-controlled trials of ACE inhibitors reduced the risk of stroke by 30% (95% CI: 15–43), without significant differences between these groups of regimens. More "intensive therapy" was associated with a 20% stroke risk reduction (95% CI: 2–35) compared with "normal" BP reduction. The differences in BP between the two BP lowering strategies ("normal" versus "intensive") were only 3 mmHg.

Later meta-analyses of randomized controlled trials confirmed an approximately 30–40% stroke risk reduction with BP lowering (85). The statement on BP lowering and stroke prevention of the International Society of Hypertension (ISH) (48) recommends any of the five classes of antihypertensive drugs—diuretics, betablockers, calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers (ARBs)—because of the priority in BP reduction, per se. However, some trials in hypertensive patients have suggested a protective effect of ARBs in the primary prevention of stroke. The Losartan Intervention for Endpoint (LIFE) (86) study compared losartan and atenolol in hypertensive patients older than 55 years with electrocardiographically detected LVH. Losartan significantly reduced CV endpoints (13%) with minimal differences in BP changes between treatments. The benefit of losartan was mainly due to a decrease in the rate of stroke (25% reduction; $p = 0.001$), with no differences on myocardial infarction or total mortality. The Study on Cognition and Prognosis in the Elderly (SCOPE) (87) included hypertensive patients aged 70–89 randomly assigned to candesartan or placebo with open-label, active, antihypertensive treatment added as needed. The primary composite endpoint, a combination of cardiovascular death, stroke, and myocardial infarction, was reduced by 10.9%, a difference that did not reach statistical significance. Of all the components of the primary endpoint, only the reduction in nonfatal stroke (27.8%; 95% CI: 1.3–47.2; $p = 0.04$) was statistically significant. However, there were marked differences in BP reduction (3.2/1.6 mmHg) between candesartan and placebo-treated patients.

SECONDARY PREVENTION OF STROKE

A systematic review of the relationship between BP reduction and the secondary prevention of stroke and other vascular events (88) included seven published, randomized, controlled trials with a combined sample size of 15,527 participants with ischemic or hemorrhagic stroke, studied from 3 weeks to 14 months after the event and followed up for 2 to 5 years. Treatment with antihypertensive drugs was associated with significant reductions in all recurrent strokes. The overall reductions in stroke and all vascular events were related to the degree of BP lowering achieved, while data on the relative benefits of specific antihypertensive regimens for secondary stroke prevention were not clear.

The Perindopril Protection against Recurrent Stroke Study (PROGRESS) (89) was specifically designed to test the effects of a BP lowering regimen, including an ACE inhibitor, in 6,105 patients with stroke or transient ischemic attack within the previous 5 years. Randomization was stratified by intention to use single (perindopril) or combination (perindopril plus the diuretic indapamide) therapy in both hypertensive and normotensive patients. The combination therapy reduced BP by an average of 12/5 mmHg and resulted in a 43% (95% CI: 30–54) reduction in the risk of recurrent stroke. The effects were present in both the hypertensive and normotensive groups. However, there was no significant benefit when the ACE inhibitor was given alone (reducing BP by an average of 5/3 mmHg). Recently, the MOSES study of an ARB, eprosartan, on secondary stroke prevention found that the comparison of eprosartan versus nitrendipine in patients with a previous stroke resulted, despite a similar BP reduction, in fewer cerebrovascular and cardiovascular events in eprosartan-treated patients (90). A total of 1,405 high-risk hypertensives with cerebral events during the last 24 months were

randomized to eprosartan or nitrendipine (mean follow-up 2.5 years). The primary endpoint was the composite of total mortality and all cardiovascular and cerebrovascular events, including all recurrent events. The combined primary endpoint was significantly lower in the eprosartan group, mainly due to a reduction in cerebrovascular events.

In summary, according to the American Heart Association (91), antihypertensive treatment is recommended for the prevention of recurrent stroke. Because this benefit extends to persons with and without a history of hypertension, this recommendation should be considered for all ischemic stroke and transient ischemic attack patients (Class IIa; level of evidence B). Absolute target BP level and reduction are uncertain and should be individualized, but the benefit has been associated with an average reduction of ≈10/5 mmHg, while normal BP levels have been defined as <120/80 mmHg (Class IIa; level of evidence B).

PREVENTION OF COGNITIVE IMPAIRMENT/DEMENTIA

Cross-sectional and longitudinal data from observational studies have shown some beneficial effects of antihypertensive treatment against cognitive impairment, cognitive decline, and dementia in elderly people (41). Three large-scale placebo-controlled clinical trials have assessed the potential role of antihypertensive therapy in preventing cognitive impairment, dementia, and stroke-related cognitive decline. The SHEP (92) study found that active treatment with thiazide diuretics significantly reduced the risk of stroke and cardiovascular events (primary endpoints), but not of cognitive impairment and dementia (secondary endpoints). However, re-analysis of the data indicated that differential dropout rates between treatment and placebo groups might have obscured a potential effect of antihypertensive treatment against cognitive decline and dementia (93). In the Systolic Hypertension in Europe (Syst-Eur) trial, patients with isolated systolic hypertension were initially treated by nitrendipine and, if necessary, with enalapril or hydrochlorothiazide or both. This trial showed that active therapy reduced dementia incidence by 50% over 2 years (94). After termination of the initial trial, all participants were continued on the active therapy for another 2 years in an open study. Findings from the extended trial reinforced the initial conclusion that long-term antihypertensive therapy initiated with a long-acting dihydropiridine calcium channel blocker reduced dementia risk by 55% (95% CI: 24–73%) (10). In the PROGRESS study of recurrent stroke prevention, the risk of dementia and cognitive decline were evaluated as a secondary endpoint and no significant effect of the therapeutic regimen on the overall risk of dementia was found (95). However, the regimen significantly reduced the risk of dementia with recurrent stroke by a third, the overall risk of cognitive decline by a fifth, and the risk of cognitive decline with recurrent stroke by a half (95). The absence of a treatment effect on the overall risk of dementia might be due to the limited power being unable to detect a more modest effect and to the premature discontinuation of active treatment by some patients. In addition, the SCOPE trial was initially designed to address whether candesartan-based antihypertensive therapy in older hypertensive patients reduced the risk of cardiovascular events, cognitive decline, and dementia. However, due to ethical concerns, this study was finally designed to compare the effects of both candesartan and usual antihypertensive therapy regimens. After 4 years of observation, no significant difference in dementia incidence, cognitive decline, and changes in mean mini mental state examination (MMSE) score between the two groups was found (87). The MOSES (90) study also included changes in cognitive function, measured by MMSE, as a secondary endpoint and found no differences between groups.

In summary, despite all the limitations and methodological differences, there is moderately strong evidence to support the view that hypertension in midlife, especially if not treated effectively, negatively affects cognition and contributes to the development of dementia and even Alzheimer's disease in late life. High midlife BP implies a long-term cumulative effect leading to increased severity of atherosclerosis and more vascular comorbidities in late life. There is less evidence that the same negative effect on cognition is present for hypertension in later life. Indeed, some reports on the harmful cognitive effect of low BP seem to suggest that, in older adults, and particularly in those who are very old, an appropriate level of BP may be required to retain cognitive function by maintaining adequate cerebral perfusion. However, the optimum BP remains unknown. Observational results suggest a protective effect of antihypertensive treatment against cognitive decline and dementia. Confirmation from randomized clinical trials is limited, as it is based mainly on the Syst-Eur trial (94). Other clinical trials showed no clear treatment effect or only a beneficial effect against poststroke dementia and cognitive decline.

ANTIHYPERTENSIVE THERAPY AND EARLY CEREBRAL DAMAGE

Cross-sectional population-based MRI studies have shown that treated, controlled, hypertensive patients have a lower prevalence of WML than both untreated and treated but not controlled hypertensive patients (16). Van Dijk et al. (96), studying 1,805 individuals aged 65 to 75 years from 10 European cohorts in whom BP measurements were initiated 5 to 20 years before the brain-MRI, found that patients with poorly controlled hypertension had a higher risk of severe WML than those without WML or those with controlled or untreated hypertension. Increased SBP and DBP were associated with more severe WML, and reduced DBP was associated with more severe periventricular WML. The authors suggest that successful treatment of hypertension may reduce the risk of WML, but that reducing DBP may have a potentially negative effect on the occurrence of severe periventricular WML. However, this lack of difference between controlled and untreated hypertensives could be due to the fact that the untreated group had less severe hypertension or a shorter duration of hypertension. Another study performed in 845 subjects showed that hypertension at baseline was significantly associated with an increased risk of severe WML in the brain-MRI at 4 years of follow-up. When both BP levels and antihypertensive drug intake were taken into account, the risk of severe WML was significantly reduced in subjects with normal BP taking antihypertensive medication compared with those with high BP taking antihypertensive drugs (70).

In a longitudinal study, Schmidt et al. (97) evaluated volunteers aged 50–75 years without neuropsychiatric disease who underwent brain-MRI at baseline and at 3 years (204 individuals) and 6 years (191 individuals) of follow-up. At 3 years, only DBP and WML at baseline were significant

predictors of white matter hyperintensity progression. At 6 years of follow-up, the grade of WML at baseline predicted progression of WML better than age and hypertension (97).

An MRI substudy of PROGRESS, a randomized trial of BP lowering with perindopril versus placebo in normotensive and hypertensive subjects with cerebrovascular disease, has recently found that the mean total volume of new WML was significantly reduced in the active treatment group compared with the placebo group (98). A post hoc analysis also indicates that the greatest beneficial effect of antihypertensive therapy on WML progression was observed in patients with severe WML at entry.

SUMMARY

Hypertension is the most important risk factor for stroke and may also predispose to the development of more subtle cerebral damage based on arteriolar narrowing or pathological microvascular changes. Age and high BP are responsible for silent structural and functional cerebral changes leading to WML and cognitive impairment. Hypertensive patients have a higher rate and extent of areas of cerebral WML compared with normotensives. In addition, the presence of cerebral WML is an important prognostic factor for the development of stroke, cognitive impairment, and dementia. The mechanisms that would explain these relationships remains to be elucidated, but available data suggest that arteriosclerosis of the penetrating brain vessels is the main factor in the pathogenesis of ischemic WML. Results of some studies suggest that antihypertensive drug treatment and BP control may play a role in the prevention of the progression of WML, cognitive impairment, or dementia. On the other hand, prevention of stroke by antihypertensive therapy is well established, and recent trials indicate that BP lowering is also beneficial in reducing stroke recurrence, even among stroke patients without a history of hypertension. According to the current evidence, early treatment of high BP may prevent progression of silent structural and functional cerebral disease, sustained BP reduction to target values being the main priority for primary or secondary prevention of stroke.

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LARGE ARTERY DAMAGE: MEASUREMENT AND CLINICAL IMPORTANCE

19

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INTRODUCTION

In hypertension, large arteries stiffen and pulse pressure (PP) increases due to wave reflections. A major reason for measuring arterial stiffness and wave reflections "routinely" in clinical practice in hypertensive patients comes from the recent demonstration that arterial stiffness and wave reflections have a predictive value for cardiovascular (CV) events (29,49). A recent expert consensus document has reviewed the methodological agreements for measuring arterial stiffness and wave reflections (29). This chapter does not address the issue of endothelial dysfunction and intima-media thickness (IMT).

PATHOPHYSIOLOGY OF LARGE ARTERY DAMAGE IN HYPERTENSION

PATHOPHYSIOLOGY OF ARTERIAL STIFFNESS AND WAVE REFLECTION

Aortic stiffening accompanying age and cardiovascular risk factors is caused by various phenomena, including breaks in elastin fibers, cross-links of the elastin network, accumulation of collagen, fibrosis, inflammation, medial smooth muscle necrosis, calcifications, and diffusion of macromolecules within the arterial wall (16,21,28).

In patients with essential hypertension, arterial stiffness is elevated in response to the increased loading of stiff wall materials, such as collagen. Indeed, when blood pressure (BP) increases during the cardiac cycle from diastole to systole, distensibility decreases. These short-term changes should not be confounded with long-term changes in structure and function. Particularly, whether the decrease in large artery distensibility observed in middle age hypertensive patients is due primarily to an increase in distending pressure or to hypertension-induced changes in structural properties has been much debated (24). We recently reviewed the various mechanisms explaining that the changes in arterial wall material, which accompany arterial wall hypertrophy in animal models of essential hypertension, are not necessarily associated with an increased isobaric stiffness and mechanical strength, and concluded that the increase in arterial stiffness observed in patients with essential hypertension was primarily due to an increase in distending pressure (28). Later, age, metabolic disorders, renal failure may modify this hemodynamic pattern (49).

The stiffness of large arteries, including the aorta, represents the ability of large vessels to dampen the pulsatility of ventricular ejection and to transform a pulsatile pressure (and flow) at the ascending aorta into a continuous pressure (and flow), downstream, at the site of arterioles, in order to lower the energy expenditure of organ perfusion. With high BP, aging, and diabetes, the large arteries stiffen, and pulse pressure (PP = systolic minus diastolic) increases at the site of central and peripheral arteries. Indeed, the arterial tree is approximated to a viscoelastic tube with numerous branches. Because the tube's end has a high level of resistance, waves are reflected and retrograde waves are generated. As arterial stiffness increases, transmission velocity of both forward and reflected waves increase, which causes the reflected wave to arrive earlier in the central aorta and augment pressure in late systole, and thus increase PP. This augmentation can be expressed as aortic augmentation index (AIx), which represents a percentage of the increment pressure of aortic PP caused by the reflected wave.

In peripheral arteries, wave reflections can amplify the pressure wave, because reflection sites are closer to peripheral sites than to central arteries, and pulse wave velocity (PWV) is higher in a peripheral stiffer artery than in a central elastic artery. The net result is that the amplitude of the pressure wave is higher in peripheral arteries than in central arteries—the so-called "amplification phenomenon." Thus, because of PP amplification between central and peripheral arteries, it is inaccurate to use brachial PP as a surrogate for aortic or carotid PP, particularly in young subjects, in whom brachial PP overestimates central PP.

Because central systolic BP (SBP), PP, Aix, and PWV increase with age, hypertension, diabetes mellitus, and hypercholesterolemia, and are associated with target organ damage [left ventricular hypertrophy (LVH), microalbuminuria, carotid IMT, and endothelial dysfunction] and clinical outcomes, they

are often used interchangeably as indexes of arterial stiffness. This is an oversimplification and should not be the case for various reasons. First, their determinants are different. Central SBP, central PP, and AIx are dependent on the speed of wave travel, the amplitude of reflected wave, the reflectance sites, and the duration and pattern of ventricular ejection, especially with respect to change in heart rate and ventricular contractility (38,48) whereas aortic PWV, which is the speed of wave travel (c_o), represents intrinsically arterial stiffness, according to the Bramwell–Hill formula: $c_o = \sqrt{(V\mathrm{d}P/\rho\mathrm{d}V)}$, where d$V$ is the change in arterial volume (V), dP is the change in pressure driving the change in volume, and ρ is the density of fluid. Second, pathophysiological conditions and drugs may change central PP and AIx without changing aortic PWV, suggesting a predominant effect on reflection wave, heart rate or ventricular ejection, and no change in aortic stiffness (30,62). Third, AIx is much more sensitive to the effects of heart rate than aortic PWV (1).

PATHOPHYSIOLOGY OF CARDIOVASCULAR EVENTS

A generally accepted mechanistic view is that an increase in arterial stiffness causes a premature return of reflected waves in late systole, increasing central PP, thus SBP. SBP increases the load on the left ventricle, increasing myocardial oxygen demand. In addition, arterial stiffness is associated with LVH (7,39,47,49), a known risk factor for coronary events, in normotensive and hypertensive patients. The increase in central PP and the decrease in diastolic BP may directly cause subendocardial ischemia. The measurement of aortic stiffness, which integrates the alterations of the arterial wall, may also reflect parallel lesions present at the site of the coronary arteries.

An increased arterial stiffness can increase the risk of stroke through several mechanisms, including an increase in central PP, influencing arterial remodeling both at the site of the extracranial and intracranial arteries, increasing carotid wall thickness and the development of stenosis and plaques (8,47) and the prevalence and severity of cerebral white matter lesions. As seen above, the measurement of aortic stiffness, which integrates the alterations of the arterial wall, may also reflect parallel lesions present at the site of cerebral vasculature. Another explanation is given by the differential input impedance in the brain compared with other systemic vascular beds. Finally, coronary heart disease (CHD) and heart failure, which are favored by high PP and arterial stiffness, are also risk factors for stroke.

CLINICAL MEASUREMENTS OF ARTERIAL STIFFNESS AND WAVE REFLECTIONS

Arterial stiffness can be evaluated at the systemic, regional, and local levels. In contrast to systemic arterial stiffness, which can only be estimated from models of the circulation, regional, and local arterial stiffness can be measured directly, and noninvasively, at various sites along the arterial tree. A major advantage of the regional and local evaluations of arterial stiffness is that they are based on direct measurements of parameters strongly linked to wall stiffness. Reviews have been published on methodological aspects (29,39,44,49,58). Table 19.1 gives the main features of various methods.

REGIONAL MEASUREMENTS OF ARTERIAL STIFFNESS

The aorta is a major vessel of interest when determining regional arterial stiffness for at least two reasons: the thoracic and abdominal aorta makes the largest contribution to the arterial buffering function (22,23,39,49), and aortic PWV is an independent predictor of outcome in a variety of populations (6,9,13,25,34,36,50,51,54). However, all arterial sites have potential interest. Indeed, the forearm circulation is where BP is commonly measured, and the lower limb arteries, are specifically altered by atherosclerosis. Measurement of local carotid stiffness may also provide important prognostic information, since the carotid artery is a frequent site of atheroma formation.

PULSE WAVE VELOCITY MEASUREMENTS

The measurement of PWV is generally accepted as the most simple, noninvasive, robust, and reproducible method with which to determine arterial stiffness. Carotid-femoral PWV is a direct measurement, and it corresponds to the widely accepted propagative model of the arterial system. Measured along the aortic and aorto-iliac pathway, it is the most clinically relevant, since the aorta and its first branches are what the left ventricle "sees," and are thus responsible for most of the pathophysiological effects of arterial stiffness. Carotid-femoral PWV has been used in epidemiological studies demonstrating the predictive value of aortic stiffness for CV events. By contrast, PWV measured outside the aortic track, at the upper (brachial PWV) or lower limb (femoro-tibial PWV), has no predictive value in patients with end-stage renal disease (ESRD) (45).

PWV is usually measured using the foot-to-foot velocity method from various waveforms. These are usually obtained, transcutaneously at the right common carotid artery and the right femoral artery (i.e., "carotid-femoral" PWV), and the time delay (Δt, or transit time) measured between the feet of the two waveforms (Figure 19.1). A variety of different waveforms can be used including pressure (2), distension (59), and Doppler (13). The distance (D) covered by the waves is usually assimilated to the surface distance between the two recording sites. Some authors subtract from this distance the small length between carotid transducer and sternal manubrium (49). PWV is calculated as PWV = D (m)/Δt (s).

Some limitations should be underlined. The femoral pressure waveform may be difficult to record accurately in patients with metabolic syndrome, obesity, diabetes, and peripheral artery disease (58). In the presence of aortic, iliac, or proximal femoral stenosis, the pressure wave may be attenuated and delayed. Abdominal obesity, particularly in men, and large bust size in women, can make distance measurements inaccurate (58).

The most commonly used method for estimating transit time is the "foot-to-foot" method. The "foot" of the wave is defined at the end of diastole, when the steep rise of the wavefront begins. The transit time is the time of travel of the "foot" of the wave over a known distance.

METHODS BASED ON PRESSURE SENSORS

Pressure waveforms can be recorded simultaneously to provide automated measurement of PWV using a number of devices. The Complior System® (Colson, Les Lilas, France) employs dedicated mechanotransducers directly applied on

Table 19.1 Device and methods used for determining regional, local, and systemic arterial stiffness and wave reflections

	Device	Methods	Measurement site	Ref.
Regional Stiffness	Complior®	Mechanotransducer	Aortic PWV[a]	2
	Sphygmocor®	Tonometer	Aortic PWV[a]	46
	WallTrack®	Echo-tracking	Aortic PWV[a]	19
	Artlab®	Echo-tracking	Aortic PWV[a]	43
	Ultrasound systems	Doppler probe	Aortic PWV[a]	13
Local stiffness	WallTrack®	Echo-tracking	CCA[b], CFA., BA	19
	NIUS®	Echo-tracking	RA	55
	Artlab®	Echo-tracking	CCA[b], CFA, BA	43
	Various vascular ultrasound system	Echo-tracking	CCA[b], CFA, BA	44
	MRI device	Cine-MRI	Ao	44
Systemic stiffness (waveform shape analysis)	Area method	Diastolic decay		14
	HDI PW CR-2000®	Modif. Windkessel		12
Wave reflections	Sphygmocor®	Augmentation index	All superficial art	146
	Pulse trace®	Finger photoplethysmography		38

[a]Aorta, carotid-femoral, also carotid-radial and femoro-tibial PWV.
[b]All superficial arteries, including particularly those mentioned.
Abbreviations: Ao, aorta; BA, brachial artery; CCA, common carotid artery; CFA, common femoral artery; PWV, pulse wave velocity; RA, radial artery; SV/PP, stroke volume/pulse pressure.
Source: From Ref. 29.

the skin (2). The transit time is determined by means of a correlation algorithm between each simultaneous recorded wave. The operator is able to visualize the shape of the recorded arterial waves and validate them. Three main arterial sites can be evaluated, mainly the aortic trunk (carotid-femoral), and the upper (carotid-brachial) and lower (femoral-dorsalis pedis) limbs. This system was used in most of the epidemiological studies demonstrating the predictive value of PWV for cardiovascular events.

Pressure waves can also be recorded sequentially from different sites, and transit time calculated using registration with a simultaneously recorded ECG. In the SphygmoCor® system (ArtCor, Sydney, Australia) (63) a single high-fidelity applanation tonometer (Millar®, Houston, TX, U.S.A.) to obtain a proximal (i.e., carotid artery) and distal pulse (i.e., radial or femoral), recorded sequentially a short time apart, and calculates PWV from the transit time between the two arterial sites, determined in relation to the R wave of the ECG. The time between the ECG and the proximal pulse is subtracted from the time between ECG and distal pulse to obtain the pulse transit time. The initial part of the pressure waveform is used as a reference point. It is also possible to check offline the variability of measurement over a range of pulses, according to each algorithm. Since the measurements are made a short time apart, the change in the isovolumic period of the left ventricle or heart rate variability have little or no effect on measured pulse transit times. Methods using mechanotransducers or high-fidelity applanation tonometers are well accepted for carotid-femoral PWV measurement.

Japanese researchers advocated the use of brachial-ankle pulse wave velocity (baPWV), and showed the aortic PWV was the primary independent correlate of baPWV, followed by leg PWV (52).

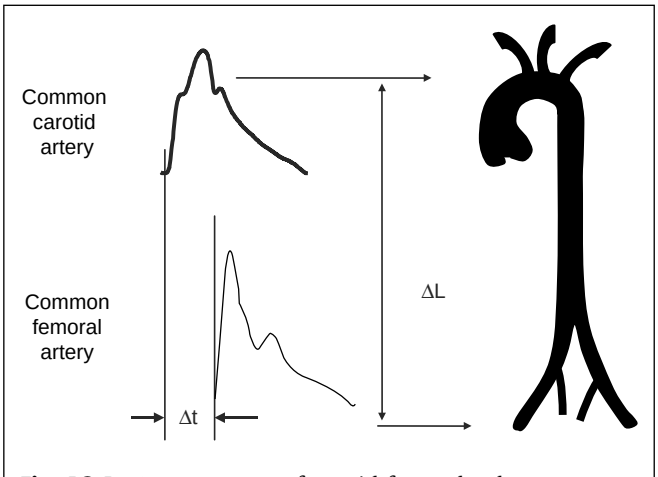

Fig. 19.1 Measurement of carotid-femoral pulse wave velocity with the foot-to-foot method. *Source*: From Ref. 29.

METHODS BASED ON DOPPLER PROBES AND OTHER METHODS

The distension waves obtained from high-definition echotracking devices (see below) can be used to calculate PWV. Like described above for the SphygmoCor® device, PWV is calculated from waves successively obtained at a short-time interval at two arterial sites (common carotid and femoral artery for instance), using the R wave of the ECG for calculating the time delay (38,59).

The transit time, required for the determination of PWV, can be measured between two flow pulses simultaneously recorded by continuous Doppler probes (13), or again sequentially with ECG gating. Measurements are usually made at the root of the left subclavian artery (i.e., suprasternal notch on the skin) and near the bifurcation of the abdominal aorta (i.e., umbilicus level on the skin). Transit time is automatically calculated following automatic recognition of the foot of the pulse. This method was used for showing the predictive value of aortic PWV for cardiovascular events in diabetic patients (13), and provides a more accurate assessment of "aortic" PWV as compared to carotid-femoral, although whether this has any specific advantage remains to be seen.

Other devices are available to calculate a PWV-based stiffness index (26,44,58). These devices are not so precise as those mentioned above as some propose aberrant transit tracts

(i.e., ankle-arm) or estimate distance from height (i.e., height in sitting position). Some do not correct for electromechanical dissociation of cardiac action or try to correct for it using a model.

LOCAL DETERMINATION OF ARTERIAL STIFFNESS

Local arterial stiffness of superficial arteries can be determined using ultrasound devices. Carotid stiffness may be of particular interest, since in that artery atherosclerosis is frequent. All types of classical, bidimensional, vascular ultrasound systems can be used to determine diameter at diastole and stroke changes in diameter, but most of them are limited in the precision of measurements because they generally use a video-image analysis. At present some researchers also measure local arterial stiffness of deep arteries like the aorta using cine magnetic resonance imaging (MRI). However, most of pathophysiological and pharmacological studies have used echo-tracking techniques.

A major advantage of echo-tracking techniques is that local arterial stiffness is directly determined, from the change in pressure driving the change in volume, i.e., without using any model of the circulation (Figure 19.2). However, because it requires a high degree of technical expertise, and takes longer than measuring PWV, local measurement of arterial stiffness is only really indicated for mechanistic analyses in pathophysiology, pharmacology, and therapeutics, rather than for epidemiological studies (29). Nevertheless, ultrasound is currently the only means to determine, noninvasively, the elastic properties of the arterial wall material (Young's elastic modulus, see below) (10,18,23,47), and the relationship between IMT and elastic properties (24), or the influence of inward or outward remodeling on arterial distensibility (8,10,17,42,56,59).

Echo-tracking devices were developed to measure diameter in end-diastole and stroke change in diameter with a very high precision. The two first devices were the Wall Track System® (Esaote-Pie Medical, Maastricht, The Netherlands) (19,20) and the NIUS 02® (SMH, Paris, France) (55). These apparatus use the radio frequency (RF) signal to obtain a precision 6 to 10 times higher than with video-image systems, which are limited by the spatial resolution of pixel analysis. Indeed, the precision in determining stroke change in diameter is as low as 1 μm (19,20,55) for echo-tracking systems, and around 150 μm (i.e., the size of the pixel) with video-image analyzers. For absolute distance measurement, the standard deviation extends from 9 to 25 μm for echo-tracking systems, and from 54 to 60 μm with video-image analyzers (19,20,55). A novel multiarray echo-tracking system having 128 RF lines (ArtLab®; Esaote-Pie Medical) is able to determine both IMT and pulsatile changes in diameter along a 4 cm long arterial segment (43).

Echo-tracking systems have other major advantages over video-image systems: from the same ultrasound data, the IMT can be extracted, which allows the Young's elastic modulus to be determined (see below) (10,23); it is possible to determine the pressure-diameter curve of the artery, thus to determine arterial stiffness for any given BP (10,18,23); from the time delay between two adjacent distension waveforms, it is possible to calculate local PWV (37); and pathophysiological and therapeutic changes in arterial stiffness can be related to geometrical changes (lumen area and IMT).

Most of these parameters require measurement of BP. This should be local pressure, which is usually obtained by applanation tonometry of the vessel in question (23,57) and calibration of the waveform to brachial mean and diastolic pressures obtained by integration of the brachial or radial waveform (57), or automatic calculation using transfer function processing (Sphygmocor, AtCor, Sydney Australia). All the superficial arteries are suitable for the geometrical investigation, and particularly the common carotid, common femoral and brachial arteries.

Table 19.2 gives the definition of various indices used to describe the elastic properties of blood vessels, noninvasively obtained with ultrasound measurements. For the calculation of wall properties, it is assumed that the cross-section of an artery is circular (Figure 19.2). The elastic properties of the artery as a hollow structure are assessed through arterial distensibility, determined from the systolic–diastolic variations in arterial cross-sectional area and local PP (17,19,23,29,44,59). The elastic properties of the arterial wall material are estimated by the Young's incremental elastic modulus (E_{inc}), which takes into account the thickness of the arterial wall (16,23,29). The IMT is taken as surrogate for arterial wall thickness. Young's elastic modulus, or incremental elastic modulus, which gives information on the wall material, should not be confused with Peterson's elastic modulus, which is inversely related to cross-sectional distensibility, and elastic properties of larges arteries as hollow structures (16,29). Calculation of Young's modulus from IMT assumes that the wall is homogeneous, and load bearing, so that values may be underestimated.

SYSTEMIC ARTERIAL STIFFNESS

A methodology based on an electrical circuit, based on a modified Windkessel model (12,35) has been developed to determine a proximal capacitive compliance and a distal oscillatory compliance (HDI/PulseWave CR-2000 Research CardioVascular Profiling System; Hypertension Diagnostics Inc., Eagan, MN, U.S.A.). This technique is based on the arterial pulse recording at the level of the radial artery and identifies the reflections in diastole as a decaying sinusoidal wave (12,35).

Systemic arterial compliance can also be determined using the "area method" (14,31), which requires measurement of aortic blood flow (velocimeter at the suprasternal notch) and associated driving pressure by applanation tonometry over the proximal right common carotid artery. Systemic arterial compliance is then calculated from the formula: $SAC = Ad/[R(Ps - Pd)]$, where Ad is the area under the BP diastolic decay curve from end-systole to end-diastole, R is the total peripheral resistance, Ps is the end-systolic BP, and Pd is the end-diastolic BP (calibrated against brachial arterial pressure).

In summary, methods used for the noninvasive determination of systemic arterial stiffness are based on analogies with electrical models combining capacitance and resistance in series. As such they rely on numerous theoretical approximations following direct measurement of one peripheral, and often distal, parameter. Their theoretical, technical, and practical limitations that impact on their widespread application in the clinical setting have been discussed and compared with methods used for the noninvasive determination of regional stiffness (35,41,44,58). Until now, they did not provide evidence, in a longitudinal study, that systemic arterial stiffness or systemic arterial compliance have independent predictive value for CV events (14).

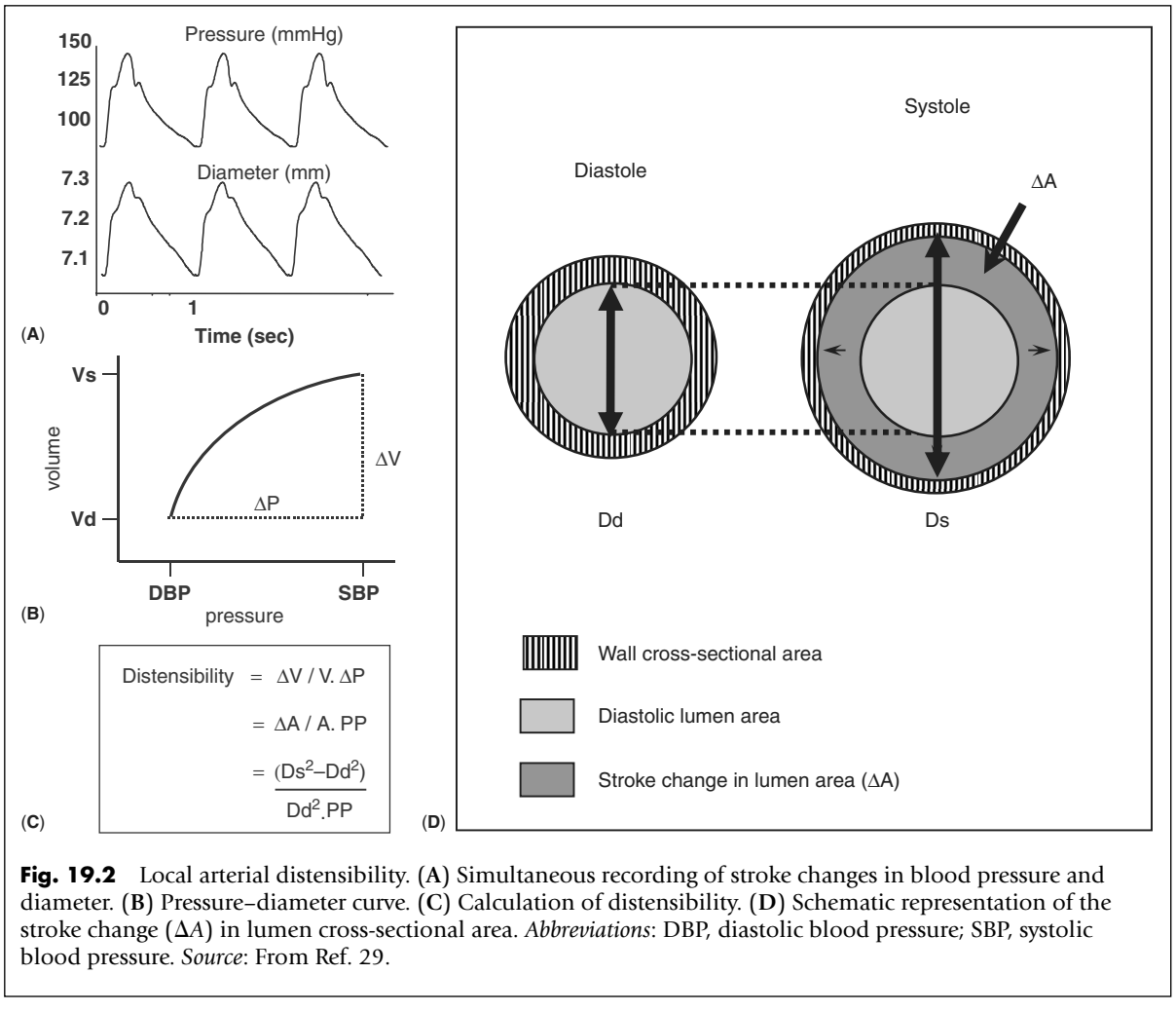

Fig. 19.2 Local arterial distensibility. (**A**) Simultaneous recording of stroke changes in blood pressure and diameter. (**B**) Pressure–diameter curve. (**C**) Calculation of distensibility. (**D**) Schematic representation of the stroke change (ΔA) in lumen cross-sectional area. *Abbreviations*: DBP, diastolic blood pressure; SBP, systolic blood pressure. *Source*: From Ref. 29.

NONINVASIVE DETERMINATION OF WAVE REFLECTIONS

CENTRAL PULSE WAVE ANALYSIS

The arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and a reflected wave. Waves are reflected from the periphery, mainly at branch points or sites of impedance mismatch. In elastic vessels, because PWV is low, reflected wave tends to arrive back at the aortic root during diastole. In the case of stiff arteries, PWV rises and the reflected wave arrives back at the central arteries earlier, adding to the forward wave, and augmenting the systolic pressure. This phenomenon can be quantified through the AIx—defined as the difference between the second and first systolic peaks (P2 − P1 = AP = augmentation pressure) expressed as a percentage of the PP (Figure 19.3) (32,33, 39,49,62). Apart from a high PWV, also changes in reflection sites can influence the AIx. In clinical investigation, not only DBP and height, which are related to reflection sites, but also age and aortic PWV, are the main determinants of AIx (30).

Arterial pressure waveform should be analyzed at the central level, i.e., the ascending aorta, since it represents the true load imposed to the left ventricle and central large artery walls. Aortic pressure waveform can be estimated either from the radial artery waveform, using a transfer function (11,46), or from the common carotid waveform (44,58). In the later case, a transfer function is not necessary. On both arteries, the pressure waveform can be recorded noninvasively with a pencil-type probe incorporating a high-fidelity Millar strain gauge transducer (SPT-301, Millar Instruments). The most widely used approach is to perform radial artery tonometry and then apply a transfer function (Sphygmocor, AtCor, Sydney, Australia) to calculate the aortic pressure waveform from the radial waveform (11,46). Indeed, by contrast to the carotid artery, the radial artery is well supported by bony tissue, making optimal applanation easier to achieve.

Generalized inverse transfer functions are applied to reconstruct the aortic waveform from radial tonometry (11,46). The estimation of central aortic pressures (PP and SBP) is accepted as more accurate than the estimation of AIx (see below) (30,38). Indeed, measurement of AIx is dependent on higher frequency signals than BP measurement, and the transfer function appears to be less accurate and to show greater between-subject variability at high frequencies (11,38,46). In addition, brachial artery pressures are used as surrogates of radial artery pressures for the calibration of central pressures, and this may introduce some errors (60). Despite these limitations, radial tonometry is popular since it is simple to perform and well tolerated.

Carotid tonometry requires a higher degree of technical expertise, but a transfer function is not necessary since the arterial sites are very close and waveforms are similar (11,29). Direct measurements obtained at the site of the

Table 19.2 Indices of arterial stiffness applied to geometrical measurements of large arteries with ultrasounds

Term	Definition (units)
Stroke change in diameter	Change in diameter during systole = systolic diameter (Ds) − diastolic diameter (Dd) (mm)
Stroke change in lumen area	Change in lumen area during systole, $\Delta A = \pi(Ds^2 - Dd^2)/4$, ($mm^2$) with D = internal diameter
Wall cross-sectional area	Surface of a cross-section of the arterial wall, WCSA = $\pi(De^2 - Di^2)/4$, (mm^2) with De = external diameter and Di = internal diameter, measured in diastole
Elastic properties of the artery as a whole Cross-sectional distensibility coefficient (DC)	Relative change in lumen area during systole for a given pressure change DC5DA/A.DP (k/Pa), with DP5local pulse pressure
Cross-sectional compliance coefficient (CC)	Absolute change in lumen area during systole for a given pressure change CC = $\Delta A/\Delta P$ (m^2/kPa), with ΔP = local pulse pressure
Peterson elastic modulus	Inverse of distensibility coefficient: the pressure change driving an increase in relative lumen area Peterson = $A\Delta P/\Delta A$ (kPa)
Elastic properties of the arterial wall material Young's elastic modulus or incremental elastic modulus	$E_{inc} = [3(1 + A/WCSA)]/DC$ (kPa)

Source: From Ref. 29.

common carotid artery using applanation tonometry can be calibrated according to the method described by Van Bortel et al. (57,60).

A transfer function may be useful when applanation tonometry cannot be applied at the site of the carotid artery, for instance in obese subjects, or in patients with major atherosclerotic plaques or calcified arteries, in whom this method may not be free from any risk. However, the use of a transfer function should be limited to the upper limb, where elastic properties remain relatively constant with age and disease, as previously discussed. It would allow assessing carotid artery and ascending aorta systolic BP and PP from radial artery PP (46,57,60).

Central AIx and central PP have shown independent predictive values for CV events in the hypertensive patients of the CAFÉ study (63) and patients undergoing percutaneous coronary intervention (61), and for all-cause mortality in ESRD patients (32,48).

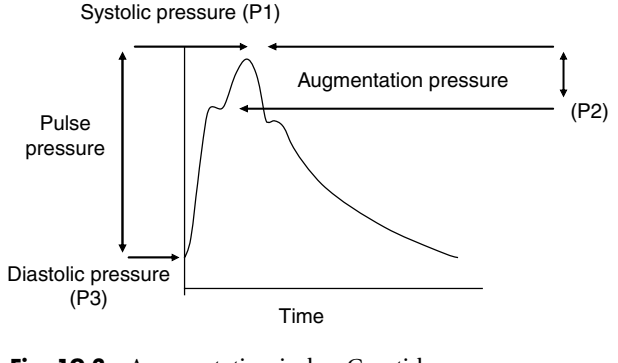

Fig. 19.3 Augmentation index. Carotid pressure waveform is recorded by applanation tonometry. The height of the late systolic peak (P1) above the inflection (P2) defines the augmentation pressure, and the ratio of augmentation pressure to pulse pressure defines the augmentation index (AIx, in percent). *Source*: From Ref. 29.

CLINICAL IMPORTANCE

ARTERIAL DAMAGE IN HYPERTENSION AND ASSOCIATED CLINICAL CONDITIONS

A large number of publications and several reviews (21,29, 33,44,58,65) have reported the various pathophysiological conditions associated with increased arterial stiffness and wave reflections. Apart from the dominant effect of BP and aging (21,33,39,49,65), they include (a) physiological conditions (29), such as low-birth weight, menopausal status, lack of physical activity; (b) the genetic background such as a parental history of hypertension, diabetes or myocardial infarction, and genetic polymorphisms; (c) CV risk factors such as obesity, smoking, hypertension, hypercholesterolemia, impaired glucose tolerance, metabolic syndrome, type 1 and 2 diabetes, hyperhomocyteinemia, and high-CRP level; (d) CV diseases such as CHD, congestive heart failure, and fatal stroke; and (e) primarily nonCV diseases, such as ESRD, moderate chronic kidney disease, rheumatoid arthritis, systemic vasculitis, and systemic lupus erythematosus.

PREDICTIVE VALUE OF ARTERIAL STIFFNESS AND WAVE REFLECTION

A major reason for measuring arterial stiffness and wave reflections "routinely" in clinical practice in hypertensive patients comes from the recent demonstration that arterial stiffness has an independent predictive value for CV events (29,49).

ARTERIAL STIFFNESS AND WAVE REFLECTION AS INTERMEDIATE END-POINTS

Several longitudinal epidemiological studies have demonstrated the predictive value of arterial stiffness, carotid PP, and AIx, as intermediate end-points, i.e., the higher the arterial stiffness the higher the number of CV events. The

largest amount of evidence has been given for aortic stiffness, measured through carotid-femoral PWV. Aortic stiffness has independent predictive value for all-cause and CV mortality, fatal and nonfatal coronary events, and fatal strokes not only in patients with uncomplicated essential hypertension (9,25,27), but also in patients with type 2 diabetes (13) or ESRD (6,50), in elderly subjects (36,54) and in the general population (34,51,64). It is now well accepted that aortic stiffness is an intermediate end-point for CV events.

The independent predictive value of aortic stiffness has been demonstrated after adjustment to classical cardiovascular risk factors, including brachial PP. This indicates that aortic stiffness has a better predictive value than each of classical risk factors. In addition, aortic stiffness retains its predictive value for CHD events after adjustment to the Framingham risk score, suggesting that aortic stiffness has an added value to a combination of CV risk factors (9). One reason may be that aortic stiffness integrates the damage of CV risk factors on the aortic wall over a long period of time, whereas BP, glycemia, and lipids can fluctuate over time and their values, recorded at the time of risk assessment, may not reflect the true values damaging the arterial wall. Another explanation may be that arterial stiffness shows the patients in which arterial risk factors were translated into real risk.

Data are less consistent concerning arterial stiffness measured at other arterial sites. The predictive value of carotid stiffness has not yet been reported in hypertensive patients. Although carotid stiffness was predictive of CV events in a small number of patients with ESRD (5) or following renal transplantation (4), no predictive value was demonstrated in a larger number of patients with manifest arterial disease (15). Upper and lower limb territories, due to their particular pathophysiology (22,29,39,49) may not reflect aortic, cerebral, and coronary artery damage. Indeed, by contrast to carotid-femoral PWV, neither brachial PWV nor femoro-tibial PWV were able to predict cardiovascular outcome in ESRD patients (45).

Central AIx and PP, either directly measured by carotid tonometry (32,48) or estimated using a transfer function from radial artery tonometry (61,63) are both independent predictors of all-cause mortality in ESRD patients (32,48), in patients undergoing percutaneous coronary intervention (61), and in the hypertensive patients of the CAFÉ study (63). In older female hypertensive patients, data from the ANBP2 study showed no benefit in use of carotid applanation tonometry (AIx or total arterial compliance) over brachial cuff pressure in prognosis (14).

PHARMACOLOGY OF ARTERIAL STIFFNESS AND WAVE REFLECTION

A large number of publications and several reviews (26, 29,40,49) reported the changes in arterial stiffness and wave reflections after various interventions, either nonpharmacologic or pharmacologic. Nonpharmacological treatments that are able to reduce arterial stiffness include (29,49) exercise training, dietary changes (including weight loss, low salt diet, moderate alcohol consumption, garlic powder, alpha-linoleic acid, and fish oil), and hormone replacement therapy (HRT).

Pharmacological treatments that are able to reduce arterial stiffness include (29,49): (a) antihypertensive treatment, such as diuretics in old people, beta-blockers, ACE inhibitors, AT1 blockers, and calcium channel antagonists; (b) treatments of congestive heart failure, such as ACE inhibitors, nitrates, and aldosterone antagonists; (c) hypolipidemic agents such as statins; (d) antidiabetic agents, such as thiazolidinediones; and (e) AGE-breakers, such as alagebrium (ALT-711). Whether the reduction in arterial stiffness after antihypertensive treatment is only due to BP lowering, or additional BP-independent effects are involved, is still debated. To our knowledge, some studies unequivocally showed that antihypertensive treatment was able to reduce arterial stiffness and/or wave reflections independently of the reduction in brachial BP, for instance either acutely after a calcium channel blocker (53) or after long-term ACE inhibition (3,56).

CONCLUSION

This chapter highlights the importance of arterial stiffness and wave reflection, not only for assessing CV risk, but also for predicting CV outcomes. Arterial stiffening also provides direct evidence of target organ damage, which is of major importance in determining the overall CV risk of the hypertensive patient. Indeed, measurement of arterial stiffness and wave reflection may avoid patients being mistakenly classified as at low or moderate risk, when they actually have an abnormally high arterial stiffness or central PP placing them within a higher risk group.

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TARGET ORGAN DAMAGE: SMALL ARTERY STRUCTURE AND FUNCTION

20

Anthony M Heagerty

INTRODUCTION

An early cross-sectional study of mild hypertension reported that the predominant hemodynamic feature was a high cardiac output, and this observation has been confirmed consistently since. Although not invariably so, the high cardiac output is accompanied by a high heart rate, and several studies have demonstrated that, when oxygen consumption is measured, both cardiac output and this parameter are raised. In the mild early stages of essential hypertension, the peripheral resistance is low, although the crucial point is that it remains appropriately high for the corresponding cardiac output. A 20-year longitudinal study of the hemodynamics of essential hypertension confirmed the finding of initially increased cardiac index heart rate oxygen consumption and blood pressure (BP) with normal peripheral resistance (1). However, over this period, the high cardiac index and normal total peripheral resistance pattern changes to a low cardiac index high resistance pattern. Again, the inappropriately high level of vascular resistance for the increase in cardiac output is a hallmark in early hypertension. Such a hemodynamic profile could be ascribed to a high sympathetic nervous tone with the resulting increased drive to the heart, peripheral circulation, and metabolic receptors, which would then promote enhanced oxygen consumption (2). Other studies have demonstrated that autonomic blockade of the heart in mild hypertensive patients restored cardiac output to normal and there was a combination of increased sympathetic tone and decreased parasympathetic activity in such individuals. This combination of increased sympathetic discharge coupled to a reduced parasympathetic activity suggests that the abnormality in essential hypertension is one of integrated function in the medulla oblongata. Recent data have proposed that this might be a consequence of neurovascular compression on the left ventrolateral medulla. Therefore, it should follow that the resulting increased sympathetic activity would be distributed to all innervated organs and vascular beds producing uniform vasoconstriction and the predicted cardiac indices. There is evidence for this in the heart, kidney, and skeletal muscle but it has not been confirmed in studies of the hepatomesenteric circulation. In other words it is difficult to provide evidence for a ubiquitous abnormality of sympathetic function in all vascular beds, although the overall integrated hemodynamic profile can be ascribed to increased sympathetic discharge.

STRUCTURAL CHANGES IN THE CIRCULATION

Since the work of Bright and Johnson, it has been recognized that the walls of medium-sized arteries are thickened in hypertension. However, it has to be conceded that their contribution to vascular resistance is small. The histopathological change appears to be hypertrophy. Indeed the heart and medium-sized blood vessels demonstrate this hypertrophic response to hypertension. In addition, until the heart dilates, it is of interest to note that the hypertrophic response takes place at the expense of the ventricular cavity: in other words there is inward encroachment on the chamber space. Therefore, the hallmark of any form of sustained hypertension is an alteration in the architecture of the circulation that inevitably occurs in consequence. At the level of the resistance artery where the internal diameter of the blood vessels is around 250 μm or less, there is evidence of a reduced lumen diameter and increased media thickness: lumen diameter ratio. This was originally reported in necropsy specimens and subsequently confirmed in segments of artery mounted as isometric ring preparations on wires and in vessels perfused in vitro. Detailed histological analyses more recently carried out have suggested that eutrophic inward remodeling occurs at this point in the circulation. By this it is meant that there is a narrowing of the vascular lumen without having to invoke a growth response of the arterial wall (3). A small amount of hypertrophy may be observed in some pathological states where hypertrophy may supervene and is an adverse prognostic sign.

To understand how hypertension produces nonhypertrophic changes in small arteries, one must look at the physiological role of the resistance vasculature. At normal pressures, these vessels exhibit a level of contraction (myogenic tone), which is independent of neurohormonal influences, and, in

functioning in this way, the response enables arteries to constrict or dilate in response to changes in upstream pressure. This process known as the myogenic response is only observed in smaller resistance arteries, which mediate autoregulation of blood flow and stabilize capillary pressure. This ensures that target organs downstream are supplied with oxygenated blood at a constant flow and pressure. Hypertrophy is observed in vessels which do not possess myogenic tone, whereas, in smaller resistance arteries, initial increase in pressure will bring about an increased myogenic constriction. If an individual has untreated hypertension, then there will be prolonged myogenic constriction, as the resistance vasculature endeavors to protect the target organs downstream from pressure-induced damage brought about by an increase in blood flow. Prolonged vasoconstriction will lead to inward eutrophic remodeling and/or a reduced arterial distensibility. The structural difference between large conduit and medium-sized arteries and downstream resistance vessels is apparent in many models of hypertension: for example, in a hypertensive model brought on by chronic nitric oxide synthase inhibition. In addition, the magnitude and duration of an increase in intraluminal pressure plays a role in determining the remodeling response.

Eutrophic inward remodeling is a process of structural adaptation observed in most forms of hypertension, including the onset of hypertension and milder hypertensive states. However, a few animal models of hypertension, such as a model developing hypertension independent of the renin–angiotensin system (BPH-2 mice), demonstrates hypertrophy as the predominating structural change. Inward eutrophic remodeling is a relatively fast functional adaptation observed after prolonged vasoconstriction and is thought to be an energetically favored mechanism to preserve a lumen diameter for long periods. The process is also the preferred physiological mechanism by which wall stress can be normalized while maintaining vasomotor tone. Studies of the well-characterized TGR (REN2) 27 rat, which develops fulminant hypertension from 4 weeks of age, have demonstrated that eutrophic inward remodeling occurs from 4 weeks and is dependent on the integrin $\alpha v\beta_3$, a multifunctional extracellular matrix (ECM) receptor. However, hypertrophy does begin to appear between 6 and 8 weeks of age. This is important and is be discussed below. The ECM of resistance arteries is subject to tensile force exerted by BP, which is transferred through integrins across the cell membrane and linked by molecular complexes to the cytoskeleton. Specific integrin subtypes are utilized initially for the mechanotransduction of pressure. Using peptides and specific antibodies, it has been shown that integrins $\alpha v\beta_3$ and $\alpha_5\beta_1$ indirectly regulate the myogenic response by influencing the control of calcium flow through ion channels; $\alpha_5\beta_1$ is responsible for the initial calcium influx required to establish vascular tone; and $\alpha v\beta_3$ mediates force maintenance by calcium sensitization of contractile components. These integrins can form complexes, which regulate cytoskeletal dynamics and maintain a vascular myogenic force at a given pressure. This is ameliorated if there is cytoskeletal disruption. Cytoskeletal proteins, such as heat-shock protein 27 (HSP27) activated by RhoA kinases, have been shown to regulate myogenic tone. It is now clear that RhoA signaling plays a central role in both calcium sensitization and regulation of actin dynamics in small artery remodeling. In contrast to molecular signaling mechanisms behind the vascular myogenic response, relatively few data are available on the role of integrins and the underlying biochemical pathways of the next stage of vascular adaptation for hypertension, which is the migration of vascular smooth muscle cells toward a narrow lumen (4).

Remodeling involves a migratory process following prolonged vasoconstriction, whereby existing vascular smooth cells reposition themselves in the vascular wall and thereby produce a narrow lumen. A characteristic of migrating cells in vitro is the presence of lamealae podial and filopodial protrusions containing focal adhesion kinase (FAK), which provides a substrate for other cytosolic proteins, such as Src, and interacts with actin-associated cytoplasmic components. Recently, it has been shown that the migration of vascular smooth muscle cells of arteries in vivo is more subtle and limited to elongation or tapering in smooth muscle cells and an increase in cellular overlap. It is thought that cytoskeletal rearrangements in subsequent force generation play a central role in these changes. The exact cellular signaling system is still uncertain. Integrin $\alpha v\beta_3$ is necessary for the pressure-induced inward remodeling process, but the rest of the biochemical sensing mechanism is still uncertain.

If the physiological response to a raised BP in small arteries is eutrophic inward remodeling, then the integrity of the circulation appears to be preserved until this breaks down. As indicated above in the TGR (REN27) rat, there is evidence of the development of vascular wall hypertrophy in small arteries from week 6 onward. This rat model of hypertension develops a severe form of the disorder, and, indeed, dams are unable to breed if they do not receive antihypertensive medication. Therefore, against this background, it would appear that the breakdown of autoregulation is associated with the vascular wall developing a growth response (hypertrophy) in an attempt to offset the increased wall stress. Recent work on the small blood vessels of patients with Type 2 (maturity onset) diabetes mellitus has demonstrated that there is vascular wall hypertrophy. These patients were selected as already having evidence of downstream target organ damage because they demonstrated microproteinuria and their myogenic tone was disordered. In other words, the onset of hypertrophy is a consequence of disruption of normal myogenic tone and the delivery of blood at a higher perfusion pressure causing cellular damage. In the kidney, this would inevitably lead to a loss of filtration capability and protein leak.

In terms of cardiovascular risk, recent data from Italy have demonstrated that there is an increased risk of development of cardiovascular events in patients whose small arteries demonstrate hypertrophy rather than eutrophic inward remodeling (5).

Recent in vitro studies support these considerations. It has been demonstrated that the myogenic response of the middle cerebral artery from prestroke, spontaneously hypertensive, stroke-prone rats (SHRSP) are impaired compared with the spontaneously hypertensive rat (SHR). This observation would explain the cerebral autoregulation that has been observed in the SHRSP before stroke occurs. This is also associated with a redistribution of collagen throughout the blood vessel wall. Other studies have demonstrated that the myogenic component of renal autoregulation is impaired in the fawn-hooded rat (FHR) (the tubuloglomerular feedback component of renin autoregulation is unchanged) compared with controls, thereby causing glomerular hypertension and hyperfiltration, which explains why the kidneys are susceptible to the deleterious effects of moderate hypertension. Furthermore, the Brown Norway rat is normotensive, but

has a greater than normal life expectancy. However, when hypertension is induced, these animals have a high incidence of cerebral hemorrhage and mortality compared with the Long Evans rat. Also, the Brown Norway rat is very sensitive to hypertension-induced renal injury and recently the myogenic component of renal autoregulation has been found to be abnormal in normotensive Brown Norway rats. Therefore, it seems reasonable to speculate that the cerebral vessels from the Brown Norway animals exhibit weaker myogenic responses compared with cerebral vessels from Wistar rats, which would explain the susceptibility of the Brown Norway rat to hypertension-induced cerebral hemorrhage. Inhibition of the renin–angiotensin system markedly delays the development of cerebral hemorrhage and mortality in salt-loaded SHRSP. In the FHR early angiotensin-converting enzyme (ACE), inhibition prevents renal damage, and this protection is associated with a normalization of glomerular pressure. The protective effect of ACE inhibition in the kidney has been presumed to be a consequence of an inhibition of angiotensin II-induced efferent arteriolar myogenic tone. Of course, it could be argued that the effects of BP lowering would be important on stroke development and, in consequence, ACE inhibition is working by its antihypertensive effects. However, dexamethasone or thyroxine increased BP in the SHRSP to a greater extent than salt loading, but stroke does not occur. Also, the antistroke effect of captopril on salt-loaded SHRSP, which occurs without an antihypertensive effect, is unchanged when BP is increased with dexamethasone. Therefore, it seems that the renin–angiotensin system inhibition improves myogenic responses and survival in salt-loaded SHRSP, largely independent of changes in BP, although this remains to be confirmed.

SMALL ARTERY FUNCTION

There is little evidence to suggest that hypertension is associated with abnormalities of contractile function. Both in vitro and in vivo studies have suggested that contraction is normal, although there is controversy about whether the structural alterations in the vascular wall lead to exaggerated constriction and vascular amplification. This has been the subject of intense debate over a number of years, although some work in intact animals really seems to suggest that vascular amplification seen in isolated vascular beds is not something that is observed when the whole of the circulation is integrated and examined.

Again, it is controversial as to whether vascular relaxation is abnormal in hypertension. The problem with interpreting studies which have been published is that many other risk factors are often abnormal and accompany hypertension. For example, there is often associated dyslipidemia and there is clear evidence that oxidized low-density lipoprotein (LDL) can reduce the bioavailability of nitric oxide, and, as a result of this, there is evidence of abnormal endothelium-dependent dilator function, which has been reported in patients with high BP and dyslipidemia, patients with dyslipidemia and coronary artery disease, or the subcutaneous vasculature of patients with hypercholesterolemia. In addition, endothelial function is recognized to decline as individuals age and therefore it is obviously complex to dissect out whether endothelial function is abnormal as a result of hypertension, per se, or as a result of other demographic abnormalities and the cohorts being examined. The overall impression that one is left with is that it is the level of oxidized LDL that is important in the bloodstream of individuals with hypertension, and that BP, per se, is not responsible for endothelial dysfunction. With regard to improvement in endothelial function, the use of statins has been demonstrated to restore endothelial integrity to near normal as soon as the cholesterol levels are improved. There is also evidence that the use of ACE inhibitors or angiotensin receptor blockers can also ameliorate abnormal endothelial function. This is because hypercholesterolemia is associated with an increased expression of Type 1 angiotensin receptors (AT1), and the binding of angiotensin II to the AT1 receptor is associated with an increase in oxidative stress and a reduced bioavailability of nitric oxide. Animal experiments have demonstrated that the use of angiotensin receptor blockers independent of their antihypertensive effect can be associated with an improvement in endothelial function and a reduction in plaque load throughout the vasculature. This has also been demonstrated in a nonhuman primate. Of course, longitudinal experiments in humans are awaited, but it is clear that endothelial function can be improved with the use of angiotensin receptor antagonists and ACE inhibitors. And, a recent study has demonstrated, in humans, that the combination of an angiotensin receptor blocker and a statin is an extremely powerful one for improving endothelial function.

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RENAL DAMAGE AND HYPERTENSION: MECHANISMS OF RENAL END-ORGAN DAMAGE

21

Hermann Haller

HYPERTENSION AND RENAL DISEASE

The kidney is one of the major target organs of hypertension. Franz Volhard and Fahr were the first to demonstrate that the kidneys from patients with hypertension are not normal (1). Early autopsy and biopsy studies showed the presence of preglomerular arteriolar disease (arteriolosclerosis) and tubulointerstitial changes in nearly all patients with hypertension (2,3). The kidney is exquisitely sensitive to a rise in blood pressure (BP): hypertension is much more closely correlated with the presence of arteriolosclerosis in the kidneys (with a frequency of 98%) than with arteriolosclerosis involving other organs (with a frequency of less than 30%). Hypertension is also closely linked to the late phases of renal disease. Hypertensive nephrosclerosis is a common cause of end-stage renal disease (ESRD), accounting for 17% of ESRD in Europe and for 24% cases of treated ESRD in the United States, according to registry data (4,5). However, it remains controversial as to whether benign essential hypertension can cause ESRD (6,7). In an early study, 500 patients with hypertension were followed up until their death; 18% of them developed renal impairment (8). Several longitudinal studies in patients with mild to moderate essential hypertension have also suggested that benign hypertension may lead to ESRD (9–11). In some *post-hoc* analysis of intervention trials, similar observations have been made (12–14).

However, a number of other studies have argued that benign essential hypertension rarely causes renal damage in Caucasian patients (15–17). In most of these studies, patients with benign essential hypertension presenting with normal protein excretion and serum creatinine have been analyzed. In these patients, especially Caucasians, progression of renal disease to ESRD seems to be rare (18). However, only in a few studies has the diagnosis of "hypertensive nephrosclerosis" been confirmed by biopsies (19–25). Analyzing these studies, it seems that more than half the patients with hypertension who present with proteinuria and/or raised serum creatinine progress to ESRD within less than 10 years. In these patients, the kidneys seem to respond more sensitive to the increase in BP or other intrarenal mechanisms of progression have been induced (see below). When discussing the relationship between hypertension, hypertensive nephrosclerosis, and progression to ESRD, it has to be kept in mind that hypertensive nephrosclerosis is often diagnosed clinically only after exclusion of other conditions in patients with chronic renal impairment associated with mild to moderate essential hypertension. It has been shown in two studies that more than 50% of these patients had another underlying cause of their renal impairment (26–28).

MECHANISMS OF HYPERTENSION-INDUCED RENAL DAMAGE

EARLY CHANGES

Hypertension and associated abnormalities in the renin–angiotensin system have long been known to contribute to the rate of progression of renal disease. Much less is known about the initial lesions caused by hypertension and/or an activated renin–angiotensin system in the kidney. A common assumption since the experiments of Harry Goldblatt is that high BP (induced by one-clip renal artery stenosis) leads to extensive glomerular damage and interstitial fibrosis. However, two groups have shown that hypertension initially induces only mild, focal microvascular and tubulointerstitial injury in the hypertensive kidneys (29–31). Furthermore, Johnson et al. observed that identical intrarenal lesions could be induced by administering angiotensin II to rats (32,33). These pathological changes are most likely mediated by hypertension-induced activation of the endothelial cells lining the vascular bed. Continuous pathological activation of the endothelium leads to endothelial dysfunction. Endothelial dysfunction may be the link between the hemodynamic alterations in hypertension and the structural alterations in the kidney.

Endothelial dysfunction has been proposed to be an early event of pathophysiologic importance in the process leading to chronic vascular disease and provides an important link between diseases such as hypertension (or diabetes) and

chronic renal failure (34). Endothelial dysfunction may also explain the high risk for cardiovascular events in these patients. The dysfunction of the damaged endothelial cells is characterized by (*i*) a loss of nitric oxide (NO) and/or increased free oxygen radicals [reactive oxygen species (ROS)], (*ii*) increased adhesion of leukocytes and platelets, and (*iii*) an increase in vascular permeability. All these mechanisms are closely interrelated. Low NO bioavailability can upregulate the vascular cell adhesion molecule 1 (VCAM-1) in the endothelial cell layer via induction of nuclear factor B expression (35). ROS also upregulates the expression of the adhesion molecules VCAM-1, ICAM-1, and E-selectin, which are important in the initiation of the inflammatory process (36). VCAM-1 binds monocytes and T lymphocytes, the first step of invasion of the vessel wall by inflammatory cells (37). In contrast, NO from healthy endothelial cells inhibits leukocyte adhesion (38). Reduction in NO results in induction of a chemokine monocyte chemoattractant protein 1 expression, which recruits mononuclear phagocytes to areas of vascular damage (39). Decreased NO and oxidative excess may activate matrix metalloproteinases (40,41). Since NO also inhibits platelet aggregation, reduced NO contributes to thrombogenicity and to the progression of the vascular disease (42). Thus, endothelial dysfunction with reduced NO bioavailability, increased oxidant excess, and expression of adhesion molecules contributes not only to initiation but also to progression of chronic renal disease and, most likely, worsening of cardiovascular events. Local renal endothelial dysfunction has also been implicated in the pathophysiology of acute renal failure, such as acute ischemic renal failure (43,44).

ISCHEMIA VS. HYPERFILTRATION

These initiating cellular and molecular mechanisms that cause renal microvascular and tubulointerstitial injury involve acute renal vasoconstriction. This observation led to the hypothesis that the renal vasoconstriction causes the early injury in hypertension-induced renal injury. This vasoconstriction could be induced by a disturbed balance of endothelial vasodilators and vasoconstrictors. A decrease in the intrarenal level of NO may occur, both as a result of its local inactivation by oxidants and as a result of loss of its enzyme, NO synthase (44,45). ROS may be produced by the adherent and infiltrating leukocytes, enhanced through angiotensin II stimulation of the NADPH oxidase pathway or generation of xanthine oxidase in the ischemic renal tissues (46). Renal vasoconstriction results in intrarenal ischemia, particularly in the outer medulla, which already exists in a state of borderline hypoxia because of countercurrent circulation and the high consumption of oxygen by tubular epithelial cells in the thick ascending limb of Henle's loop (47). Renal ischemia upregulates the expression of leukocyte adhesion molecules and induces leukocyte infiltration, thereby increasing the above described mechanisms (48). Chronic hypoxia also stimulates the proliferation of tubular and interstitial cells, extracellular matrix synthesis, and the generation of cytokines (48).

In contrast to this "ischemia" hypothesis, Brenner and others have developed a model whereby the local increase in glomerular pressure through the activation of the renin–angiotensin system is the main culprit in the induction of glomerulosclerosis and chronic renal disease in hypertensive patients (49). Anderson et al. postulated that increased glomerular capillary pressure is a key mediator of progressive renal sclerosis in a self-perpetuating vicious cycle, whereby nephron loss due to sclerosis (or other mechanisms) further increases flow and pressures in the remaining glomeruli. This increase in glomerular pressure augments and perpetuates renal injury. Importantly, intraglomerular pressure can be modulated differentially from systemic BP. Anderson et al. showed that angiotensin-converting enzyme (ACE) inhibition confers superior protection against progressive sclerosis compared with non–ACE-inhibitor antihypertensive treatment in an experimental model. Although both interventions normalized systemic pressures, only ACE inhibition decreased glomerular pressures, which remained high when systemic BP was controlled to a similar degree using antihypertensive medications other than ACE inhibitors, that is, "nonspecific therapy." However, the model of glomerular pressure and its close relation with glomerulosclerosis has been challenged by others (50). Which mechanism is actually active in individual patients or patient groups is yet unclear. However, since inhibition of the renin–angiotensin system has such an eminent effect on the progression of hypertension-induced glomerulosclerosis it is likely that the renin–angiotensin system can either have (*i*) an effect on glomerular pressure, (*ii*) enhance the mechanisms of endothelial dysfunction, or (*iii*) directly contributes to the sclerosing mechanisms by stimulating growth factors directly (51). Arteriolopathy may result when a vasoconstrictive agent stimulates the proliferation of smooth-muscle cells directly or indirectly, through shear-stress-induced endothelial-cell activation (52,53). Angiotensin II appears to be one of the key mediators in such a process. Evidence of local activation of the renin–angiotensin system in the hypertensive kidney can be seen in the upregulation of ACE at sites of interstitial injury and by the expression of angiotensin II by infiltrating T cells and macrophages (48,54–56). Intrarenal endothelin-1, a potent vasoconstrictor, is also generated in the hypokalemia model and the model based on angiotensin II infusion (57). In addition, renal injury stimulates renal afferent nerves that can activate the central sympathetic nervous system (58). The proliferation of smooth-muscle cells and mesangial cells also appears to be mediated in part by platelet-derived growth factor. A finding consistent with these data is the expression of the receptor for platelet-derived growth factor in arteriolar lesions in the kidneys of patients with hypertension (54). Finally, in models in which the initial injury is accompanied by increases in BP, pressure-mediated injury to arterioles may also contribute to the vasculopathy.

RENAL INJURY, HYPERTENSION, AND MICROALBUMINURIA

Increased pressure, ischemia, and endothelial dysfunction lead to the progressive damage of the vessel wall with hypertrophy, cell proliferation, and cell death. Within the glomerulus endothelial dysfunction leads to disturbances of podocyte function resulting in the hypertrophy of the basal membrane. A clinical finding in hypertensive patients at this stage of hypertension-induced glomerulo- and interstitial-sclerosis is microalbuminuria. Microalbuminuria in these conditions seems to be a disorder of the capillary wall in the glomerulus, with transcapillary escape of albumin. It is therefore intriguing to assume that endothelial dysfunction parallels or contributes to albuminuria. In diabetes, endothelial dysfunction has been correlated with microalbuminuria and may precede

its development (59). In hypertension, several studies have suggested that microalbuminuria may reflect endothelial dysfunction (60). However, one study did not confirm the association in hypertensive subjects (61). In another study in seemingly healthy subjects, microalbuminuria but not endothelial dysfunction correlated with cardiovascular risk factors, suggesting that microalbuminuria may precede endothelial dysfunction (62).

HYPERTENSIVE NEPHROSCLEROSIS

Further progress of hypertensive renal disease leads to increased nephrosclerosis, with accumulation of matrix molecules in the glomerulus, the vascular wall, and the interstitium. At this stage, albuminuria contributes to the increased accumulation of interstitial matrix. Tubular cells are activated by binding the pathological amounts of protein in the tubular lumen. The activation of the epithelial cells leads to dedifferentiation accompanied by increased expression of matrix molecules.

In the glomerulus, the increased sclerosis is preceded and coupled to increased mesangial proliferation. The close association between glomerular enlargement and glomerulosclerosis likely reflects the actions of multiple factors on glomerular cells, with responses of increased matrix, hypertrophy, and proliferation often occurring in concert. Thus, increased glomerular size is a sign of a growth response to hypertension-induced factors that often also lead to increased matrix accumulation, the hallmark of sclerosis. Although the sclerotic glomerulus appears acellular and "dead," cell turnover continues; thus, even at advanced stages of sclerosis, modulation of cell growth and consequent regeneration can occur (63). Glomerular growth is influenced by numerous cytokines and hormones, including angiotensin II. The angiotensin II type 1 receptor mediates cell hypertrophy and/ or hyperplasia, and is widely expressed in the kidney, including mesangial, glomerular visceral epithelial, endothelial, and vascular smooth-muscle cells (64). Thus, treatment with antagonists of the renin–angiotensin system may provide additional benefit at later stages of the hypertensive renal disease.

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Diagnosis

SECTION 5

BLOOD PRESSURE MEASUREMENTS 22

Jean-Michel Mallion, Denis L Clement

A. OFFICE BLOOD PRESSURE

INTRODUCTION

Excluding invasive measurement methods, the principle of non-invasive blood pressure (BP) measurement has not changed over time (1–3). It is based on fitting a cuff containing an inflatable bladder around the arm and inflation of the cuff halting blood flow in the subjacent artery. The inflatable bladder is connected to an inflation system and a manometer which measures the pressure in the cuff.

This procedure assumes that the pressure in the cuff is equal to that in the compressed artery (which assumes perfect transmission of forces through the tissues separating them). However, the arterial wall may be sclerotic or the volume of soft tissue may disrupt transmission.

It is based on arterial vibrations, induced by the difference in blood flow, caused by the pressure gradient between systolic and diastolic beats, which are sources of systolic sound. These sounds described by Korotkoff and comparable to that made by a fabric when it is suddenly stretched, like a flag flapping in the wind, vary with the flow regime and disappear when there is no more stress.

The technique has been the subject of recent reviews and only a summary of the technique is presented here (4,5).

MEASUREMENT METHODS

AUSCULTATORY METHOD

This was first described by Korotkoff in 1905, and is still used as the reference. As its name indicates, it refers to an analysis of sound variations using a stethoscope or microphone connected to an automatic measuring device. After inflating the cuff to a pressure at which blood flow is halted in the artery, sounds are monitored as the cuff is deflated. According to Korotkoff's recommendations, five phases can be described—phase I: a clear, repetitive sound, coinciding with perception of a palpable pulse; phase II: sustained, soft sound; phase III: shorter louder sound; phase IV: muffled soft sound; phase V: sound disappears.

With reference to invasive methods (intra-arterial puncture) phase I of Korotkoff's sounds corresponds to intra-arterial systolic pressure. Phase V (disappearance) gives intra-arterial diastolic pressure to the nearest 2 mmHg. Phase I defines systolic or maximum pressure, phase V diastolic or minimal pressure.

In certain specific cases, when sounds are difficult to hear, or when they are perceived down to zero pressure, we refer to phase IV for the minima.

The "auscultatory hole" corresponds to a disappearance of phase II and phase III sounds. This may lead to underestimating systolic pressure or overestimating diastolic pressure.

In the event of irregular heart rate (extrasystolic beats, atrial fibrillation), the intensity of phase I and/or phase V sounds may vary, which can make it difficult to determine systolic or diastolic pressure.

When it is difficult to perceive these sounds, the oscillometric method may be used.

OSCILLOMETRIC METHOD

Oscillations occur in the bladder during deflation; begin in slightly before systolic arterial pressure is reached and disappear in just after diastolic pressure is reached. Systolic and diastolic arterial pressures are assessed with reference to automatic methods of calculation which may vary according to the device used, thus they must be validated.

DEVICES

Cuff and measuring devices must be considered successively.

CUFF

The cuff contains an inflatable bladder of appropriate dimensions for the circumference of the arm; it is important for the pressure exerted in the cuff to be distributed evenly across

the artery. If the bladder is too narrow the pressure is overestimated if too large it is underestimated.

In practice, the width of the bladder must be two-thirds of the length of the arm and its length two-thirds of the circumference of the arm. This neccessitates a cuff for small arms (children), one for normal arms and one for large arms (obese or heavily-muscled patients). An average cuff must have an inflatable bladder 13 to 15 cm wide and 30 to 35 cm long. There is now a cuff (tricuff) with three inflatable bladders, automatically adapted according to arm circumference (4).

The inflation system can be manual or automatic using either a bulb (manual inflation) or a pump or gas cylinder (automatic method). The fall in pressure during deflation must be slow and controlled by 2 mmHg per heart beat.

MEASURING DEVICES

- *Mercury column manometer*: In some countries mercury is now prohibited because of its toxicity (rapid evaporation at 20–25°C). Using a mercury manometer requires respect of a certain number of rules: checking the level of mercury, which must be set to zero; ensuring that the column is vertical and indirect communication with the atmosphere.
- *Aneroid manometer*: This measures pressure mechanically so it is important to calibrate it regularly to a mercury column. It is less accurate than the mercury manometer which is accurate to 2 mmHg.
- *Electronic devices*: These generally use the oscillometric method, but the auscultatory method is still used with the possibility of switching to an oscillometric method when the pressure is incorrect. The devices should have been validated according to the British Hypertension Society (BHS), the Association for the Advancement of Medical Instrumentation (AAMI), or the European Society of Hypertension (ESH) protocols (4).

EXPRESSION OF RESULTS

Depending on the device used, results are expressed in different forms. The expected minimum must be systolic arterial pressure, diastolic arterial pressure and heart rate. With electronic devices, one must have error codes (sensors incorrectly positioned, inadequate inflation, battery status, etc.), and data printout with the date and time of measurement.

MEASURING CONDITIONS

It is important to differentiate between measurements taken at rest in the doctor's clinic or at home and measurements taken under conditions of physical or psychosensory stress, particularly home or ambulatory measurements outside the doctor's office or hospital.

MEASUREMENTS TAKEN AT REST

At the clinical measurement the doctor must be well-trained in the technique which requires good sight and hearing. This includes possession of a good stethoscope, visual correction if necessary and, if this is the case, to be positioned in front of and level with the mercury column. The measuring conditions and circumstances are detailed and recalled in the latest recommendations of the working group of the European Society of Hypertension (4); subjects must be seated on a chair with back support, the arm first relaxed and positioned at heart height (supported if necessary). In some specific cases, measurement can be taken with the patient supine. A standing measurement is useful to check orthostatic hypotension, recorded when the patient stands up and again a few minutes later. The accuracy of the reading must be to the nearest 2 mm, the measuring unit being millimeters of mercury (mmHg), even though international recommendations have used the kilo Pascal (1 kPa = 7.5 mmHg).

Measurement must be taken after 5 min of rest, the patient must not have smoked or ingested caffeine during the 30 min before the examinations. Two measurements or more must be taken 2 min apart and the mean of these is used as the result. If there is a difference of more than 5 mmHg between the two measurements, more must be taken and averaged. Measurements must be taken in a calm environment, with the patient relaxed, not exposed to cold and with the bladder emptied. BP must be measured on both arms to detect anisotension. If there is a difference of more than 20 mmHg in systolic measurement further investigation is needed to detect an arterial anomaly. It is recommended to use the measurement from the arm giving the highest pressure in this case.

DEFINITION AND CLASSIFICATION OF BP LEVELS

The continuous relationship between the level of BP and cardiovascular risk makes any numerical definition and classification of hypertension (HT) arbitrary.

Therefore, 2007 ESH–European Society of Cardiology (ESC) classification (5) has been retained in Table 22.A1, with the reservation that the real threshold for HT must be considered as flexible, being higher or lower based on the total cardiovascular risk profile of each individual. Accordingly, the definition of high normal BP in Table 22.A1 includes values that may be considered as "high" (i.e., HT) in high-risk subjects or acceptable in individuals at lower risk.

When a patient's systolic and diastolic BPs fall into different categories, the higher category should apply. Isolated systolic HT can also be graded (grades 1, 2, 3) according to systolic BP values in the ranges indicated, provided diastolic values are <90.

CONCLUSION

BP measurement remains the determining factor in defining HT. In daily practice, measurement in the practitioner's office is the reference used for diagnosis and follow up. According to the classification established, the upper normal value is below 139 mmHg for systolic and 89 mmHg for diastolic pressure. HT cannot be confirmed by a single high measurement or at a single consultation. In addition, it should be remembered that other possibilities of measurement are now available, particularly self BP measures and ambulatory measurement: self-measurement at home should remain under medical control; exercise tolerance tests, often using an ergometric bicycle,

Table 22.A1 Definition and classification of blood pressure levels (mmHg)

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension (mild)	140–159	and/or	90–99
Grade 2 hypertension (moderate)	160–179	and/or	100–109
Grade 3 hypertension (severe)	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

demonstrate the possibility of cardiovascular adaptation to physical exercise (6).

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B. AMBULATORY BP MONITORING

INTRODUCTION

Ambulatory BP monitoring (ABPM), although initially largely developed for research purposes, has gradually entered standard medical practice, and is now a widely used clinical tool both for diagnosis and treatment of HT.

TECHNICAL ASPECTS

The number of devices available for ABPM continues to increase. Devices are based on auscultatory or, more frequently, on oscillometric methods or both. To be acceptable, all devices must be validated. The Working Group on ABPM of the European Society of Hypertension has described a protocol ad hoc (1). The list of instruments is available on http://www.dableducational.org.

All clinically used ABPM devices only allow intermittent sampling, but it is advised not to exceed 20 to 30 min. Usually, longer sampling intervals are used at night to avoid sleep disturbance, although this may cause errors in estimating average night-time BP (2). Before starting monitoring, BP at both arms should be compared to ensure that differences do not exceed ±5 mmHg. Recordings should be performed during a regular working day but avoiding strenuous exercise; unusual events and quality/duration of night sleep should be noted (3). An example of 24 h recordings is given in Figure 22.B1 (4).

DIAGNOSTIC USE

Evidence is available that ABPM values correlate better with organ damage than office figures. Also, they are more predictive of cardiovascular risk both in general and in hypertensive populations (5,6); moreover, ABPM is more closely related to treatment-induced regression of organ damage like left ventricular hypertrophy (7). Finally, large scale studies on treated hypertensive patients have shown that cardiovascular morbidity and mortality over 5 years or more is significantly better correlated to ABPM even after adjustment of all possible confounding factors, including office pressure (4). These finding justify the increasing use of ABPM for diagnostic purposes (8). However, it should be kept in mind that "normal" ABPM values are lower than the corresponding office values: the upper normality limit for 24 h is set at 125/80 mmHg. approximately corresponding to 140/90 mmHg at the office (9).

ISOLATED OFFICE (WHITE COAT) HT

ABPM has allowed identification of a condition characterized by a persistently elevated office (>140/90 mmHg) and a normal ambulatory BP (125/80 mmHg) (10). Isolated office,

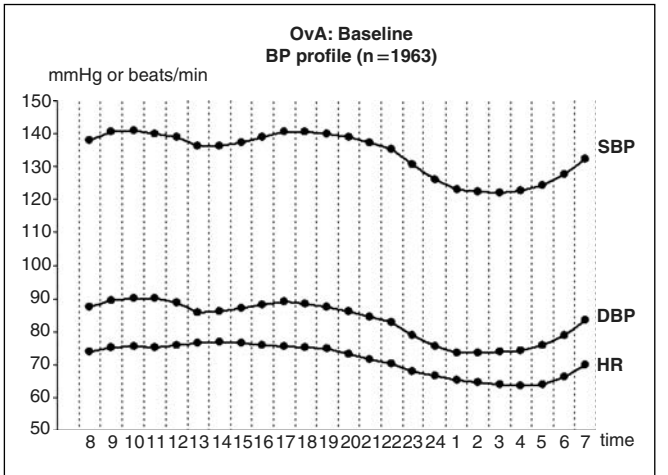

Fig. 22.B1 Example of 24-h recording. This curve is the mean of the curves obtained in the 1,963 patients included in the OvA study. *Abbreviations*: HR: heart rate; SBP and DBP, systolic and diastolic blood pressures. *Source*: From Ref. 12.

or white coat, HT occurs in about 10% of the population and may carry a lower cardiovascular risk than the condition characterised by elevation of both an office and an ambulatory BP (4); still, data remain conflicting especially about proneness to future HT; therefore, it still is uncertain whether it represents a truly innocent phenomenon (4,11–17), and management of such patients should be done with caution. Lifestyle adaptation should always be implemented; antihypertensive drugs should be used in case of organ damage or a high cardiovascular risk profile. In all cases, a close follow-up is recommended.

MASKED HT (REVERSE WHITE COAT HT)

More recently an opposite BP pattern has been described, i.e., normal office pressure but elevated ambulatory pressure (15,16). As the elevated pressure cannot be discovered by routine office readings and only by ABPM, it was called "masked" HT (18).

Many aspects of this phenomenon are not well known yet. In the PAMELA study, a population study on 3200 Italians, its prevalence was about 9% (10). Although its reproducibility is not entirely clear yet, there is evidence that masked HT is not an innocent phenomenon; patients show an increased left ventricular mass and carotid atherosclerosis, close to "true" hypertensives (19). Recent epidemiological prospective studies suggest that it might be an independent predictor of cardiovascular morbidity (14,20–22); in the PAMELA study (19) there was a trend in progressive increase of cardiovascular mortality when comparing normal subjects and those with masked HT, and figures were very close to those obtained in isolated office HT, regardless of whether 24 h or home BPs were used.

Masked HT poses a number of challenges, not in the least at practical level (23); it opens an argument that, in some patients, ABPM should be made even if office pressure seems to be under control.

There is no consensus yet concerning treatment of masked HT. However, in light of the above-mentioned arguments, it seems likely that these patients should be treated with antihypertensive drugs, certainly in case organ damage has been demonstrated.

CLINICAL USE OF THE DIFFERENT PARTS OF 24-H BP RECORDINGS

Several parts of the 24-h BP profile have been given clinical importance.

MORNING BP RISE

In many patients, there is a steep rise in BP when shifting from the asleep to the awake state. The only evidence for this phenomenon to be of clinical importance stands on its association with a morning peak incidence of coronary heart disease and stroke, although in both instances also other factors play a role (24). Clinical experience has shown that antihypertensive treatment often is unable to fully control early morning peaks. Nevertheless, it seems advisable to ensure that antihypertensive treatment effectively controls BP after getting up without escape.

DIPPING AND NON-DIPPING

BP falls at night but more so in some subjects. This has led to the subdivision of hypertensive patients into dippers and non-dippers, based on a nocturnal BP fall of, respectively, greater or less than 10% of the daytime values (24). This definition is not based on very solid grounds because the magnitude of night-time pressure decrease is poorly reproducible (25) and the 10% cutoff value is arbitrary.

Yet, several studies have shown night-time BP to be related to organ damage and cardiovascular risk (26–30) and to a superior prognostic value (5); still, in most hypertensive patients, day and night BP values and changes with treatment are closely related (7,25,30); this was also confirmed in the long-term prognostic OvA study (4). In clinical practice ABPM definitely should include night recordings and treatment should ensure that both day and night-time BP values are reduced. No reduction at night or even an increase (after adjustment for quality of sleep) may suggest significant vascular organ damage or autonomic dysfunction. On the other hand, attention should also be given to subjects with a very pronounced reduction in night-time pressure (>20%, so-called extreme dippers) because such may lead to brain under-perfusion, particularly if a further BP fall is produced by treatment (31).

BP VARIABILITY

Evidence is available that for a given increase in BP, organ damage and prognosis are worse in the presence of a greater than 24-h BP variability (32–34). However, this measure is still in a research phase and not ready for clinical use. Moreover, it has been proven very difficult to influence significantly the amplitude of the variations by antihypertensive treatment (35).

EFFICACY OF ANTIHYPERTENSIVE TREATMENT

ABPM has drastically improved the ability to assess the efficacy of antihypertensive treatment both in clinical studies and in medical practice (36,37). In clinical trials advantages such as a greater reproducibility, the lack of placebo effect and the absence of an alerting-dependent pressure response (38) make ABPM the ideal approach to quantify the efficacy of antihypertensive treatment. The technique also enables to study the relationship between drug intake and BP changes using indices such as the trough-to-peak ratio and the smoothness index (38). However, our knowledge on ambulatory BP is still limited concerning the values to be reached by treatment; this is in contrast to the office BP targets from which the protective properties have been well defined in the past.

INDICATIONS FOR 24-H BP RECORDINGS

Besides defining the real 24-h BP profile, there are several bits of valuable information that can uniquely be obtained by ambulatory recordings (Table 22.B1). These include, in first instance, the particular patterns of BP, such as isolated

Table 22.B1 Indications for ambulatory blood pressure recordings

Particular patterns of blood pressure (such as isolated office hypertension, masked hypertension, etc.)
Increased blood pressure variability
Resistant hypertension
Evaluation of efficacy of antihypertensive treatment
Low blood pressure
Research

office HT, masked HT, dipping, or no dipping of pressure. Each of these has clinical relevance (see above) and are by themselves a solid argument to perform 24-h recordings in every newly discovered hypertensive patient (39).

Ambulatory recordings can provide objective documentation on increases in BP variability, as suspected by large differences in consecutive office recordings. Ideally, variability should be analyzed by intra-arterial recordings; however, non-invasive ambulatory recordings can offer, at least partially, an acceptable alternative.

Sometimes, patients are labeled as "treatment resistant" in HT clinics; a non-negligible part of these patients show at the time of 24-h recordings, BP values are much lower than the office readings, illustrating a much more satisfactory response to treatment.

Ambulatory recordings provide an excellent tool to evaluate the characteristics of drug or non-drug treatment. The information obtained includes the effect on mean BP, duration of the antihypertensive effect, influence on the different parts of the diurnal curve. Also the absence of a placebo effect can facilitate the study protocol.

A number of patients presenting with fatigue, syncope, etc., in fact suffer from episodes of low BP. Both orthostatic and sustained low BP can elicit such symptoms. The episodes of hypotension cannot be detected by office readings; ambulatory recordings are very helpful in this respect.

Finally, ambulatory recording is a unique tool for research. Many aspects of BP behavior, including study on the mechanisms of BP control, can be studied using 24-h recordings.

COSTS AND QUESTIONS ON REIMBURSEMENT

In the above paragraph, the widespread information that can be obtained by 24-h recordings is highlighted. Still, in most countries, ABPM is not reimbursed yet or only in a few very specific conditions. It is remarkable that it remains as such even after many years of experience with the technique that presently, has come to age, is well accepted by the vast majority of the patients and can avoid many problems of false or incomplete diagnosis. Also ambulatory recordings allow for a much better definition of treatment with antihypertensive drugs and can by doing so, substantially safe costs and compensate for the expenses. Governmental and insurance responsible leaders should be advised to reconsider their position in this respect.

CONCLUSIONS

ABPM has opened new horizons for HT research as in clinical practice; its increasing use has had a positive impact on the management of HT. Ambulatory recordings of BP should be implemented provided validated facilities are available. Further research is needed on several issues such as ambulatory BP variability, the targets to be reached by treatment, the clinical importance of isolated clinic and of masked HT and the relative value of separate parts of the 24-h BP curve.

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C. HOME BP

INTRODUCTION

In recent years the development of self-measurement has become widespread. The first description of home BP (HBP) measurement was by Brown, around 1930, when he described the use of the technique in a young man over a period of 3 years. Other key dates were the integration of the sphygmomanometer and cuff in 1967 and, in 1975, the first electronic sphygmomanometers for self-measurement. In 1985, the first oscillometric measure was described, and finally, in 1992, the first measurements at the wrist and in the finger were possible.

It is of interest to examine the elements which led to the use of home measures instead of surgery-based measures or other measures such as ABPM.

These elements include the discovery, in 1940 by Ayman and Goldshine, that the BP levels at home were lower than those found in surgery. The cumulation of studies over the years, which have revealed such data, can yield interesting information of a diagnostic, prognostic, and therapeutic nature.

The advancement of technology with the appearance of reliable automatic devices that are easy to use by the patient and relatively low priced explains, for one part, the large utilization of this type of measurement.

DEFINITION

Self BP measurement can be defined as the measurement by the subject of BP in a conscious and voluntary manner. This measurement is usually carried out at home and is, thus, called "home BP". Of course, BP can and should be measured by the patient in other circumstances.

TECHNIQUE—MEASUREMENT CONDITIONS

Home BP should be considered as a medical act, which means that the doctor and the patient must respect certain recommendations. Some of these recommendations are the same as for taking BP readings in the surgery and others are elated to the intervention of the subject and will render the technique inapplicable if there is not a real education of the subject (1–7).

MEASUREMENT TECHNIQUE

The types of monitors available for BP measures (SBPM) include mercury column sphygmomanometers, aneroid manometers, and electronic semi-automatic or automatic devices.

The automated devices available all use the oscillometric technique in clinical practice. There are two types of devices that measure BP on the upper arm and the wrist.

Upper arm devices, which measure the BP in the upper arm (brachial artery), appear to be the most reliable; therefore, their use is recommended. The recommendations that apply to BP in general are applicable to these automated devices.

Wrist devices that measure BP at the wrist are not recommended because of the inaccuracies that occur due to measurement distortion with the peripheral site. There are reservations about the correct use of these devices, especially with regard to the correct placement of the occluding cuff at heart level, and the correct position of the hand (wrist flexion or hyperextension). Despite these limitations, automatic wrist monitors have become quite popular due to their convenience for patients.

It is necessary to use validated devices. In this regard, the working group of European Society of Hypertension regularly published lists of validated devices. The list is accessible by internet on the website. Recently, the telephone transmission of self measured BP has been proposed.

MEASUREMENT CONDITIONS

Whatever the objectives of the measurement, it is necessary to carry out the readings under strict conditions as follows: before meals, after 5 min rest, in a calm and relaxed environment, without alcohol or tobacco; after the placement of the

cuff, the arm should be situated at the level of the heart (below this level the BP is overestimated and vice versa).

The ideal position, which should always be recommended to the subject, should be seated, with the arm extended and resting on a table and, if the cuff cannot be inflated automatically, then it should be placed on the opposite arm to that which inflates the cuff.

The number of measurements that maximizes the prognostic value of home BP is not known. However, for clinical purposes, two measurements in the morning and one in the evening for at least three working days are advised. The frequency may vary according to the severity of HT and the need for adjustments of pharmacological treatment. All recorded data except those from the first day should be used to calculate the mean home BP (8,9).

The instruction of the patient is a medical act and thus implies a level of competence and investment of time. It should be carried out by a doctor or a nurse and should include some simple explanations about the BP and its variations and consequences as well as the ideal conditions of measurement and the explanation of the equipment to use.

The results are adequate when a sufficient number of recordings have been acquired and thus it is recommended that three successive measures be obtained at each time. At least two measurements during the day before meals and between 6:00 and 8:00 in the morning and between 6:00 and 8:00 in the evening are recommended.

During a week with two estimations per day at least 3 or 4 days should be completed taking into account days of activity and of rest.

Over longer periods (months or years) this frequency should be adapted in relation to the clinical state of the subject. When the diagnosis of HT is present, or when antihypertensive treatment is commenced, the frequency could be once or twice a month, while it could be once or twice every 3 to 6 months in subjects without any particular diagnostic problem or in whom the treatment is well tolerated.

It is very important that the results of systolic BP and diastolic BP and of heart rate be written into a record book and shown at each consultation, which is kept by the patient.

REFERENCE VALUES

There is limited data available for SBPM threshold values based on cardiovascular outcome.

The data from studies to date have been subject to a meta-analysis performed by Thijs et al. (10) and refer to 17 studies of which 9 referred to normotensive populations. The results of this meta-analysis need to be interpreted with particular caution for a variety of reasons. The studies were carried out on very varied populations, including volunteers, students, or occupational groups, and, likewise, the equipment used varied a lot with automatic machines, in some cases using auscultatory or oscillometric methods. The values accepted for upper values differed little whether calculated by parametric or non-parametric methods and Thijs et al. (10) accepted 135 to 137 mmHg for the SBP and 86 to 89 mmHg for DBP. The reference and threshold values proposed in the recommendations of the ESC 2003 are 135/85 mmHg (4). The values found are fairly similar to those obtained by ambulatory recordings over the daytime (11,12).

In any case, the following facts are crucial (12–14): that BP at any age is higher in men than women, increases with age, and is also higher in the morning than the evening, as well as in the winter compared with the summer (15). These values are lower than those obtained during surgery (140/90 mmHg).

This difference between the measures at home and in the surgery is found in normotensives and hypertensives. It does not seem that patients classed as anxious (outside formal scales) are more susceptible to having higher values in surgery. For elderly subjects, the increase with age is less important with self-measurement than in the surgery but lower than ambulatory recordings. In any case, a significant correlation is found between the values measured in surgery and in self-measurement and also between self-measurement and ambulatory values.

The reproducibility of self-measurement is satisfactory over a short period both for measures carried out at home and at work (16). Over longer periods of about a year, the reproducibility of measures outside surgery is greater than measures during surgery (17).

DIAGNOSTIC DATA

MILD OR MODERATE HT

It is important to clearly identify patients with mild to moderate HT. The most recent recommendations indicate that the diagnosis of HT cannot only be retained in a consultation. At consultation, two or more readings 2 min apart should be averaged. If the first two readings differ by more than 5 mmHg, additional readings should be obtained and averaged. These measures should be repeated at least three times over a period of 1 month.

In practice, these recommendations are not always easy to follow because of the shortage of doctor's time and because of patient indisposition, and, thus, self-measurement seems to be an interesting alternative in a number of cases to confirm genuine HT (18–21).

WHITE COAT OR ISOLATED HT

White coat HT is an entity defined as the presence of elevated BP in the doctor's office, but normal BP outside this setting. There is a current consensus that defines white coat hypertensives as those subjects who, in the office, have BP values $>140/90$ mmHg and outside the office at $<130/85$ mmHg.

Some authors prefer ambulatory measures over the daytime to define reference values outside the office because of the possibility of numerous measures over prolonged periods under resting conditions and during periods of activity.

The use of self-measurement at home is also useful for identifying the subject with a white coat HT. It should be noted that it was by this means that the white coat effect was first identified and in this context that the "BP lowering effect of home recording" was noted (22–25).

As in the case of ABPM, the frequency of white coat effect is variable and depends on the reference values used. For example, in the Tecumseh study, the reference values are elevated and the white coat HT occurs in 7% of that population, compared to the much larger incidence (30%) in the paper by Nagai, where the reference values for home BP are low at 131/79. It is clear that one of the major indications for home measurement is the identification of white coat HT,

while the use of ABPM has other advantages and applications, such as a disturbance of the diurnal rhythm of BP.

Generally, there is a good concordance between BP data from ABPM and self-measurement results in 80% of subjects (20). One cannot expect identical results from the two methods, however, as they are performed under different conditions and, in particular, self-measurement is carried out after 5 min rest in a seated position, while ABPM recording can be in the upright or seated position as well as during rest or activity.

MASKED HT (REVERSE WHITE COAT HT)

The phenomenon is characterized by the presence of normal clinic BP (<140/90 mmHg) and elevated HBP values (≥135/85 mmHg) (26,27).

The prevalence is diversely appreciated between 8% and 45%. Patients had cardiovascular risk factors nearer to the hypertensive subjects than normotensive subjects. Target organ damage is more frequently found (28,29).

The studies of morbidity and mortality indicate cardiovascular risks identical to those with true hypertension (30–37) (Figure 22.C1). These findings justify the systematic practice of home BP measurement, more specifically in subjects with BP values near the threshold in clinic.

HT AND PREGNANCY

The occurrence of hypertensive disorders in pregnancy is common. HT is one of the major causes of morbidity and mortality for the mother and the baby, directly accounting for 15.5% of maternal deaths (39). Several attempts of classification have been made in order to differentiate these disorders and to more easily identify patients at risk. Currently, there is no means of detecting this problem at an early stage and, once the diagnosis of HT has been established, there is no means of quickly identifying which mother is going to develop pre-eclampsia or eclampsia. The only possibility is regular and close supervision in order to reduce the risks by early intervention. In this situation, the use of self-measurement could reduce the frequency of visits and hospitalizations while motivating the expectant mother with her greater liberty. By this means, BP can be controlled daily, but these measures should be associated with parallel measures of weight as well as the daily estimation of proteinuria by dipstick (38–40).

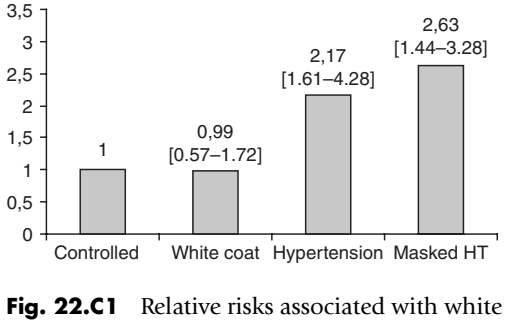

Fig. 22.C1 Relative risks associated with white coat and masked hypertension (HT) (reference: controlled hypertension), from SHEAF study. *Source*: From Ref. (35).

PROGNOSTIC DATA

The data from BP measurement in the office have been widely useful for the evaluation of morbidity and mortality. The use of ambulatory measurements or self-measurement is no longer controversial. Investigation of the effects of BP measured in the office does not show any correlation between the level measured and the end-organ effects on the kidneys or heart, such as left ventricular hypertrophy or microalbuminuria. In contrast, such correlations have been found in numerous studies investigating BP by ambulatory measures, but few studies using self-measures have been performed.

With regard to the cardiovascular prognosis, the data we have collected are those of the Osahama study (41,42) and the SHEAF study (26–31). From these studies, it appears that HBP measurements have a better prognostic accuracy than those of office BP measurements.

COMPLIANCE

All the studies examining the level of compliance of hypertensive subjects are in agreement that, after a year of follow-up, on average only 50% of subjects regularly take their treatment. This poor compliance is particular to hypertensive populations perhaps because of its seeming innocuousness. Patients can pass many years without any obvious effects and are thus unmotivated in regular consumption of tablets, which could cause negative side effects.

The analysis of predictive factors for non-compliance, such as age, sex, social class, level of education, intelligence, etc., is no doubt of interest but does not provide a solution to the problem. The use of self-measurement is inevitably to encourage compliance but the few studies carried out are relatively old and based on non-automated measurement systems (43). These studies have shown an improvement in compliance related to a better awareness of the disorder and the antihypertensive effects of the doses prescribed. To date there is no format evidence that this improvement in compliance leads to a better BP control. A study by Myers (44) draws attention to the possibility of reporting bias with certain subjects recording only the BP values "of interest" and thus it is recommended to use machines with a memory. Teletransmission may also be used for self-measures of BP. This can be done directly by modem or by a system of exchanging information, also recording other elements such as compliance, the consumption of medications, and the presence of possible secondary effects. This mode of approach seems to lead to a better compliance and to an important reduction in BP in non-compliant subjects (45).

THERAPEUTIC APPLICATIONS AND THERAPEUTIC TRIALS

THERAPEUTIC APPLICATIONS

In daily practice, the interest of this tool derives from the data acquired previously: the elimination of imprecision and operator errors, plus the possibility of multiple measures during the day or over time in reproducible conditions of rest or activity; the demonstration of a white coat effect,

which could lead to a diagnosis of HT and to the introduction of treatment; the uncovering of falsely resistant HT when treatment is incorrectly given to patients with white coat HT; the possibility of improving compliance in patients who accept the principle of self-measurement and thereby are more implicated in the follow up of their treatment as they can appreciate immediately the effect on their BP are benefits to be achieved. Ultimately, one could envisage that the patient could learn to modulate his own treatment according to self-measurement results but, in such a case, care has to be taken that the situation is correctly managed.

THERAPEUTIC TRIALS

These reflections above are also valid in the context of clinical trials, but with the proviso that the doctor would not be led to overestimate the benefits since the results are not blinded. However, the use of self-measurement could improve the precision and the sensitivity of therapeutic studies by reducing the standard deviation and the mean difference and improve the correlation coefficients between BP measures. By decreasing the variability of the BP values obtained, the sample size of HT trials to detect even minor BP changes can be reduced (46–50).

Even if the number of trials using self-measurement is limited, the results are concordant on a number of points. Studies are practically possible even involving a large number, such as 1,000 or 4,000 patients (30). The use of HBP measurement increases the power of co-operative trials, allowing one either to study fewer subjects or to detect a smaller difference in BP. The use of measures taken in the morning and the evening allows some assessment of the peak trough effects if the time of the recording is well noted as well as the time of taking the medication. Thus, the duration of action of a treatment can be better appreciated. So we should consider that this type of measure could be a good choice in chronopharmacology studies in HT.

At the dawn of the 21th century one cannot discuss medical innovation without attention to cost. Theoretically, self-measurement should reduce costs because of more precise and reproducible BP values by allowing repeated measures. This should reduce the number of consultations and allow better use of therapeutic interventions with a more precise assessment of effects and evolution. Several studies have confirmed this impression.

CONCLUSION

Self-measurement of BP at home has developed enormously in recent years and has been, in large part, driven by technological development of uncumbersome, lightweight, automatic electronic devices. Nonetheless, it is crucial that the technique be recognized as a medical intervention and that the doctor needs to be involved at several levels: advice on choice of material, decisions about type and conditions of recordings, interpretation of results.

For each of these steps, there now exists precise recommendations and rules. Reference values have been revised and are lower than surgery normal values. The advantages of the technique in diagnosis are well defined: more data are collected than from measurement in the surgery, identification of white coat effect, and masked hypertensive follow up of high-risk pregnancy. As regards to prognosis, currently active studies may yield results, but it already appears that the method is superior to surgery estimates.

Therapeutic applications of self-measurement are varied: verify HT before treatment; repeated, untroublesome measurements for the patient and the doctor; more objective, repeated, and reproducible results in research trials, allowing a smaller population to be studied.

More generally, it seems that self-measurement may lead to better compliance in patients who can adapt to it because of their greater participation in their treatment. This may lead to better BP control. Thus, the technique is about to undergo widespread development, particularly as the technology of the equipment develops.

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BLOOD PRESSURE RESPONSE TO ACUTE PHYSICAL AND MENTAL STRESS

23

Robert Fagard, Guido Grassi

INTRODUCTION

Both physical and mental stressors have been applied in the laboratory to assess the blood pressure (BP) response to stress. Physical stress may involve active physical activity, including dynamic or static exercise, or passive physical stress, such as in the cold pressure test (CPT). Mental stress is evoked via a problem of mathematical, technical, or decisional nature (1). Whereas all of these stressors increase BP, correlations between BP responses to the various stressors are limited (2,3). In addition, laboratory stress tests, in general, do not reflect real life stress (3,4). Nevertheless, the BP responses to these stressors are of interest because they may relate to target organ damage and predict future hypertension and cardiovascular disease.

DYNAMIC EXERCISE

BP AND HEMODYNAMICS

Dynamic exercise involves rhythmic contractions of large muscle groups in dynamic activities and is performed against a relatively constant load (5). Walking, running, cycling, and swimming are examples of predominantly dynamic activities. Laboratory tests usually consist of treadmill or cycling exercise of varying load and duration. BP rises during such activities, and, in general, the BP during exercise is proportional to the BP at rest. As can be seen in Figure 23.1, intra-arterial systolic pressure clearly rises with bicycle exercise in men with a normal BP at rest. In patients with borderline or definite hypertension, the exercise-induced increases in systolic pressures are roughly parallel to the changes in the normotensive subjects (6), with increases of about 50 mmHg from rest to peak exercise. It is noteworthy, however, that the BPs achieved during maximal dynamic effort, such as cycling, can be quite high in hypertensive patients. In a previous study (7), the exercise-induced change in systolic pressure was similar in hypertensive individuals and normotensive individuals at a young age, but the systolic pressure showed a greater increase in older hypertensive patients. It has also been shown that the BP increase at fixed submaximal exercise is somewhat greater in women than in men (8) and less in fit than in unfit individuals (9,10). The changes in intra-arterial diastolic pressure are less pronounced, but the differences in BP at rest persist during exercise (Figure 23.1). Cardiac output (CO) behaves similarly in the three BP groups, and the differences in pressure are clearly related to systemic vascular resistance (SVR)—those individuals with the highest BP at rest have the highest SVR during exercise, which may be explained by structural pathophysiological changes in arteries and arterioles. There is no convincing evidence that the acute exercise-induced increase in BP is harmful, at least not in patients with no ischemic heart disease or other cardiovascular disease.

POSTEXERCISE HYPOTENSION

Kraul et al. (11) were the first to observe an immediate reduction in BP after exercise. These BP reductions below control levels following acute exercise have been termed postexercise hypotension (PEH) (12). Currently, there is a growing body of evidence in the literature that a single bout of aerobic exercise significantly reduces BP during the postexercise period in young, middle-aged, and older subjects (13). Although PEH can be detected in normotensive individuals, it was found to be much less consistent and of lesser magnitude than in hypertensive individuals (14,15). Baseline BP is a significant predictor of PEH, such that men with the highest baseline BP experience the largest postexercise reduction in BP. BP reductions range from 4 to 15 mmHg. It has been shown, by use of ambulatory BP monitoring, that the hypotensive effect of a short-term exercise session may last for up to 22 h (16). Regularly repeated acute bouts of exercise may therefore contribute to BP control in hypertensive patients (17,18).

Significant reductions of BP after exercise have been observed, with relatively low-intensity exercise, at 40–50% of maximal oxygen uptake (16,19). More intense exercise was followed by a more sustained and substantial reduction in BP,

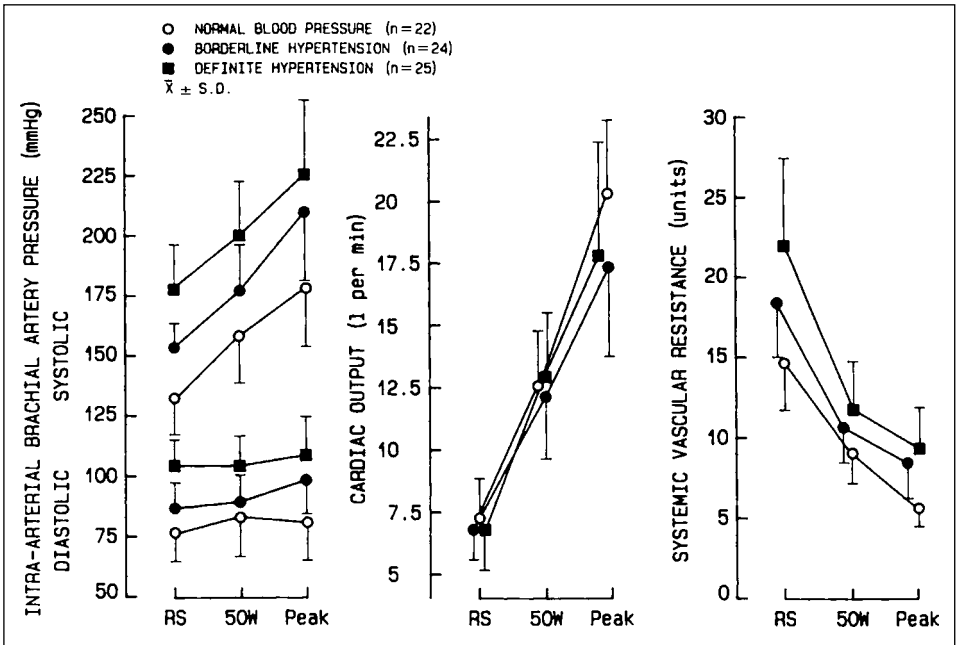

Fig. 23.1 Systolic and diastolic blood pressure, cardiac output, and systemic vascular resistance at sitting resting position (RS), 50 W exercise, and peak exercise (peak) in subjects with normal blood pressure, borderline hypertension, and definite hypertension, according to intra-arterial brachial artery pressure at rest and the 1978 World Health Organization criteria.

according to some authors (20), but not according to others (19). More research is required to define the optimal exercise dose in terms of duration, intensity, and frequency.

ASSOCIATION WITH TARGET ORGAN DAMAGE

There is no unanimity on the association of exercise BP with target organ damage, such as left ventricular hypertrophy, after adjustment for resting BP (21). Systolic BP in normotensives during submaximal exercise (22,23) and during peak exercise (24,25) was not significantly and independently related to echocardiographic left ventricular mass and electrocardiographic indices. These reports include large studies on 4,907 men (22) and on 860 men and 1,118 women (24). The latter analysis of data from the Framingham Heart Study presented several multivariate models. Together with age and body mass index, systolic BP of subjects at rest explained 18% of the variance of left ventricular mass for men and 27% for women; these percentages were similar when peak exercise BP was substituted for resting BP in the equations; that is, 20 and 28%, respectively. In an analysis of 3,742 participants of the CARDIA study (26), reactivity of systolic BP to exercise explained only 3% of the variance in left ventricular mass among white men and 1% among black men ($P < 0.01$), after adjustment for resting BP, weight, and other covariates, whereas the increment in the explained variance was not significant for women. By contrast, Kokkinos et al. (27) reported that the change in systolic BP from rest to submaximal exercise (5 METs) was a strong predictor of left ventricular hypertrophy in prehypertensive individuals. Studies in hypertensive patients did not observe independent and positive relationship of BP at submaximal exercise (28,29) and at peak exercise (25,28,30) with echocardiographic left ventricular mass and electrocardiographic voltages.

PREDICTION OF FUTURE HYPERTENSION

A number of studies have investigated whether an exaggerated BP response to exercise predicts future hypertension. In a population-based study of middle-aged normotensive men, Miyai et al. (31) reported a significant and independent threefold higher risk for incident hypertension during a 4.7-year follow-up period in those with a disproportionate exercise BP response. Contrasting results were reported by Manolio et al. (32) in a population-based sample of 18- to 30-year-old men and women. Individuals with an exaggerated exercise BP response at baseline were 1.7 times more likely to develop hypertension over the next 5 years than were persons with a normal exercise BP response, but the association was no longer significant after multivariate regression analysis. In middle-aged normotensive subjects from the Framingham Offspring Study (33) who were followed for 8 years after baseline exercise testing, an exaggerated diastolic, but not systolic, BP response to exercise was a significant and independent predictor of hypertension in men and women, with odds ratios of 4.2 and 2.2, respectively. Matthews et al. (34) compared 151 cases of physician-diagnosed hypertension with 201 age-matched controls who were normotensive. In multiple regression analysis, those who developed hypertension at follow-up were three times more likely to have had an exaggerated exercise BP response. Several studies examined BP at variable time intervals in the immediate recovery period after exercise testing and found a higher BP after acute exercise significantly predicted future hypertension (33,35).

Current studies do not seem to justify the widespread use of exercise testing to predict future hypertension because of a number of limitations including: exercise tests and the definition of an exaggerated BP response were not standardized across the various studies; confounding variables were not

always adequately accounted for in the analyses; and noninvasive BP measurements during exercise have inherent limitations, particularly with regard to diastolic BP. However, when exercise testing is performed for other reasons, BP measurements may provide useful prognostic information (15).

PREDICTION OF CARDIOVASCULAR COMPLICATIONS

Few studies assessed the significance of exercise BP for mortality or the incidence of cardiovascular events. In healthy men, the exercise-induced increase in systolic BP from baseline to 164 W during cycle ergometer exercise independently and significantly predicted mortality from cardiovascular, noncardiovascular, and total mortality (22), and submaximal systolic BP at a work load of 100 W, but not maximal systolic BP, contributed independently to the prediction of cardiovascular mortality and myocardial infarction (36,37). In another study, maximal systolic BP during a progressive exercise test to volitional fatigue predicted all-cause and cardiovascular mortality in men and women (38).

Exercise BP significantly enhanced the prognostic value of resting BP in hypertensive men in population studies (39), but apparently not in established more severe hypertension (40). In these patients, exercise SVR added prognostic precision to vascular resistance at rest, most likely due to attenuated arterial dilatation during exercise as a result of structural vascular abnormalities in those with worse prognosis. The impaired vasodilation was not expressed in an abnormal rise in BP because of a blunted rise of CO. The crucial role of CO and cardiac function is highlighted by the fact that exertional hypotension is associated with a worse prognosis in cardiac patients and in persons with chronic heart failure, probably due to left ventricular dysfunction (41–43).

In conclusion, the prognostic importance of exercise BP depends on the population studied. A worse prognosis is associated with a hypertensive response in healthy subjects and a hypotensive response in patients with heart failure, whereas the results may be variable in hypertensive patients depending on cardiac function and the associated CO (Figure 23.2) (21).

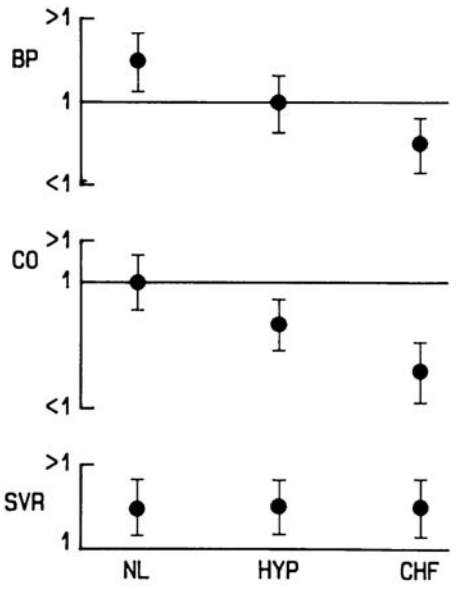

Fig. 23.2 Risk ratios of exercise blood pressure (BP), cardiac output (CO), and systemic vascular resistance (SVR) on top of the hemodynamic values, measured with subjects at rest, for normal subjects (NL), hypertensive patients (HYP), and patients with congestive heart failure (CHF). A risk ratio above unity means that a higher value is associated with a greater risk, whereas a risk ratio below unity means that a lower value represents a greater risk.

STATIC EXERCISE

Static or isometric exercise involves muscle contractions with limited or no movement and is, thus, performed at a relatively constant muscle length (5). The most frequently used laboratory test consists of handgrips of varying strength and duration. Static exercise has been less well studied than dynamic exercise, but it is generally accepted that the increase in BP is more pronounced during predominantly static effort, such as strength training, particularly when the intensity exceeds 40% of the maximal voluntary contraction. The increase in BP is associated with increased heart rate, CO, and SVR.

Whereas dynamic exercise produces large increases in systolic BP and moderate increases in diastolic BP, static exercise produces large increases of both systolic and diastolic BP. For example, knee extension at 30% of maximal voluntary contraction for 3 min increased systolic BP by an average of 35 mmHg and diastolic BP by an average of 29 mmHg (44). Extremely high BP elevations have been observed during heavy-resistance exercise, such as weight-lifting, and are related to pronounced increases in intra-thoracic and intra-abdominal pressures (45).

The BP response to handgrip was significantly larger at higher age and higher resting BP (2). However, a number of other studies found similar responses in subjects with normal BP and hypertensive patients (1,46). The limited evidence on the effect of static exercise on postexercise BP suggests that this type of exercise has no or only small effects on BP after exercise (15,47).

There is also little information on the association between BP reactivity to static exercise and target organ damage. al'Absi et al. (48) observed that there was no significant association between the BP response to a handgrip challenge and left ventricular mass, although there was some association with relative wall thickness.

COLD PRESSURE TEST

The CPT consists of the immersion of a hand in ice-water, normally for 60 s, which induces a considerable increase in BP due to vasoconstriction. The BP response appears to be similar in hypertensive and normotensive subjects (1) and appears to be inversely related to fitness level (49). Rostrup et al. (50) observed that BP during the CPT was not an independent explanatory variable of left ventricular mass, whereas Markovitz et al. (26) found that systolic BP reactivity was related to left ventricular mass in white men and women in multivariable analyses.

MENTAL STRESS AND OTHER LABORATORY STRESSORS

OVERVIEW

The most traditional mental stressor is the mental arithmetic (MA) test in which, for example, the subject has to subtract or add 1 digit number from a given 6 digit number during 5 min, vocally and at a required speed. Such mental stress increased mean BP by 23 mmHg and heart rate by 15 beats/min in patients with mild BP elevation (51).

Other mental challenges consist of: interviews on emotional and conflicting aspects of a subject's life; the mirror drawing test, which consists of the manual reproduction of a geometric drawing as reflected by a mirror; the Stroop color-word conflict test, which consists of the selection of the appropriate color under the influence of conflicting auditory and visual commands; video-game tests, which require operational decisions to video tasks of progressive complexity to be made in a progressively shorter time; a reading task performed under the disturbing influence of the subject's voice out-of-phase; the response to an unpleasant noise (1).

METHODOLOGICAL LIMITATIONS OF THE LABORATORY STRESSORS TESTING APPROACH

As mentioned above, the evaluation of the hemodynamic responses to laboratory stressors encompasses a number of limitations. These include: (*i*) the lack of standardization of the procedure (time of exposition, variables measures, time of measurements, etc.) among different laboratories; (*ii*) the limited power of the stimulus in triggering measurable responses in different subjects; (*iii*) the need to assess on a beat-to-beat basis the hemodynamic responses (in particular BP) to stress; and (*iv*) the limited correlation between the responses to laboratory stressors and the cardiovascular responses to daily emotional physical stimuli (3,52).

Two other issues related to the assessment of the cardiovascular effects of stress need to be briefly addressed. The first one, which was examined years ago in a study by the Milan group (53), refers to the reproducibility of the BP (and heart rate) responses to laboratory stressors. When isometric exercise, mirror-drawing test, or cold pressure test were repeated several times in the same experimental session at regular time intervals, it was found that both the BP and the heart rate responses were markedly different from each other (53). Thus, cardiovascular responses to laboratory stressors have a limited within-subject reproducibility, making the accurate evaluation of the typical responses of a subject to a single stressor difficult, particularly when the responses are evaluated only at a single stressor exposure. The second issue refers to the limited intra-individual relationship among the responses to different laboratory stressors, suggesting that a subject may display a hyperactivity to one test but not to another (Figure 23.3) (3).

RESPONSES IN HYPERTENSION

Despite the limitations mentioned above, a number of studies assessed whether the BP response to mental stress differs between hypertensive and normotensive subjects. The results have been conflicting. Whereas some studies reported that the pressure and tachycardic effects are greater in essential hypertensives than in normotensives, this was not confirmed by others. Also the concept that borderline hypertensive subjects and normotensive adolescents with hypertensive parents display greater BP and heart rate responses than normotensives is not generally accepted (1,54). Izzo (54) concluded that an individual's BP response to stress is largely independent of resting pressure level, but with extremely wide interindividual variations. There is evidence that acute bouts of aerobic exercise (55) as well as physical fitness (49) have a significant impact on the BP response to a psychological stressor.

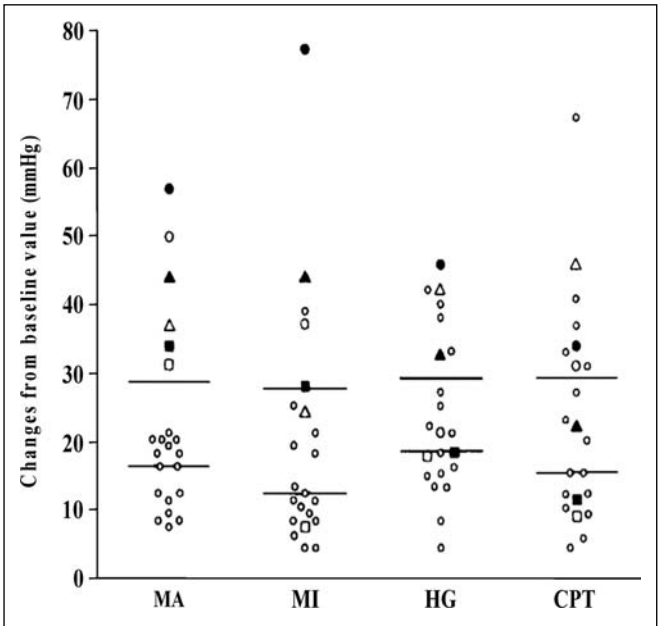

Fig. 23.3 Changes in mean arterial pressure (MAP) induced in different subjects (different symbols) by mental arithmetic (MA), mirror test (MI), handgrip (HG), and cold pressure test (CPT). Horizontal lines indicate 95% confidential interval. Note that one subject may display an abnormal response to one stressor test but a normal one to another. *Source*: Modified from Ref. 3.

The BP response to MA was more pronounced in men than in women, with increases of 22/10 mmHg in men and 14/7 mmHg in women (48). al'Absi et al. (56) investigated, in a random community sample, whether BP reactivity to stress contributes to left ventricular hypertrophy, a major risk factor for cardiovascular morbidity. They found that the BP response to MA was not significantly related to left ventricular mass. However, there was a significant association between the systolic BP response to the arithmetic task and relative wall thickness in men, suggesting that BP reactivity is related to concentric remodeling (56). However, other studies with large samples have failed to find a positive association between left ventricular mass and BP reactivity (26,50).

PREDICTION OF FUTURE HYPERTENSION

Carroll et al. (57) examined whether BP reactions to mental stress predicted future BP and hypertension at 10-year follow-up in male public servants. Systolic BP reactions to mental stress were positively correlated with follow-up screening of

systolic BP and, to a lesser extent, follow-up diastolic BP. In multivariable tests, by far the strongest predictors of follow-up BP were initial screening BPs. In the case of follow-up systolic BP, reactions to stress emerged as an additional predictor of follow-up systolic BP, but accounted for less than 1% of the variance. The results of the study provide modest support for the hypothesis that heightened BP reactions to mental stress contribute to the development of high BP but question the clinical utility of stress testing as a prognostic device (57).

CONCLUSIONS

In conclusion, results on the independent relationships of the BP response to physical and mental stressors with target organ damage, future hypertension, and incident cardiovascular disease are not unanimous and, if significant, the additional explained variance is usually small. In addition, test protocols and the definition of an abnormal BP response to the various stressors have not been standardized, and the noninvasive BP measurements during some tests may not be reliable. The overall results question the clinical utility of physical and mental stress tests in the management of uncomplicated hypertension.

ACKNOWLEDGMENT

The authors gratefully acknowledge the secretarial assistance of N. Ausseloos.

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THE DIAGNOSTIC APPROACH IN UNCOMPLICATED AND COMPLICATED HYPERTENSION

24

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DIAGNOSTIC APPROACH TO UNCOMPLICATED HYPERTENSION

Before any diagnostic evaluation begins, it is essential that the appropriate diagnosis is established. The initial diagnostic approach must have five major objectives: (*i*) establish whether hypertension is sustained and would benefit from treatment; (*ii*) identify or rule out secondary forms of hypertension; (*iii*) determine the presence of other risk factors for cardiovascular disease; (*iv*) detect target organ damage and to identify coexisting disease; and (*v*) identify factors that may contribute to or exacerbate hypertension.

BLOOD PRESSURE MEASUREMENT

Because of blood pressure (BP) variations, the diagnosis should be based on multiple BP readings taken on separate occasions. At least three BP measurements on three separate visits should be made following the guidelines. This period can be extended in patients without other risk factors and target organ damage. The proper width of the BP cuff is important (12–13 cm long and 35 cm wide) but have a larger and a smaller bladder available for fat and thin arms. Cuffs that are too small will overestimate the pressure, and those large will underestimate it (1). A difference of 10 mmHg of mercury or more between the two arms should be confirmed by repeated measurements. Ambulatory blood pressure monitoring (ABPM) can be helpful to exclude "white-coat" hypertension. In other chapters of this book there are all the details for the accurate measurement of BP. The basic evaluation includes the family and clinical history, the physical examination, the laboratory evaluation, and basic subclinical or clinical evaluation.

FAMILY HISTORY

The family history should include information for a history of stroke, coronary heart disease and events in relatives <60 years old. A positive family history may suggest a hereditary basis for the patient's high BP.

CLINICAL HISTORY

The clinical history should include information for the duration and previous levels of high BP, information from home and other BP measurements. This will assist the clinician to discriminate between real BP white coat, and masked hypertension. The presence of isolated systolic hypertension typically occurs in the elderly and is associated with increased cardiovascular risk.

Early or uncomplicated hypertension is usually free of symptoms. Young patients may have symptoms of hyperdynamic circulation. Emotional and psychological factors should include attention in view of the evidence that may increase BP. A history of angina or previous myocardial infarction, heart failure, peripheral artery disease, diabetes mellitus, dyslipidemia, stroke or transient ischemic attack, and renal disease should be explored. Headache may be a neurologic symptom of hypertension. Lethargy and proximal muscle weakening often accompany metabolic disorders.

Questions about the patient's lifestyle, such as smoking, salt and alcohol intake, physical inactivity, obesity, and dietary intake of fat, may uncover hypertensive risk factors that may be controlled.

Hypertension is an asymptomatic disease, but some symptoms could assist the clinician help to recognize secondary forms of hypertension. For example, chronic renal insufficiency can be ruled out by the absence of proteinuria and normal creatinine levels (2). Renovascular hypertension should be suspected in the presence of young patients, in sudden increases of BP in well-controlled hypertensive patients, if there is a failure of triple drug treatment, and in new onset of hypertension in elderly with atherosclerotic disease (2). Pheochromocytoma should be suspected if there is a history of tremor, headaches, sweating, weight loss, and orthostatic hypotension (3). Primary aldosteronism should be suspected in the presence of muscle weakness and cramps. Sleep apnea is commonly associated with hypertension, and should be

suspected in obese individuals with sleep disorders, snoring, and daytime somnolence.

PHYSICAL EXAMINATION

In addition to BP measurement, physical examination should search for signs of secondary hypertension. The presence of abnormalities on the cardiovascular examination contributes significantly to assessment of target or subclinical organ damage and to cardiovascular risk stratification.

Physical examination of the heart includes the auscultation and the evaluation of rate and rhythm. In recent years, evidence has been accumulated that an elevated heart rate is also an important risk factor for cardiovascular and noncardiovascular death in middle-aged persons. Heart rate may be an index of sympathetic activation. The close association between sympathetic activity and hypertension, as well as target organ damage, such as left ventricular hypertrophy, coronary heart disease, and others, is well established. High heart rate may increase the risk in patients with acute coronary syndrome and heart failure and may predispose to lethal ventricular arrhythmias. A loud first heart sound suggests a hyperadrenergic circulatory state. A third heart sound suggests systolic dysfunction, while the presence of a fourth heart sound suggests diastolic dysfunction or ischemic heart disease. Valvular murmurs are not usually related to hypertension, but longstanding hypertension may cause dilatation of the aortic ring, while the presence of ischemic heart disease may cause a diastolic murmur of the mitral valve. A systolic murmur can frequently be heard in elderly hypertensive patients. Systolic and diastolic murmurs in the upper quadrants of the abdomen suggests renovascular hypertension, while in carotid arteries suggests stenosis of carotid arteries and increased risk for stroke. The aorta should be carefully palpated in all patients because of the increased prevalence of aortic aneurysms in hypertensive patients. Examination of the carotid femoral and extremity arterial pulses is important, because a delay and reduced volume in femoral artery suggests the possibility of coarctation of the aorta.

FUNDUSCOPIC EXAMINATION

Funduscopic examination is not very helpful in hypertensive patients because the majority of hypertensive patients present early. Grade 1 and 2 arteriolar changes are often noted, but grade 3 (hemorrhages and exudates) and grade 4 (papilledema) are rarely observed and suggests the presence of significant arteriosclerosis and longstanding, uncontrolled hypertension.

LABORATORY EVALUATION

According to the European Society of Hypertension/European Society of Cardiology guidelines, there are routine, recommended tests and additional tests for hypertensive patients with target organ damage or associated conditions and tests for secondary hypertension (Table 24.1). The younger the patient, the more detailed the diagnostic work-up should be. Baseline blood chemistry is recommended to include those tests to provide information for the treatment of hypertension as well as other risk factors, such as diabetes and hyperlipidemia.

Table 24.1 Evaluation of uncomplicated hypertension

Blood pressure levels
Family history
Clinical history
Duration and previous levels of blood pressure
Other risk factors (hyperlipidemia, smoking, obesity, diabetes mellitus, exercise)
Dietary habits
Previous and current treatment
Symptoms related to secondary hypertension, coronary heart disease, heart failure, and brain, kidney, and peripheral artery disease
Physical examination
Blood pressure measurement in both arms
Signs of secondary hypertension
Auscultation for arrhythmias, heart sounds, and murmurs
Examination of carotid arteries and peripheral arteries
Fundoscopic examination
Laboratory evaluation
Hemoglobin, hematocrit
Plasma glucose
Lipid levels (total, HDL, and LDL cholesterol, triglycerides)
Serum uric acid
Blood urea nitrogen
Serum creatinine
Serum potassium, sodium, calcium
Urinalysis
Electrocardiogram

The presence of anemia may be a concomitant finding in a number of diseases, including chronic renal insufficiency. White and red blood cells with proteinuria suggest the presence of accelerated or malignant hypertension or renal parenchymal disease.

Close to 15% of hypertensive patients have diabetes mellitus, while 60% of diabetic patients have hypertension. Diabetes is a well established risk factor for cardiovascular disease. In diabetic patients, the selection of antihypertensive drugs should be tailored to avoid drugs that impair glucose tolerance (i.e., diuretics) or mask the adrenergic response to medication-induced hypoglycemia (i.e., β-adrenergic receptor blockers). Also, in hypertensive patients, it is very important to choose drugs that prevent the new onset of diabetes (i.e., angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) (4).

An association between serum uric acid concentration and cardiovascular risk has been recognized for many years (5). Hyperuricemia (uric acid levels $>416\,\mu mol/l$ or 7 mg/dl) is frequently seen in essential hypertension. About 25 to 35% of hypertensive subjects exhibit hyperuricemia. Diuretics stimulate the uric acid reabsorption by the proximal tubule, elevate uric acid levels, and may promote acute gouty arthritis in predispose patients. However, their use is not absolutely contraindicated, especially in small doses, in patients with a history of gout or asymptomatic hyperuricemia. An elevated

serum uric acid level is an important marker for preeclampsia in hypertensive, pregnant women.

Hypercholesterolemia is an independent risk factor for developing cardiovascular disease. It has been shown that the presence of dyslipidemia is more frequent in hypertensive than in normotensive subjects. Low HDL cholesterol and high triglyceride levels are clusters of the metabolic syndrome. Antihypertensive drugs, such as α-blockers, have favorable effects on the lipid profile, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers have neutral effects, while diuretics and some β-blockers have adverse effects on the lipid profile.

Although blood urea nitrogen and creatinine levels are relatively insensitive markers, they provide an important marker for its progressive decline. The diagnosis of hypertension-induced renal damage is based on the finding of an elevated value of serum creatinine, of a decreased creatinine clearance, or a detection of an elevated urinary excretion of albumin. The presence of mild renal insufficiency has been defined recently as serum creatinine values equal to or above 133 μmol/l (1.5 mg/dl) in men and 124 μmol/l (1.4 mg/dl) in women, or by the finding of estimated creatinine clearance values below 60 and 70 ml/min (6). A routine urinalysis, including microscopic examination of the urinary sediment, is an important screening test for renal parenchymal disease. Abnormally increased excretion of albumin during a 24-h urine collection or from a spot urine sample is a more sensitive measurement of impaired renal function, and has been shown to predict the development of overt diabetic nephropathy in both type 1 and type 2 diabetics. Microalbuminuria in hypertensive patients has been shown to predict cardiovascular events. Therefore, microalbuminuria is recommended to be measured in all diabetic patients and, whenever possible in non-diabetic hypertensive patients.

The presence of hypernatremia, particularly when accompanied by hypokalemia, should alert the physician to the possibility of the primary aldosteronism, while when the glomerular filtration rate (GFR) falls below 30 ml/min, patients with acute or chronic renal failure manifest difficulties with water handling and develop hyponatremia. Another disease that may be present with hyponatremia and hypertension is hypothyroidism.

Hyperkalemia is a common finding in hypertensive patients with acute and chronic renal insufficiency. It is even more common in diabetics, in the elderly, in patients receiving immunosuppressive drugs, and in some patients receiving potassium sparing drugs, or, rarely, in patients receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Hyperkalemia is a potentially lethal effect of renal failure that may be exacerbated by some antihypertensive drugs.

The presence of hypokalemia is perhaps the most helpful clue to secondary hypertension from the screening blood tests. In the untreated patient, a low serum potassium level (<3.6 mEq/l) when associated with urinary potassium wasting (urinary K > 40 mEq/l) points to a disorder of aldosterone excess. If the serum potassium level is borderline or low, it should be repeated on two or three separate occasions. Other diseases related to hypokalemia are renovascular hypertension, pheochromocytoma, and Liddle's syndrome (7). Disorder of serum potassium can have a significant impact on choices of antihypertensive drugs. The presence of hyperkalemia sometimes limits the use of special antihypertensive drugs, while the use of these agents in renal disease or congestive heart failure requires monitoring of serum potassium. Diuretics may worsen preexisting hypokalemia and hyponatremia, and especially the loop diuretics. The presence of diuretic-induced hypokalemia (serum K < 3.0 mEq/l) that is not corrected by exogenous potassium and is not associated with hypomagnesaemia suggests primary aldosteronism and is accompanied with an increased risk of arrhythmias and sudden death.

DIAGNOSTIC APPROACH OF COMPLICATED HYPERTENSION

Hypertension, a progressive cardiovascular syndrome, is strongly associated with functional and structural cardiac and vascular abnormalities that consequently damage the heart, kidneys, brain, vasculature, and other organs, leading to premature morbidity and mortality (8). Target organ damage may occur in the context of a not well controlled chronic hypertensive or pre-hypertensive status (1). The routine diagnostic workup for hypertension is a highly insensitive approach to the detection of high-risk patients since up to 50% of hypertensives may be mistakenly classified as at low or moderate added risk. Based on the recent results of the Assessment of Prognostic Risk Observation Survey (APROS), routine cardiac and vascular ultrasonography are both required to reliably identify high-risk individuals, determining left ventricular mass and intima–media thickness (IMT) (9). Additional evidence of complications by using retinal fundoscopy, evaluation of arterial elastic properties and urinary albumin excretion (UAE) rate assay (detection of microalbuminuria or proteinuria), or emerging molecular assays [indices of subclinical inflammation, brain natriuretic peptide (BNP)], further ameliorates cardiovascular risk assessment (Table 24.2) (10).

DETECTION OF CARDIAC DAMAGE

Electrocardiography (ECG) has a pivotal role in the assessment of hypertensive cardiac disease, with respect to ischemia, rhythm or conduction abnormalities, and left ventricle hypertrophy (LVH). Despite the lower sensitivity of ECG compared to echo in detecting LVH, indexes such as Sokolow-Lyons ($SV_1 + RV_{5-6} > 38$ mm) or the modified Cornell (>2440 mm*ms) and patterns of left ventricle systolic strain have been correlated with adverse cardiovascular (CV) outcome. The detection of the non-valvular atrial fibrillation (AF) is associated with two- to seven-fold increase in the risk of ischemic stroke, while the combination of hypertension and AF further increases cardiovascular risk. In the LIFE study, baseline AF was associated with a 3.5-fold increase in the risk of stroke,

Table 24.2 Evaluation of complicated hypertension

Same as for uncomplicated hypertension (see Table 24.1) plus:
Echocardiogram
Carotid ultrasound
Detection of urinary albumin excretion rate
Estimation of glomerular filtration rate
C-reactive protein
Pulse wave velocity recording

while occurrence of new AF during treatment was associated with a five-fold increase in stroke risk (11).

Echocardiography is the gold standard method for evaluating the structural and functional adaptations in the cardiac hypertensive disease course. It provides valuable information regarding left ventricular geometry—hypertrophy, systolic, and diastolic function—as well as left atrial and ascending aorta dilatation and function. The classical evaluation includes measurements of interventricular septum, posterior wall thickness, and end-diastolic diameter for the calculation of left ventricular mass according to available formulas indexing for anthropometric characteristics, such as body surface area or height. The prevalence of LVH increases with the duration and the severity of hypertension and ranges from <10% in subjects with stage 1 hypertension to 90% among those with stage 3. Risk increases proportionally, even in the conventionally normal range of LV mass index, according to gender-specific criteria (normal values: $<116\,g/m^2$ in men and $<104\,g/m^2$ in women). The determination of the geometry of LV according to LV mass index and relative wall thickness values (≥0.43 or <0.43) provides further prognostic data. There is a graded continuous incremental effect of left ventricle geometrical adaptations on CV risk, ranging from normal LV pattern, to LV concentric remodeling, LV eccentric hypertrophy, and, finally, LV concentric hypertrophy pattern (12). Furthermore, a global assessment of LV wall contraction abnormalities due to ischemia or previous infarction and the estimation of LV ejection fraction constitute a reliable predictor of CV events (Table 24.3).

Even prior to the establishment of LVH, hypertension mediates diastolic dysfunction due to impaired relaxation and increased stiffening of the left ventricle, resulting in a clinical equivalent of diastolic heart failure with preserved ejection fraction. Diastolic function can be assessed by Doppler measurement of the ratio between E and A waves of transmitral blood flow, accomplished by deceleration time of E wave and isovolumic relaxation time measurements. Valsalva maneuvers and pulmonary vein flow patterns may be necessary to uncover diastolic dysfunction in the setting of pseudo-normalized transmitral patterns. Tissue Doppler imaging (TDI), describing the velocity of myocardial tissue independently of the loading conditions and the geometry of left ventricle, is superior to conventional Doppler in assess-ing diastolic function. This method accurately describes left ventricle systolic and diastolic function, with reproducible measurements of the systolic (S wave) and diastolic waves (E and A) from the diaphragmatic, lateral, anterior, and inferior wall proximally to mitral annulus. By TDI, characteristic patterns of diastolic dysfunction are the reduction of E and the reduction of E/A ratio. Furthermore, increased ratio of E/A >15 reflects significantly increased left ventricular end diastolic pressure (13).

Table 24.3 Indices reflecting complicated hypertension

LV hypertophy (LVH)
ECG
Sokolow-Lyons index = $S_{V1} \pm R_{V5-6}$ >38 mm
Cornel index = $R_{AvI} + S_{V3\ (+8\ if\ female)}$ >35 mm
(Cornel index) × (duration of QRS) >2440 mm/ms
ECHO
LV mass indexed for BSA (g/m^2) >116 (M) and >104 (F)
LV mass indexed for height (g/m) >143 (M) and >102 (F)
LV mass (g) = 1.04 [(IVS ± PWT + EDD)^3 – EDD^3] – 13.6 (Devereux formula)
LV mass (g) = 0.8 [1.04 (EDD + PWT + IVS)^3 – EDD^3] (Penn formula)
LV geometry
LVH (+) and RWT > 0.43: concentric LVH
LVH (+) and RWT ≤ 0.43: eccentric LVH
LVH (–) and RWT > 0.43: concentric remodeling
LVH (–) and RWT ≤ 0.43: normal
RWT = (IVS + PWT)/EDD

Left atrium (LA) dilatation is an early and common finding in hypertensive disease: in the LIFE study, 56% of female and 38% of males had increased LA size. The best index of LA size estimation is the LA volume because it enlarges asymmetrically. LA volume index (an echocardiographic measurement of LA volume indexed for the body surface area—normal values: 20 ± 6 ml/m^2, 32 ml/m^2 the upper limit) was found closely associated with advanced age, high systolic BP, increased LV mass index, and BNP levels (14). LA volume is a more robust marker of CV events than LA area or diameter, while, in subjects with AF, the predictive value of LA size for CV events was poor, irrespective of the method of LA size quantization.

Thoracic aorta should always be included during a baseline echocardiographic study to detect possible ectasia or aneurysms, which are alternative expressions of widespread hypertensive atherosclerotic processes.

Exercise treadmill test has a moderate specificity (about 70–80%) and a low sensitivity (30–40%) to reveal an ischemic exercise-mediated pattern in hypertensives, albeit provides a measure of inotropic response of the left ventricle. In addition, BP response at peak exercise and recovery has a prognostic role for future hypertension in normotensives and increased risk for adverse events in hypertensives. When treadmill exercise testing is not indicated or it is inconclusive, other diagnostic procedures, such as cardiac scintigraphy or echo stress test with dobutamine (with or without perfusion imaging), should be performed to uncover an ischemic background.

Last, but not least, a molecular approach of left ventricle dysfunction in hypertensives with LVH could be an assay of BNP, which predicts CV events better than CRP.

DETECTION OF VASCULAR COMPLICATIONS

CEREBRAL AND RETINAL CIRCULATION

In subjects with a history of stroke, imaging techniques (computed tomography or magnetic resonance imaging) could determine the nature and the location of the lesion. Furthermore, cognition evaluation tests should more often be used in elderly hypertensive subjects.

CAROTID ARTERIES

High-resolution B-mode ultrasonography of the carotid and/or femoral arteries may allow the measurement of the intima–media complex and the detection of atheromatous plaques in the arterial wall. Available data from population studies

have clearly demonstrated that systolic BP, age, and sex are the major determinants of the increase in IMT in the carotid arteries. The normal IMT values may be better defined in terms of increased risk and many data indicate that IMT >1 mm is associated with a risk of myocardial infarction and/or stroke. There are different protocols for carotid IMT estimation: (*i*) mean of the maximal IMT of the four far walls of the carotid bifurcations and distal common carotid arteries, (*ii*) mean maximum thickness of up to 12 different sites (right and left, near and far walls, distal common, bifurcation and proximal internal carotid), and (*iii*) overall single maximum IMT. Measurements of carotid IMT could be performed by manual cursor placement or by automated computerized edge detection with acceptable reproducibility in experienced laboratories. Data from a number of studies (ACAPS, MIDAS, ELSA, VHAS) have shown a high prevalence of increased IMT and plaques in hypertensive subjects. More specifically, in the ELSA study, 82% of middle-aged hypertensives had a plaque. The presence of a plaque (focal thickening >1.3 mm) or a diffuse common carotid artery IMT (averaged IMT ≥ 0.8 mm) was present in 27.4% of the untreated and uncomplicated middle-aged essential hypertensives of the APROS study, making risk stratification of hypertensives more precise (9).

PERIPHERAL ARTERIES

The determination of the ankle-brachial index (ABI), which is a simple ratio of systolic pressures in the ankles and arms, is still the golden standard for the diagnosis of peripheral arterial disease (PAD), a condition frequently associated with hypertension (15). Normal values of ABI ranged 0.9–1.3, while values <0.90 are diagnostic for PAD and constitute a strong predictor of morbidity and mortality during the follow-up, even in subjects with no clinical symptoms of PAD. Not all patients have symptoms of classic claudication, but new evidence suggests that a large number of patients, once felt to be "asymptomatic," in fact have a profound limitation in their function due to the arterial occlusive disease process. More attention should be paid to the determination of ABI in the strategy of total cardiovascular risk detection in hypertensive patients and should also be considered in the planning of future large cardiovascular prevention trials.

FUNCTIONAL VASCULAR ASSESSMENT (ARTERIAL STIFFNESS, ENDOTHELIAL DYSFUNCTION)

Large arterial stiffness, a common disorder in hypertension, is considered as a marker of vascular aging, and is exacerbated by many modifiable and not modifiable CV risk factors. Particularly, in hypertensive subjects, increased systolic BP, non-dipping status, sodium sensitivity, presence of microalbuminuria, subclinical inflammation, or obstructive sleep apnea syndrome are associated with impaired arterial elastic properties (16). Arterial stiffness acting either as a marker for the development of future atherosclerotic disease, or directly involving in the process of atherosclerosis is associated with adverse cardiovascular outcome in hypertensives with end-stage renal disease, as well as in healthy subjects. There are several different methods of assessing arterial stiffness, one of which the carotid-femoral pulse wave velocity measurement may be more suitable for clinical use due to its simplicity (17). Furthermore, the augmentation index, another parameter of arterial stiffness, takes into consideration the reflected waves which augment central systolic pressure, and can provide an assessment of aortic BP from peripheral artery measurement. The latter is intriguing since systolic BP in the aorta may be different from that in the arm and may be differently affected by different antihypertensive drugs. It is conceivable that measurement of arterial stiffness will become an important part of the routine assessment of patients in the cardiovascular practice.

Lastly, increased attention is paid to investigate endothelial dysfunction by a variety of methods (plethysmography, brachial flow mediated dilatation), a state closely related to hypertension and atherosclerotic process. However, the lack of a reliable and rather simple non-invasive method for the assessment of endothelial responsiveness to various stimuli has limited their use in the clinical evaluation of the hypertensive patient (18). Currently, circulating markers of endothelial damage (ICAM, VCAM, selectins, ADMA, von Willebrand factor, etc.) may provide an earlier alternative way to investigate endothelial dysfunction.

DETECTION OF KIDNEY COMPLICATIONS

The diagnosis of hypertension-induced renal damage is based on the finding of slight elevations of serum creatinine, of a diminished GFR, and of an elevated UAE (19,20). According to the Joint National Committee (JNC-7), microalbuminuria and decreased GFR should be considered as major cardiovascular risk factors, while, according to the European Society of Hypertension, both the increase of creatinine and microalbuminuria should be considered as evidence of target organ damage. Data from many studies in hypertension (HOT, INSIGHT, SYST-EUR, SHEP) have confirmed the close link of serum creatinine elevation with adverse outcome: creatinine above >1.5 mg/dl (133 μmol/l) in men and >1.4 mg/dl (124 μmol/l) in women are indicative of mild renal insufficiency. However, serum creatinine levels are strikingly influenced by muscle mass and other confounders, leading to under-recognition of renal failure especially in females and elderly and in these cases serum cystatin C is better predictor of renal failure than creatinine. The need to estimate GFR levels for renal function impairment has been emphasized by the National Kidney Foundation and by the American Heart Association Kidney and Cardiovascular Disease Council. Since the standard tests for estimation of GFR are time-consuming and not cost-effective, in the typical office setting, GFR is evaluated by validated estimation equations that use easily obtained data. The Cockcroft–Gault method is simple but not as precise as that developed by the Modification of Diet in Renal Disease (MDRD) study. Based on the MDRD study, GFR (ml/min per 1.73 m^2) = 186 × (serum creatinine) – 1.154 × (age) − 0.203 × (0.742 if female) × (1.210 if black). In clinical practice, presence of a GFR below 60 to 70 ml/min per 1.73 m^2 identifies the presence of mild renal insufficiency and it is related to increased cardiovascular risk in hypertension. Moreover, classification of the different stages of chronic kidney disease on the basis of GFR is widely accepted.

In the case of diabetes, urine albumin testing is obligatory, and microalbuminuria is a prognosticator of both renal and cardiovascular risk. In non-diabetic hypertensives, microalbuminuria is recognized as a predictor of atherosclerotic cardiovascular disease (19). In a 10-year prospective study, an albumin to creatinine ratio (ACR) >1.07 mg/mmol strongly and independently predicted ischemic heart disease, more

than doubling the risk (21). In the HOPE study, the risk was increasing with augmenting ACR, starting well below the microalbuminuria cut-off, even as low as 0.5 mg/mmol. The novel evidence regarding the inflammatory component of microalbuminuria in the progression of the hypertensive atherosclerotic disease further enhances the prognostic role of urinary albumin excretion (22–24).

PROTOCOL FOR MEASURING MICROALBUMINURIA IN HYPERTENSION

Patients should be tested only when in stable conditions, without other acute complications, such as exacerbations of congestive heart failure, volume overload, urinary tract or other systemic infections, fever, as well as after strenuous exercise. Due to the fact that urinary albumin excretion follows a circadian rhythm, the "gold standard" for assessing microalbuminuria is the 24-h urine collection. More practical methods are the collection of overnight timed urine samples and a morning sample. Microalbuminuria is defined as a UAE of 30–300 mg/24 h or 20–200 μg/min in at least two of three consecutive samples of non-ketonic sterile urine or by measuring ACR with values between 2.5–30 mg/mmol in males and 3.5–30 mg/mmol in females or 22–300 mg/g in males and 31–300 mg/g in females in a morning sample. Although even a single determination of ACR within the microalbuminuric range can predict, albeit with reduced precision, renal and cardiovascular disease complications, diagnosis of microalbuminuria should always be confirmed by timed urine samples or 24-h urine collections. In consideration of the above, we propose the following procedure in clinical practice for all hypertensives:

1. Estimation of serum creatinine, determination of urinary protein by dipstick, and, if possible, calculation of GFR by means of validated formulas (the use of MDRD equation is preferable). Regardless of the presence or absence of diabetes, estimation of UAE should be done by measurement of ACR in a morning spot urine sample.
2. Those patients with ACR with morning urine sample values above the gender-specific values of 25 mg/g in males and 35 mg/g in females should perform a second estimation. If this also shows ACR within the microalbuminuric range, then two positive out of three non-consecutive 24-h collections are needed to confirm microalbuminuria. If the second ACR test is negative, a third test should follow.
3. For the follow-up of patients, ACR in a morning spot urine sample is recommended. Although not fully scientifically solid, the proposed frequency is once a year for better risk stratification and guiding therapy. The use of the absolute levels of ACR, avoiding categorization with a given threshold, should be encouraged.

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THE TOTAL CARDIOVASCULAR RISK 25

Claudio Borghi, Ettore Ambrosioni

INTRODUCTION

Cardiovascular (CV) diseases are the most important cause of death in the Western world and are responsible for a large proportion of the overall mortality and morbidity currently observed in the population of the developed countries (1,2). For many patients, the first clinical manifestation is a potentially catastrophic event, such as stroke, myocardial infarction, or sudden death, and, among the 50-year adults enrolled in the Framingham Heart Study, the lifetime risk for developing symptomatic disease was 52% in men and 39% in women (3). Moreover, despite the advancement in the knowledge of the epidemiology and prevention of clinical atherosclerosis, the burden of CV disease remains very high and should increase within the next 20 years (4). Accordingly, CV prevention, that is, preventing or delaying clinical disease among asymptomatic and already exposed individuals, remains an issue of major public health interest.

The overall incidence of CV disease and its complications depends on the prevalence and clinical expression of several major CV risk factors that are involved, directly or indirectly, in the development and progression of the atherosclerotic disease (5–7). The estimation of the established risk factors provides remarkably good ability to discriminate the subjects at risk of CV disease and must represent the most effective tool to quantify the global CV risk and to prevent its clinical impact. Most of these risk factors coexist in the same subject and are cumulatively responsible for the development of CV complications (8). Any effective strategy of primary care or primary prevention of CV diseases depends on the identification of multivariate models that can predict, with reasonable reliability, the absolute risk for future CV events in large segments of the population (9). In particular, the absolute and relative risk for the future development of disease can be predicted for very few diseases, much less with the precision afforded by current CV risk prediction models. These risk scores are a major advance over clinical risk prediction and CV prevention is certainly one of the few areas in clinical practice where such approach is irreversibly included into practice guidelines. The concept of "total cardiovascular risk" has been recently developed as an estimate of the overall propensity of a subject to fall outside the boundaries of average CV risk based on the levels of different risk factors (5–7). Accordingly, most of the currently available risk scores have been developed in accordance with the notion of total CV risk, which actually represents the theoretical rationale behind any effective strategy of clinical risk management.

DEFINITION

The traditional approach to the prevention of CV diseases is based on the identification and treatment of some specific CV risk factors [e.g., high blood pressure (BP), lipid abnormalities, elevated blood glucose, etc.] when they exceed the thresholds of therapeutic intervention according to epidemiological and clinical evidence. However, the results of several large-scale, epidemiological studies (8,10,11) clearly demonstrate that, in a large proportion of the individuals at risk, the different risk factors are used to cluster and to negatively interact to increase the risk of CV disease. This is particularly true for complex, multifactorial diseases, such as atherosclerosis, for which continuous variables, including BP and cholesterol levels, conspire to increase the CV risk across a wide spectrum of individual values. In particular, population-based studies have demonstrated that most of the public burden of CV disease can be attributed to apparently "low-risk" individuals with relatively "normal" levels of risk factors, such as serum cholesterol and BP (12,13). This suggests that the mandatory role for a comprehensive approach to the prevention of CV diseases must be based on the quantification of the "global" risk profile, considered the product of the reciprocal interaction between the modifiable and non-modifiable risk factors irrespectively of any cut-off point for prespecified "normality".

RISK FACTORS CONTRIBUTING TO TOTAL CV RISK

Established, modifiable risk factors for CV disease include hypertension, dyslipidemia, diabetes mellitus, and cigarette smoking, and all of them, along with non-modifiable factors (e.g., age, gender, family history of CV disease), have been incorporated into algorithms for risk assessment in the general population. More recently, several other independent risk

factors have been identified (overweight/obesity, elevated C-reactive protein) to fully explain the amount of CV risk in the population. The European Society of Hypertension–European Society of Cardiology (ESH–ESC) Guidelines have added an estimate of the presence/absence of target organ damage (6) to the evaluation of global CV risk in patients with hypertension, while any evidence of concomitant CV disease is currently considered as expression of very high-risk profile, irrespectively of the presence of concomitant risk factors. As clearly demonstrated by epidemiology, CV risk factors rarely occur in isolation but, rather, tend to cluster in the same subjects. The results of the Framingham Heart Study (10) and the Brisighella Heart Study (14) have clearly demonstrated the presence of a combination of two or more CV risk factors in over 80% of the hypertensive patients. Moreover, the long-term (over 25 years) observation of a large sample of the population of Brisighella has displayed the progressive increase in the proportion of subjects bearing multiple CV risk factors (Figure 25.1). This was largely in agreement with the observations provided by the recent update of the Heart Disease and Stroke Statistics (15) that support the pivotal role of high BP and metabolic risk factors as determinants of global CV risk in the general population.

The concomitant presence of multiple CV risk factors in the same subject significantly increases the CV event rate, and persons with a combination of risk factors are at particularly high risk of CV disease and, in particular, coronary artery disease (Figure 25.2) (8,16). The cumulative effect on mortality and morbidity is directly proportional to the number of risk factors that aggregates in the same individual (8) where global risk profile is also involved in the development and progression of target organ damage (17,18). All these observations have contributed to emphasize the importance of the estimate of "global" CV risk profile as a reliable measure of the underlying interaction between different CV risk factors including, of course, hypertension.

The negative effect of the interaction between different CV risk factors has been confirmed in patients with the metabolic syndrome, where the prevalence of BP abnormalities ranges from 30% to 70% of the affected subjects and is associated with a significant increase in the relative risk of a coronary event (19). Again, in the subjects with the metabolic syndrome, the rate of CV complications seems to be largely proportional to the number of the different components that contribute to the definition of the syndrome (20), supporting the strong relationship between the rate of CV events in the population and the global CV risk profile.

HOW TO ASSESS THE GLOBAL CARDIOVASCULAR RISK?

The risk status in subjects without overt CV disease or other clinical forms of atherosclerotic disease can be easily determined by a "two-step" procedure that involves: (*i*) a quantitative estimate of the number of individual risk factors and (*ii*) the application of such risk factors to an interactive mathematical model (equation) that allows the estimate of the probability that the subject develops an overt CV disease within a short-term interval, usually of 10 years. A similar procedure can be also applied to patients with previous CV disease, where the presence of multiple risk factors can provide a reliable estimate of the probability of a recurrent CV event. This would increase the possibility to identify, from the general population of subjects exposed to CV risk factors, those whose risk profile warrants consideration of intensive treatment. Estimation of the overall risk of CV disease adds a step to the strategy of "single-factor" risk assessment and allows a better targeting of intensive treatment to those subjects who will benefit from it.

Over the last 10 years, several different methods have been developed for the estimate of global CV risk in patients with multiple risk factors, including hypertension. In general, all of them agree that the correct assessment of CV risk in a single patient results from the combined estimate of all the well established determinants of CV risk, including those

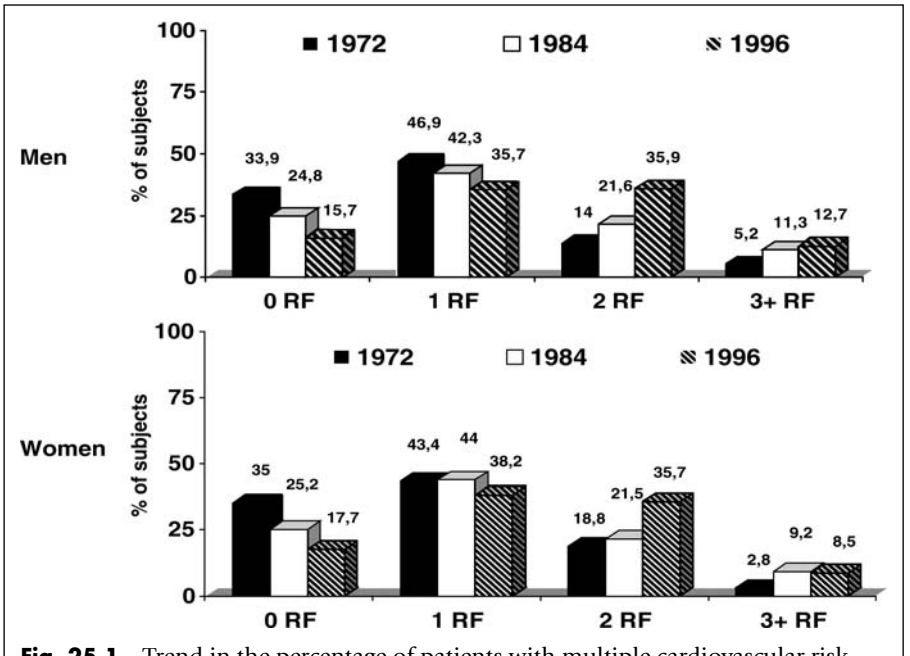

Fig. 25.1 Trend in the percentage of patients with multiple cardiovascular risk factors (RFs) over a 14-year period in the Brisighella Heart Study.

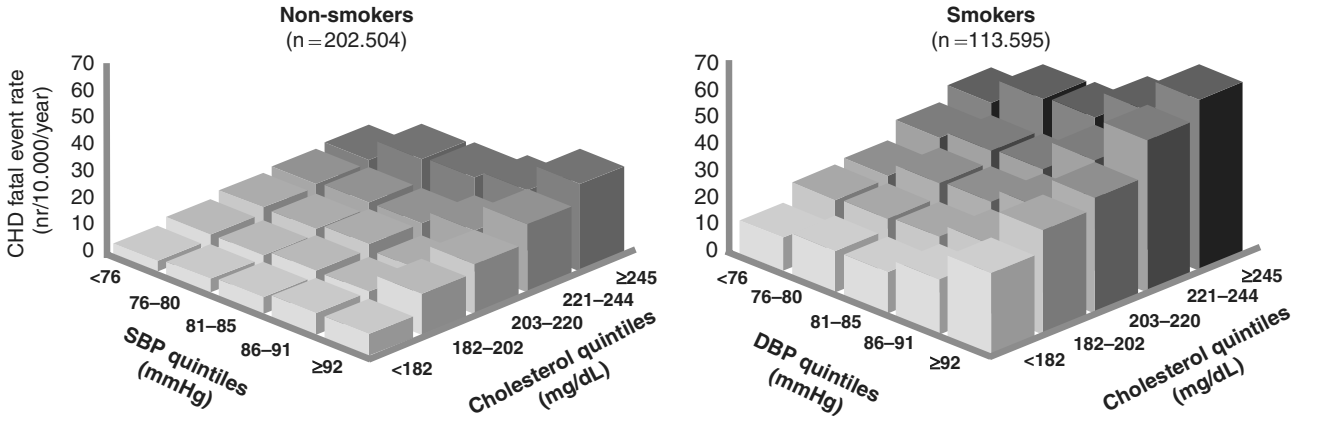

Fig. 25.2 Incidence of fatal coronary events and combination of multiple risk factors in the MRFIT study. *Abbreviations*: CHD, coronary heart disease; DBP, diastolic blood pressure; SBP, systolic blood pressure. *Source*: From Ref. 8.

showing only borderline abnormalities. Most of the systems employed for risk estimation are based on the Framingham database, which has a major limitation represented by the fact that it is only partially applicable to low-risk European populations, including those living in the Mediterranean area (21). In these subjects, the risk estimation based on the Framingham algorithm requires some recalibration due to relevant differences in the prevailing incidence of myocardial infarction and stroke. This problem has been partially overcome by the release of some methods of risk estimate directly relevant to various European population with or without hypertension. In particular, the SCORE project has provided separate tables that predict 10-year absolute risk of death for CV disease for higher risk countries in the Northern Europe and lower risk countries in the southern Europe (Figure 25.3) (5). In addition, the SCORE approach to CV risk allows an estimate of absolute individual risk profile that can be projected to the age of 60 years, thereby increasing the possibility of identifying those younger subjects (particularly women) who are unlikely to reach high-risk threshold, despite being at high risk relative to their peers, because of the presence of multiple risk factors. This approach has some important clinical implications and particularly support the primary role for a preventive treatment in those subjects who should not been otherwise treated despite a greater predicted shortening of their hypothetical longer lifespan.

All these "risk scores" must be considered a major advance over clinical risk prediction using relative risk estimates, and CV prevention is one of the few areas in clinical practice to incorporate the use of absolute risk prediction into clinical practice guidelines. In the specific field of hypertension, the ESH–ESC Guidelines have proposed stratification for total CV risk in the hypertensive population that is based on the categorical estimate of the excess in global CV risk in comparison to subjects with optimal BP values without additional risk factors (Figure 25.4) (6). In particular, the terms *low*, *moderate*, *high*, or *very high added risk* indicate either an absolute 10-year CV risk, ranging from <15% to >30% according to Framingham criteria, or an absolute risk of death, ranging from <4% to >8% according to the SCORE chart (6). This categorical approach is derived from a scheme included in the 1999 World Health Organization/International Society of Hypertension (WHO/ISH) guidelines (22), but extended to indicate the added risk in some groups of subjects with "normal" or "high-normal" BP where it introduces the important concept of the "relative role" of BP values as a risk factor for CV disease. In particular, patients with normal or high-normal BP values combined with additional CV risk factors can exhibit levels of added CV risk, ranging from high to very-high, that suggest the implementation of an aggressive treatment strategy of hypertension that would have not been justified by the absolute level of BP. The same categories have been proposed as estimates of relative risk of CV diseases, allowing for a more effective identification of those subjects whose risk profile could be significantly underestimated by an arbitrary absolute definition of the level of risk. This category includes a large proportion of those young subjects whose absolute estimate of CV risk does not entirely reflect the expected reduction in the lifespan that could follow a longer term exposure to the negative effect of CV risk factors. A recent review of the Framingham database has clearly demonstrated that even a small increase in the overall CV risk at the age of 50 is followed by a higher rate of CV events in the next two decades (3), thereby supporting the importance of an early detection of even a small increase in the global CV risk profile. This means that, irrespectively of the methodology applied to define it, the global assessment of individual CV risk must be currently considered as one of the cornerstones of CV prevention and the only reliable quantification of the individual susceptibility toward CV diseases.

GLOBAL CV RISK AND PATHOPHYSIOLOGICAL BACKGROUND

The concept of global risk profile that is currently applied to estimate the CV risk of the population is based on the assumption of a multiple and interactive effect among the different risk factors that co-segregate in the same subject. This interaction can occur at two different levels. The first level is that resulting from the direct negative impact of the different risk factors over the processes that lead to tissue damage at the vascular level. The pathophysiological sequence of events includes oxidative stress, endothelial dysfunction inflammatory processes, and vascular remodeling, followed by the development of atherosclerotic diseases, whose complications are responsible for a large proportion of CV diseases.

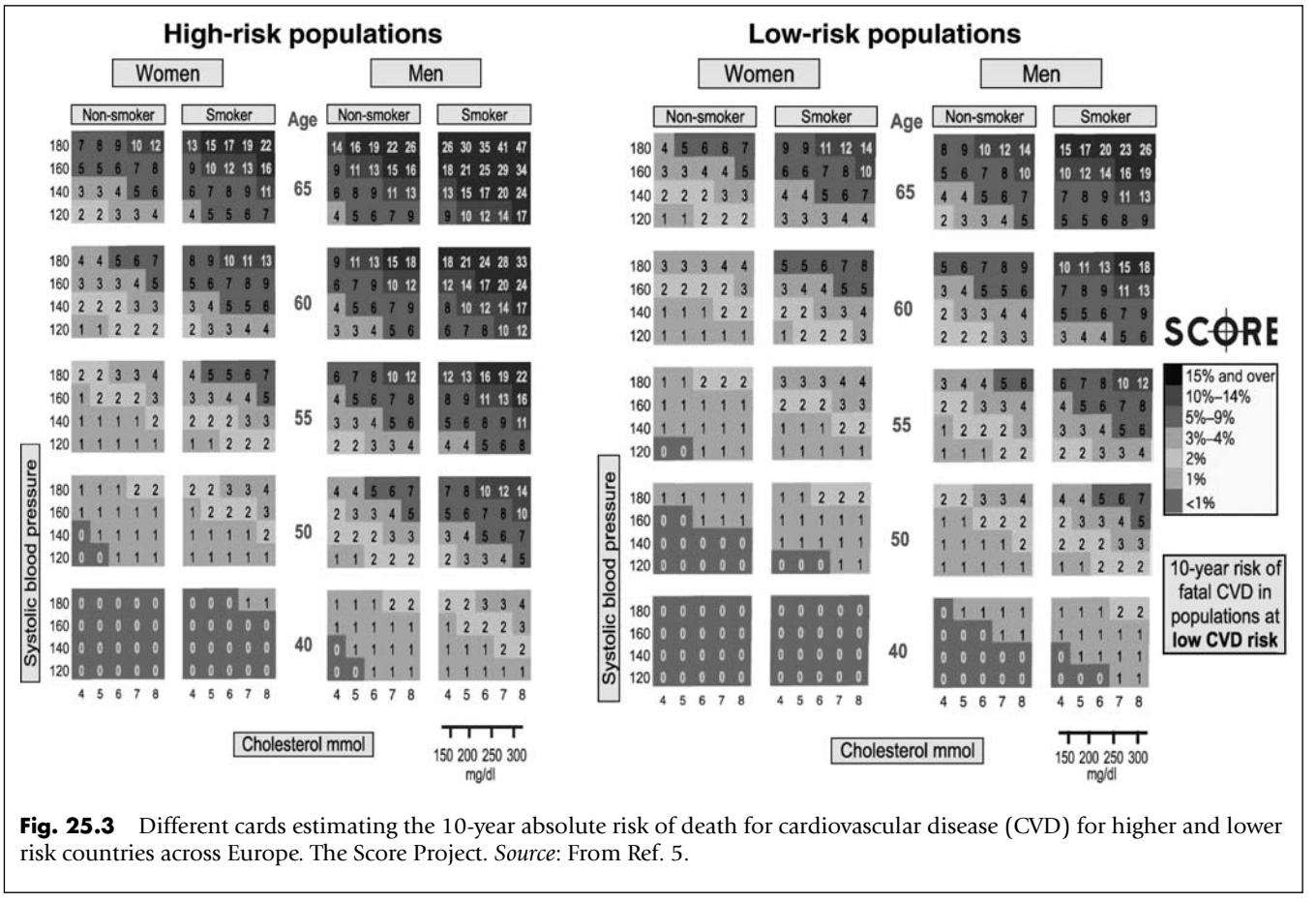

Fig. 25.3 Different cards estimating the 10-year absolute risk of death for cardiovascular disease (CVD) for higher and lower risk countries across Europe. The Score Project. *Source*: From Ref. 5.

This sequence of events directly or indirectly involves most of the CV risk factors that are currently included in the estimate of global CV risk profile (e.g., hypertension, dyslipidemia, diabetes, smoking, etc.). The second level of interaction is related to the capacity of the different risk factors to promote the development of other conditions that might directly contribute to worsen CV risk profile. For example, the presence of diabetes is associated with a significant increase in the rate of hypertension, and the prevalence of elevated BP values in the diabetic patients has been estimated in over 70% of the population, with a further increase in those patients who develop renal abnormalities or proteinuria (23). At the

	Blood pressure (mmHg)				
Other risk factors, OD, or disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥ 180 or DBP ≥ 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors, MS, OD, or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

Fig. 25.4 Risk stratification to quantify prognosis in patients with HT and additional risk factors according to European Society of Hypertension–European Society of Cardiology Guidelines. The dashed line indicates how the definition of HT may be variable, depending on the level of total CV risk. *Abbreviations*: CV, cardiovascular; DBP, diastolic blood pressure; HT, hypertension; MS, metabolic syndrome; OD, organ damage; SBP, systolic blood pressure. *Source*: From Ref. 6.

same time, the results of the ARIC study have suggested the possibility of an increase in the relative risk for the development of diabetes in patients with hypertension (24) and this susceptibility can be significantly enhanced in patients treated with diuretics and β-blockers. The presence of diabetes is also responsible for the development of the so-called "atherogenic dyslipidemia" [elevated triglyceride, small low-density lipoprotein (LDL) particles, low high-density lipoprotein (HDL) cholesterol] that significantly contributes to increase the extent of CV risk in combination with glucose abnormalities. More recently, some intriguing observations have been published supporting the association between the presence of lipid abnormalities and in particular hypercholesterolemia and the increase in the relative risk of arterial hypertension (25–27). The negative effects of hypercholesterolemia seems to be more directly related to the plasma levels of LDL and non-HDL cholesterol, and might be directly related to the activation of the tissue renin–angiotensin–aldosterone system, leading to an overexpression of AT_1 receptors for angiotensin II (28). A well-known example of the relationship between the complexity of the pathophysiological interaction among risk factors and the individual CV risk profile are the patients with metabolic syndrome with abdominal obesity and/or impaired glucose/insulin homeostasis. In this population of patients, the increase in the rate of CV complications is mediated by the combination between the synergistic effect of different risk factors at the vascular level and the capacity of the underlying metabolic disease of eliciting the progression of glucose and lipid abnormalities (19).

The demonstration that several pathophysiological mechanisms might support the concept of global CV risk beyond the epidemiological evidence considerably increases the clinical relevance of CV risk profile and strongly supports a primary role for preventive strategies interfering with the single risk factors as well as with the mechanisms responsible for their possible interactions.

GLOBAL CV RISK AND CV PREVENTION

The evidence that the interventions addressing the different modifiable risk factors disrupt the progression of the atherosclerotic disease supports the validation of the concept of total CV risk in clinical practice. In the large cohort of the MRFIT study, the long-term extension of the observation has demonstrated the benefit of a global approach to risk factors (e.g., hypertension, high-LDL cholesterol, etc.) by showing a lesser event rate in those subjects undergoing a combined intervention involving multiple risk factors (29). In addition, in the late 1980s, Samuelsson et al. published some interesting data in patients with multifactorial risk profiles by demonstrating that the preventive impact of a reduction in BP or total serum cholesterol diminishes in patients showing no changes in the added single risk factor (Figure 25.5) (30). All these data raise the concept that the reduction of global CV risk should be the future target of intervention for clinical trials addressing the prevention of CV disease. Unfortunately, despite the fact that several different trials have aggressively targeted individual risk factors, and a number of additional studies have been conducted in patients with >1 risk factor (particularly in patients with hypertension), only few endpoint trials have targeted the global risk profile.

In patients with hypertension, two large trials of patients with multiple risk factors included both a hypertension arm and a lipid-lowering arm: ALLHAT (31) and ASCOT (32). ALLHAT is the largest, randomized, double-blind clinical trial with CV end-point carried out in hypertensive patients with multiple risk factors. Patients enrolled in the ALLHAT trial with hypertension and hypercholestolemia have been randomized to the treatment with different antihypertensive drugs combined with pravastatin or placebo. However, due to the small difference in serum cholesterol (≈9%) in response to randomized drugs, the trial was unable to demonstrate any favorable interaction between combined treatments in terms of preventive effect and reduction of global CV risk. The ASCOT study, which involved 19,342 high-risk hypertensive patients with at least three CV risk factors, had two primary objectives directly pertinent to global CV risk. First, to assess whether the combination therapy with newer antihypertensive agents (amlodipine ± perindopril) is more effective than the traditional combination therapy (atenolol ± thiazide diuretic) in reducing the rate of major coronary events. Second, to assess whether the addition of a statin (atorvastatin) to these combinations would increase the extent of the CV benefit in a subgroup of patients with normal or mildly elevated total cholesterol levels (≤6.5 mmol/l). In this high-risk population, even a small difference in BP decrease in favor of the amlodipine-based treatment (–2.7 mmHg for systolic BP and –1.9 mmHg for diastolic BP) resulted in a lower incidence of all-cause mortality and stroke. On the other hand, of the 10,305 patients who were eligible for the lipid-lowering arm, the treatment with atorvastatin significantly reduced serum cholesterol levels and led to a lower incidence of fatal and non-fatal coronary heart disease (CHD), stroke, and total CV events. Interestingly, the beneficial effect of atorvastatin was confirmed in the subpopulation of high-risk patients with serum cholesterol levels well within the normal range (<5.6 mmol/l). All these data clearly support the importance of global CV risk as a measure of the impact of the pharmacological preventive strategies against CV diseases. In particular, the results of the ASCOT trial support some very important concepts that emphasize the

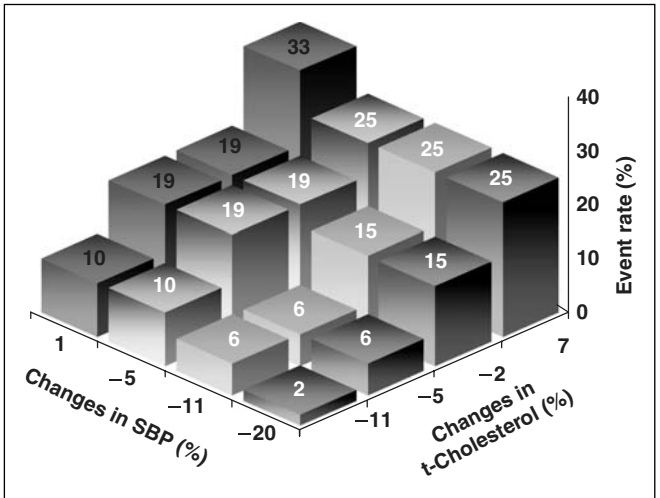

Fig. 25.5 Effect of reciprocal changes in systolic blood pressure (SBP) and total serum cholesterol levels on the incidence of major coronary heart disease events in patients with hypertension and hypercholesterolemia.

role of global CV risk. The first is the demonstration that, in patients with high global CV risk, the modifiable risk factors may play a pathogenetic role, even when they do not exceed the "normal" range. The second is that even the achievement of a small reduction of modifiable CV risk factors may be largely effective in patients with high global CV risk. The third concept is that any preventive approach toward modifiable risk factors is more successful in patients with high-risk profiles. As a consequence, the estimate of global CV risk must be considered as a mandatory procedure for the identification of preventive strategies against CV diseases. Accordingly, an effective approach to CV prevention should always consider the possibility of treating patients at risk according to their global CV risk profile. This means that, in the future, we should probably also include among the targets of treatment those risk factors whose level is within the normal range when they belong to subjects with an elevated CV risk profile. A typical example of this comprehensive approach are the results of the Heart Protection Study (HPS) that provided evidence that the benefit of statin therapy extend to all patients with elevated CV risk profile, irrespectively of age, gender, and presence of hypertension or diabetes (33). In the HPS, the treatment with simvastatin for 5 years, in a very large cohort of about 20,000 patients, significantly reduced the risk of all-cause mortality by 13% and of any vascular death by 17% compared with placebo. An important finding from the HPS was that lipid lowering therapy with a statin decreased the risk of CV events both in patients with elevated baseline LDL-cholesterol levels and in those with LDL-cholesterol levels within the normal range (<100 mg/dl). These results provide support for the primary role of the estimate of global CV risk as a measure of the appropriateness of CV preventive strategies either in patients with the unambiguous elevation of a single risk factor (e.g., hypertension, hypercholesterolemia) or in those showing borderline abnormalities of multiple risk factors who are responsible for a large proportion of public clinical risk for CV diseases in the general population (12,13).

The only trial addressing the preventive effects of a global approach to CV risk was the STENO-2 study that was carried out in a population of patients with hypertension and type-2 diabetes (34). In terms of CV risk, glycemia is directly related to CV risk (35) and in people with diabetes the risk of CV disease approaches that in non-diabetic population with previous coronary artery disease (36). However, diabetes mellitus is typically associated with a multifactorial risk profile and diabetic patients are prone to a number of CV risk factors beyond hyperglycemia, including hypertension and lipid disorders. A recent publication, involving the population of the Framingham study, has demonstrated that the increase in the relative risk of CV event reported in the diabetic population is restricted to those patients where hyperglycemia combines with additional CV risk factors (37). The excess in CV risk that affects the diabetic population is the consequence of the interaction between the multiple risk factors and is proportional to the extent of absolute global CV risk. In the diabetic population of the STENO-2 study, the implementation of a comprehensive strategy of CV prevention, improving glucose control, BP control, and lipid profile, and reducing the platelet aggregation, determined a significant decrease in the rate of major CV events. This confirms the contribution of multiple risk factors to the global CV risk and the pivotal role of a large-scale approach to global CV prevention, particularly in high-risk patients.

CONCLUSIONS

According to worldwide epidemiological facts, the premature morbidity and mortality is substantially due to CV disease, with tobacco use, diabetes, dyslipidemia, and hypertension being the most important modifiable risk factors. The absolute risk of coronary and cerebrovascular disease is directly proportional to the number and the reciprocal interaction between the various modifiable and non-modifiable risk factors. Number and interaction are the concepts that contribute to define the notion of "global CV risk." The estimate of global CV risk is a crucial step for the identification of those subjects whose risk profile warrants consideration of a preventive treatment, including those subjects with only borderline abnormalities of several risk factors. This approach has important clinical implications. In particular, it allows the extension of any effective preventive strategies of CV disease to the many subjects who should not have been otherwise treated according to a more "traditional" and less comprehensive approach to CV prevention focused on the identification and treatment only of the "abnormal" risk factor.

In conclusion, the available data suggest that clinicians who see the patients for the prevention of CV disease should focus their practice on multivariate models that can predict, with reasonably reliability, the global risk of CV events in large segments of the population.

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Therapeutic aspects

SECTION 6

MORBIDITY AND MORTALITY TRIALS 26

Sverre E Kjeldsen, Gordon T McInnes

MORBIDITY AND MORTALITY TRIALS COMPARING ACTIVE TREATMENT WITH PLACEBO

Meta-analyses (1–4) of trials performed in mostly systolic–diastolic hypertension and in elderly individuals with isolated systolic hypertension have concluded that antihypertensive treatment results in significant and similar reductions of cardiovascular and all-cause mortality in both types of hypertension. In mainly younger subjects with diastolic hypertension, Collins et al. (5) observed a significant reduction in fatal stroke (-45%; $P < 0.001$), but not in fatal coronary heart disease (-11%; NS). This discrepancy might be related to age, because coronary mortality was reduced by 26% ($P < 0.01$) in elderly individuals with systolic–diastolic hypertension (6). Fatal and non-fatal strokes combined and all coronary events were significantly reduced in both types of hypertension. The Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC) (7) performed separate meta-analyses of placebo-controlled trials in which active treatment was initiated by a calcium antagonist or by an angiotensin-converting enzyme (ACE) inhibitor, and showed the reductions in cardiovascular endpoints were similar to those found in the trials in which active treatment was based on diuretics or beta-blockers.

Additional information has more recently been provided by other trials. In placebo-controlled trials, the angiotensin receptor antagonists losartan (8) and irbesartan (9,10) were renoprotective in patients with type 2 diabetes and nephropathy. There was no evidence of benefit for secondary cardiovascular endpoints, but these trials were underpowered for this analysis.

MORBIDITY AND MORTALITY TRIALS COMPARING TREATMENTS INITIATED BY DIFFERENT DRUG CLASSES

During the last 10 years, several randomized clinical trials have compared antihypertensive regimens initiated with different classes of antihypertensive agents, most often comparing older (diuretics and beta-blockers) with newer drugs (calcium antagonists, ACE inhibitors, angiotensin receptor antagonists, alpha blockers). Only occasionally were newer drug classes compared. Several trials (11–19) with >67,000 randomized patients, comparing calcium antagonists with older drugs, have recently been reviewed (20). The pooled odds ratios were close to unity and non-significant for total mortality, cardiovascular mortality, all cardiovascular events and myocardial infarction. Calcium antagonists provided slightly better protection against fatal and non-fatal stroke. The odds ratio reached formal statistical significance (0.90, 95% confidence interval $0.82-0.98$, $P = 0.02$) only after the results of CONVINCE (19), a large trial based on verapamil, was excluded. For heart failure, calcium antagonists appeared to provide less protection than conventional therapy, regardless of whether or not the CONVINCE trial was incorporated in the pooled estimates.

Six trials with about 47,000 randomized patients compared ACE inhibitors with older drugs (12,15,21,22). The pooled odds ratios were close to unity and non-significant for total mortality, cardiovascular mortality and myocardial infarction. Compared with older drugs, ACE inhibitors provided slightly less protection against stroke, heart failure and all cardiovascular events. For all cardiovascular events and heart failure there was significant heterogeneity between the trials due to the ALLHAT (12) findings. Compared with chlorthalidone, ALLHAT patients allocated to lisinopril had a greater risk of stroke, heart failure, and hence combined cardiovascular disease (12). Similar findings were previously reported for the comparison of the alpha-blocker doxazosin with chlorthalidone, an ALLHAT arm that was interrupted prematurely (11). Although ALLHAT (11,12) stands out as the largest double-blind trial undertaken in hypertensive patients, interpretation of its results is difficult. In ALLHAT 90% of the patients at randomization were already on antihypertensive treatment, most often diuretics; thus, ALLHAT tested continuing a diuretic versus switching drug classes. Patients on diuretics with latent or compensated heart failure were deprived of their therapy when they were not randomized to chlorthalidone. The achieved systolic pressure was higher on doxazosin, amlodipine, and lisinopril than on chlorthalidone. These factors may explain why the Kaplan–Meier curves started to diverge immediately after randomization for heart failure and approximately 6 months later also for stroke. The sympatholytic agents used for step-up treatment (atenolol, clonidine and/or reserpine at

the physician's discretion) led to an unusual treatment regimen, which does not reflect modern clinical practice, is not usually recommended, and is known to potentiate the blood pressure (BP) response to diuretics much more than that to ACE inhibitors or α-blockers. Finally, ALLHAT did not include systematic endpoint evaluation, what may have particularly affected evaluation of "softer" endpoints, such as congestive heart failure.

These limitations notwithstanding, ALLHAT (11,12), either alone or in combination with the other trials, supports the conclusion from meta-analyses (7,23) that the benefits of antihypertensive therapy largely depend on BP lowering. The conclusion that a substantial portion of the benefit of antihypertensive treatment depends on BP reduction, per se, is also supported by the findings of the recently published INVEST study (24) in which cardiovascular disease was similarly frequent in patients treated with verapamil as compared to those treated with atenolol (± hydrochlorothiazide). The Second Australian National Blood Pressure study (25) found ACE inhibitor-based treatment to be more protective against cardiovascular disease than diuretic-based treatment. The difference was modest, however, and significant only in men. The paramount importance of BP control for prevention of cardiovascular complications is supported by the results of VALUE (26,27) in which the greater BP reduction on amlodipine in the first months following randomization was accompanied by a lower risk of events on that drug compared with valsartan. Nonetheless, the primary cardiac outcome did not differ between the regimens.

Apart from VALUE, two other trials have studied the new class of angiotensin receptor antagonists. The LIFE study (28) compared losartan with the beta-blocker atenolol in hypertensive patients with left ventricular hypertrophy. After an average of 4.8 years, there was a significant 13% reduction in major cardiovascular events on losartan, mostly due to a significant 25% reduction in stroke incidence. There were no BP differences between the treatment groups. The SCOPE study (29) was initiated as a comparison of elderly patients receiving candesartan or placebo, but since, for ethical reasons, 85% of the placebo-initiated patients received antihypertensive therapy (mostly diuretics, beta-blockers or calcium antagonists) the study is an underpowered comparison of antihypertensive treatment with or without candesartan. After 3.7 years of treatment there was a non-significant 11% reduction in major cardiovascular events, and a significant 28% reduction in non-fatal strokes among candesartan-treated patients, with an achieved BP slightly lower (3.2/1.6 mmHg) in the candesartan group.

A recent meta-analysis (23) concluded that ARB-based regimens showed a greater effect than other control regimens on the risk of stroke, heart failure and major cardiovascular events, but not on coronary heart disease, cardiovascular death and total mortality. In VALUE, the heart failure finding was similar, while the stroke finding was confounded by the BP difference.

TRIALS ON INTERMEDIATE ENDPOINTS

LEFT VENTRICULAR HYPERTROPHY

The most recent meta-analysis suggests that, for similar BP reduction newer agents (ACE inhibitors, calcium antagonists, and angiotensin II antagonists) may be more effective than conventional drugs (30). The LIFE study is particularly relevant, since the greater regression of electrocardiographically or echocardiographically determined left ventricular hypertrophy with losartan compared with atenolol was accompanied by a reduced incidence of cardiovascular events (28).

ARTERIAL WALL AND ATHEROSCLEROSIS

Several randomized trials have compared the long-term (2–4 years) effects of different antihypertensive regimens on carotid artery wall intima–media thickness. The most convincing evidence is with calcium antagonists, including results from a long-term trial in more than 2,000 patients (31). The data (31–33) show that, for a similar reduction in BP, carotid artery wall thickening and plaque formation is slowed more with these drugs than with conventional therapies. Similar evidence although less consistent is also available for ACE inhibitors (34).

RENAL FUNCTION

The most abundant evidence concerns renal function in diabetic patients (35). More intensive BP lowering reduces consistently urinary protein, both overt proteinuria and microalbuminuria. Several comparisons of different agents (21,36,37) failed to show a difference in the renal protective effect, whereas the angiotensin antagonist irbesartan was superior to the calcium antagonist amlodipine in retarding development of renal failure (9), and losartan was more efficacious in reducing the progression to new overt proteinuria compared with the beta-blocker atenolol (38). Progression of renal dysfunction can be retarded by introducing an angiotensin receptor antagonist (8,9) in diabetic patients with advanced nephropathy.

A recent meta-analysis of 11 randomized trials comparing antihypertensive regimens, including ACE inhibition in patients with non-diabetic renal disease (39), indicates a significantly slower progression in patients achieving BP of 139/85 rather than 144/87 mmHg. It is not clear, however, whether the benefit could be ascribed to ACE inhibition, or to the lower BP achieved. In the recently completed AASK study (40,41), ACE inhibitors were shown to be somewhat more effective than beta-blockers or calcium antagonists in slowing the decline in glomerular filtration rate. It appears, therefore, that in patients with non-diabetic renal disease the use of an ACE inhibitor may be more important than aggressive BP reduction, whereas in diabetic patients aggressive lowering of BP and blockade of the renin–angiotensin system may be equally important.

NEW ONSET DIABETES

Several trials have monitored the incidence of new-onset diabetes during treatment follow-up. With few exceptions (15, 16), studies have shown a lower incidence in patients treated with an ACE inhibitor, a calcium antagonist or an angiotensin II antagonist when compared with diuretics or beta-blockers (11,12,18,22,24,29,42,43), and when administration of the angiotensin II antagonist valsartan was compared with administration of amlodipine (26). Differences between different antihypertensive drugs are likely to be clinically relevant

because, in the long term, treatment-induced diabetes is accompanied by an increased incidence of cardiovascular disease of a magnitude similar to that with naturally occurring diabetes (44,45). The duration of morbidity and mortality trials has been insufficient to allow detection of the adverse cardiovascular consequences of new onset diabetes since these become apparent only after several years.

TRIALS ON HYPERTENSION AND CONCOMITANT DISEASES

DIABETES MELLITUS

The prevalence of hypertension is increased in patients with diabetes mellitus (46). Type 2 diabetes is by far the most common form, occurring about 10–20 times as often as type 1 diabetes. Hypertensive patients frequently exhibit the "metabolic syndrome," i.e., the association of insulin resistance (with the concomitant hyperinsulinemia), central obesity, characteristic dyslipidemia (high plasma triglyceride and low high-density lipoprotein cholesterol), and hypertension (47,48). These patients are prone to develop type 2 diabetes.

In type 1 diabetes, hypertension often reflects the onset of diabetic nephropathy (49), whereas a large fraction of hypertensive patients still have normoalbuminuria at the time of diagnosis of type 2 diabetes (50). The prevalence of hypertension (defined as a BP $\geq$140/90 mmHg) in patients with type 2 diabetes and normoalbuminuria is very high, at 71%, and increases even further to 90% in the presence of microalbuminuria (51).

The co-existence of hypertension and diabetes mellitus (either type 1 or 2) substantially increases the risk of macrovascular complications, including stroke, coronary heart disease, congestive heart failure, and peripheral vascular disease, and is responsible for excess in cardiovascular mortality (49,52). The presence of microalbuminuria is both an early marker of renal damage and an indicator of increased cardiovascular risk (53,54). Hypertension also accelerates the development of microvascular complications (nephropathy and retinopathy) (49,55). The level of BP achieved during treatment influences greatly the outcome of diabetic patients. In patients with diabetic nephropathy, the rate of progression of renal disease is in a continuous relationship with BP down to levels of 130 mmHg systolic and 70 mmHg diastolic. Aggressive treatment of hypertension protects patients with type 2 diabetes against cardiovascular events. The primary goal of antihypertensive treatment in diabetics should be to lower BP below 130/80 mmHg whenever possible, the best BP being the lowest one that is well tolerated.

Weight gain is a critical factor in the progression to type 2 diabetes. It is therefore essential to tackle overweight by all means possible, particularly by calorie restriction and a decrease in sodium intake, as there is a strong relationship exists between obesity, hypertension, sodium sensitivity, and insulin resistance (56).

No major trial has been performed to assess the effect of pharmacological BP lowering on cardiovascular morbidity and mortality in hypertensive patients with type 1 diabetes. There is however good evidence that β-blocker- and diuretic-based antihypertensive therapy delays the progression of nephropathy in these patients (57). In albuminuric patients with type 1 diabetes the best protection against renal function deterioration appears to be obtained with ACE inhibition (58). It remains unknown whether angiotensin II receptor antagonists are equally effective in this indication.

In type 2 diabetes (59), evidence of the superiority or inferiority of different drug classes is still vague and contradictory. Superiority of ACE inhibitors in preventing the aggregate of major cardiovascular events is limited to two trials, one against diuretics/beta-blockers (22), the other against a calcium antagonist (37), or on analyses of cause-specific events for which the trial power was even less. The ALLHAT trial (11,12) also failed to find differences in cardiovascular outcomes in the larger number of type 2 diabetes included in the trial, randomized to a diuretic, an alpha-blocker, a calcium antagonist or an ACE inhibitor. Recent evidence with angiotensin II receptor antagonists has shown a significant reduction of cardiovascular events, cardiovascular death and total mortality in diabetics when losartan was compared with atenolol (38), but not when irbesartan was compared with amlodipine (9). If renal endpoints are also considered, the benefits of angiotensin II receptor antagonists become more evident; IDNT (9) showed a reduction in renal dysfunction and failure by the use of irbesartan rather than amlodipine, and LIFE (28) indicated losartan reduced incidence of new proteinuria compared with atenolol. In view of the consensus that BP in type 2 diabetic patients must be lowered, whenever possible, to $<$130/80 mmHg, it appears reasonable to recommend that all effective and well-tolerated antihypertensive agents can be used, generally in multiple drug combinations. Available evidence suggests that renoprotection may be improved by the inclusion of an angiotensin receptor antagonist and that, in patients with high normal BP, who may sometimes achieve BP goal with monotherapy, the preferred first drug should be an angiotensin II receptor antagonist.

HYPERTENSIVE PATIENTS WITH DERANGED RENAL FUNCTION

Renal vasoconstriction is found at the initial stages of essential hypertension, and this is reversed by the administration of calcium channel blockers and ACE inhibitors. In more advanced stages of the disease, renal vascular resistance is permanently elevated as a consequence of structural lesions of the renal vessels (nephrosclerosis). Before antihypertensive treatment became available, renal involvement was frequent in patients with primary hypertension. Renal protection in diabetes has two main requirements: first to attain very strict BP control ($<$130/80 mmHg and even lower, $<$125/75 mmHg, when proteinuria $>$1 g/day is present), and second to lower proteinuria or albuminuria (micro- or macro-) to values as near to normal as possible. In order to attain the latter goal blockade of the effects of angiotensin II (either with an ACE inhibitor or an angiotensin receptor blocker) is required. In order to achieve the BP goal, combination therapy is usually needed, even in patients with high normal BP (59). The addition of a diuretic as second step therapy is recommended (a loop diuretic if serum creatinine $>$2 mg/dl), but other combinations, including calcium antagonists, can also be considered. To prevent or retard development of nephrosclerosis, blockade of the renin–angiotensin system has been reported to be more important than attaining very low BP (41). It seems prudent to start antihypertensive therapy in patients (diabetic or non diabetic) with reduced renal function, especially if accompanied by proteinuria, with an ACE inhibitor or an

angiotensin receptor antagonist, and then to add other antihypertensive agents in order to further lower BP.

HIGH RISK IN GENERAL

In the VALUE trial (26), 15,245 hypertensive patients with high cardiovascular risk for various reasons were randomized to valsartan- or amlodipine-based treatment for an average of 4.2 years, when 1,599 primary endpoints defined as the composite of serious cardiac morbidity or cardiac mortality had accumulated. There was no difference between the treatment arms with respect to the primary endpoint; however, amlodipine lowered BP more effectively than valsartan, and the difference in BP was associated with less stroke and myocardial infarction early in the study. Toward the end of the study, valsartan reduced new onset diabetes (26) and serious heart failure, particularly if the data were adjusted for the difference in BP (27). Prompt control of BP is desirable in high-risk individuals and blockade of the renin–angiotensin system may be desirable in the long term.

HYPERTENSION, ANTIHYPERTENSIVE TREATMENT, AND DEMENTIA

As cognition disturbances in the elderly are, at least in part, hypertension-related (60,61), suitable cognition evaluation tests, such as the Mini-Mental State Evaluation (MMSE), should be considered in the clinical assessment of the elderly hypertensive. In the Syst-Eur study (62), active treatment based on a dihydropyridine calcium antagonist reduced the risk of developing dementia compared with placebo. In the PROGRESS study (63) ACE inhibitor and diuretic treatment (perindopril + indapamide) was associated with a reduction of dementia compared with placebo treatment in patients who had previously suffered stroke, but the finding was in parallel with and explained by stroke reduction. In the SCOPE study (29) there was no difference between the ARB candesartan and standard treatment in the development of dementia. However, SCOPE participants had, on average, a very high MMSE at outset of the study, and there was a benefit of candesartan in those with MMSE below average at baseline (29). More research is needed in this field.

HYPERTENSION IN THE ELDERLY

There is little doubt from randomized controlled trials that older patients benefit from antihypertensive treatment in terms of reduced cardiovascular morbidity and mortality, whether they have systolic–diastolic hypertension (6) or isolated systolic hypertension (4). Whereas trials in the elderly usually include patients who are at least 60 years old, a recent meta-analysis concluded that fatal and non-fatal cardiovascular events combined were significantly reduced in participants in randomized, controlled trials of antihypertensive drug treatment aged 80 years and over, but all-cause mortality was not reduced (64). The seminal trials of antihypertensive treatment versus placebo or no treatment in elderly patients with systolic–diastolic hypertension used a diuretic or a beta-blocker as first-line therapy (6). In trials on isolated systolic hypertension, the first-line drug consisted of a diuretic (65) or a dihydropyridine calcium channel blocker (62,66,67). In all these trials, active therapy was superior to placebo or no treatment. Other drug classes have only been used in trials in which "newer" drugs were compared with "older" drugs (11, 12,15,28,29,68). Benefit has been shown in older patients for at least one representative agent of several drug classes, i.e., diuretics, beta-blockers, calcium channel blockers, converting enzyme inhibitors, and angiotensin receptor antagonists.

Initiation of antihypertensive treatment in elderly patients should follow the general guidelines. Many patients will have other risk factors, target organ damage, and associated cardiovascular conditions, to which the choice of the first drug should be tailored. Furthermore, many patients will need two or more drugs to control BP, particularly since it is often difficult to lower systolic pressure to below 140 mmHg (69,70) and most elderly subjects have systolic hypertension.

SECONDARY CARDIOVASCULAR PREVENTION

CONCOMITANT CORONARY HEART DISEASE AND CONGESTIVE HEART FAILURE

The risk of a recurrent event in patients with a coronary heart disease is significantly affected by the BP level (71), and hypertension is frequently a past or present clinical problem in patients with congestive heart failure (72). However, only a few trials have tested the effects of BP lowering in patients with coronary heart disease or congestive heart failure. The HOT study showed a significant reduction of strokes the lower the target BP in hypertensives with a previous history of ischemic heart disease and found no significant evidence of increased coronary heart disease risk at low diastolic BP (73,74).

Beta-blockers, ACE inhibitors, and anti-aldosterone compounds are well established in the treatment regimens for preventing cardiovascular events and prolonging life in patients after an acute myocardial infarction and with heart failure, but how much of the benefit is due to concomitant BP lowering and how much is due to specific drug actions has never been clarified. There are also data to support the use of angiotensin receptor antagonists as alternatives to ACE inhibitors in congestive heart failure, or in combination with ACE inhibitors (75,76). The role of calcium antagonists in prevention of coronary events has been vindicated by the ALLHAT trial, which showed a long acting dihydropyridine to be equally effective as the other antihypertensive compounds (12). Calcium antagonists are possibly less effective in prevention of congestive heart failure and, where possible, should be avoided in patients with heart failure.

CONCOMITANT CEREBROVASCULAR DISEASE

Evidence for the benefits of antihypertensive therapy in patients who had already suffered a stroke or a TIA (secondary prevention) was equivocal (78), until recent trials showed the benefits of lowering BP in patients with previous cardiovascular disease events, even when their initial BP was in the normal range (63). Treatment was restricted to patients beyond the acute phase (2 weeks) of stroke. Whether elevated

BP should be lowered during the acute phase is still disputed. Trials are in progress. A statement by a special ISH panel has recently been published (79).

PROTECTION AS A FUNCTION OF GENDER AND ETHNICITY

The proportional reduction of cardiovascular risk from BP reduction in randomized clinical trials appears to be similar in women and in men (80); women had only small and non-significant benefits of acetylsalisylic acid compared with significant reduction in myocardial infarction in men in the HOT study (81). Information on ethnicity is limited as trials have mostly included Caucasians; however, both the ALLHAT (12) and LIFE (82) studies suggested that African-Americans may achieve lesser cardiovascular risk reduction with drugs which block the renin–angiotensin system.

BP THRESHOLD FOR TREATMENT

Guidelines for initiating antihypertensive treatment are based on two criteria: (*i*) the level of total cardiovascular risk, and (*ii*) the level of systolic and diastolic BPs. For individuals with systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg, antihypertensive treatment is recommended only for those with stroke (63), coronary artery disease (43), and diabetes (36), or if total cardiovascular risk is high. Close monitoring of BP without BP intervention is recommended for patients at moderate or low total risk, who will benefit from lifestyle measures and correction of other risk factors (e.g., smoking).

In patients with grade 1 and 2 hypertension, antihypertensive drug treatment should be initiated promptly in subjects classified as at high or very high risk, whereas subjects at moderate or low added risk BP, as well as other cardiovascular risk factors, should be monitored for extended periods (from 3 to 12 months) while the influence of non-pharmacological treatment is monitored (83). If after extended observation, systolic values $\geq$140 or diastolic values $\geq$90 mmHg persist, antihypertensive drug treatment should be initiated in patients at moderate risk, and considered in patients at lower risk. In the latter group, the decision whether to adopt drug treatment should be influenced by the patient's preference and/or available resources. In subjects with grade 3 hypertension, confirmation of elevated BP values should be obtained within a few days, and drug treatment instituted, without waiting to establish the absolute risk (high even in absence of other risk factors). Complete assessment of other risk factors, target organ damage or associated disease can be carried out after initiation of treatment; lifestyle measures can be instituted in parallel.

Several studies have shown that, in high or very high-risk patients, treatment of hypertension is very cost-effective, i.e., the reduction in the incidence of cardiovascular disease and death largely offsets the cost of even lifetime treatment. Some pharmacoeconomical studies suggest that treatment may be less cost-effective in grade 1 or 2 hypertensives at low or moderate added risk. This may be more apparent than real, however, because in these patients the purpose of treatment is not to prevent an unlikely morbid or fatal event in the subsequent few years but rather to delay the onset and/or progression of organ damage that will make the patient a high risk one in the long term. Several trials of antihypertensive therapy, particularly HDFP (84) and HOT (73), have shown that, despite intensive BP lowering, residual cardiovascular risk remains higher in relatively high risk patients than in patients with initial moderate risk. This suggests that some of the major cardiovascular risk changes may be difficult to reverse, and that restricting antihypertensive therapy to patients at high or very high risk may be a far from optimal strategy.

BP TARGETS

The primary goal of treatment of the patient with high BP is to achieve the maximum reduction in the long-term total risk of cardiovascular morbidity and mortality. This requires treatment of all the reversible risk factors identified, including smoking, dyslipidemia, or diabetes, and the appropriate management of associated clinical conditions, as well as treatment of the raised BP, per se.

Randomized trials comparing less with more intensive treatment (36,37,73,85) have shown that, in diabetic patients, more intensive BP lowering is more protective (7,36,85,86). This is not yet conclusively established in non-diabetic subjects. The only trial not exclusively involving diabetics is the HOT study (73), in which, the small achieved diastolic BP differences between the groups randomized to $\leq$90, 85, or 80 mmHg, may have precluded the detection of significant differences in the risk of cardiovascular events between adjacent target groups. The results of the HOT study failed to indicate an increase in cardiovascular risk in the patients randomized to the lowest target group. Thus, setting rigorous BP goals is not likely to be harmful. Furthermore, a recent subgroup analysis of the HOT study (87) suggests that except in smokers, a reduction of diastolic BP to an average of 82 rather than 85 mmHg significantly reduces major cardiovascular events in non-diabetic patients at high/very high risk (50% of HOT study patients), as well as in patients with previous ischemic heart disease, in patients older than 65 years and in women. In patients with a history of stroke or transient ischemic attack, the PROGRESS trial (63) showed less cardiovascular mortality and morbidity by reducing diastolic BP to 79 mmHg (active treatment group) rather than 83 mmHg (placebo group). Similar observations have been made in patients with coronary disease although the role of BP reduction in this trial has been debated (69). Evidence of a greater benefit from a more rigorous reduction in systolic BP is limited to the UKPDS study (85), which has shown, through retrospective analysis of the data, less cardiovascular morbid events at values below 130 and 120 as compared with 140 mmHg. Most trials, however, have been unable to reduce systolic BP below 140 mmHg, and in no trials on diabetic and non-diabetic patients values below 130 mmHg have been achieved (69).

For patients with non-diabetic renal disease, data about the effects of more or less intensive BP lowering on cardiovascular events are scanty: the HOT study (88) was unable to find any significant reduction in cardiovascular events in the subset of patients with plasma creatinine $>$115 μmol/l ($>$1.3 mg/dl) or $>$133 μmol/l ($>$1.5 mg/dl) when subjected to more versus less intensive BP lowering (139/82 versus 143/85 mmHg). However, no trial suggests an increased cardiovascular risk at the lowest BP achieved.

In conclusion, on the basis of current evidence from trials, it can be recommended that BP, both systolic and diastolic,

be intensively lowered at least below 140/90 mmHg and to lower values if tolerated, in all hypertensive patients, and below 130/80 mmHg in diabetics. The achievable goal may depend on the pre-existing BP level and systolic values below 140 mmHg are difficult to achieve, particularly in the elderly.

When home or ambulatory BP measurement are used to evaluate the efficacy of treatment, it must be remembered that daytime values provided by these methods (compared with office measurement) are on average at least 10 mmHg lower for systolic and 5 mmHg lower for diastolic BP. These differences tend to become smaller at lower office BP values, such as those recommended as treatment goals (89–91).

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27 THE NEPHROPROTECTIVE EFFECT OF ANTIHYPERTENSIVE TREATMENT

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INTRODUCTION

A large amount of clinical and epidemiologic evidence has been accumulated in support of the importance of blood pressure (BP) control in order to reduce chronic kidney disease (CKD) progression. It is also generally accepted that suppression of the renin–angiotensin–aldosterone system (RAAS) must be considered in any patient with CKD, in particular if albuminuria is present. However, the analysis of renal outcome through the estimation of glomerular filtration rate (GFR) in trials primarily devoted to cardiovascular (CV) protection in hypertensive patients, in particular the ALLHAT trial, has come to question the superiority of the suppression of the RAAS upon BP control in order to protect the kidneys in hypertensive patients. The topic is particularly interesting because the existence of an increased CV risk associated with renal function decline has been amply demonstrated in many different clinical situations, including arterial hypertension. The enhancement in global CV risk accompanying CKD would force the need to use drugs suppressing the RAAS for CV protection independently of the influence on renal outcome.

The term CKD includes the development and evolution of chronic renal failure of many different origins (1). Trials investigating the effect of different therapies on the evolution of renal function have usually included patients with early or established primary renal diseases and/or diabetic nephropathy. Most patients presented at entry with macroalbuminuria to ensure that a short duration of follow-up (2 years in most cases) enabled the differentiation of the therapies tested with placebo or between themselves for the protection of renal function. In the case of microalbuminuria the primary aim has been the change in this parameter without considering the evolution of renal function through changes in serum creatinine or estimated GFR.

Current international guidelines devoted to arterial hypertension recognize microalbuminuria, elevation of serum creatinine values, and the existence of a reduced value of estimated GFR (eGFR) as major CV risk factors (2,3) that provide a high added risk on top of the preexisting one provided by other CV risk factors (2–4). In fact, patients developing end-stage renal disease (ESRD) are a minority in the group of individuals developing the different forms of CKD, and could be considered as survivors because CV disease accounts for the death of the great majority of patients with CKD before the development of ESRD. The fact that CKD and CV disease are so closely related has raised the interest for investigating the evolution of renal function in trials involving hypertensive, as well as heart failure (HF) and post-myocardial infarction (MI) patients. This interest is fully justified by the demonstration, in all these situations, of the predictive capacity of renal function alterations for the development of CV events or death. Since its earlier stages, the presence of CKD must then be considered as a situation of high-added CV risk in any hypertensive patient and in any patient presenting with established forms of CV disease (4,5).

Reduction of CV events in CKD population requires the implementation of effective integral therapeutic interventions that protect simultaneously both the kidney and the CV system. These interventions have to be implemented since the very initial stages of CKD, and the attainment of a strict BP control occupies the first position in the list of things to be done in any patient with an elevated global CV risk, provided BP is found to be elevated (2,3).

This brief review contains the most recent data of clinical trials aimed to evaluate renal endpoints in trials primarily devoted to renal function as well as in those dedicated to arterial hypertension and its CV consequences.

THE KIDNEY AND BP

The kidney plays a key role in the control of BP, and impairment of renal function usually leads to the development of arterial hypertension. Thus, high BP can be both a cause and a consequence of CKD (6) and will contribute to an unfavorable renal and CV prognosis. Hypertension-related mechanisms involved in the progression of CKD include the systemic BP load, its direct transmission to the renal microvasculature and glomeruli, and also local factors dependent on the existence of other diseases, like diabetes or primary glomerulonephritis, which by themselves can cause progressive renal damage, even

in the absence of elevated BP. Elevated BP and the amount of albumin present in urine are the two most relevant factors facilitating the progression of renal failure till ESRD (7).

The renoprotection provided by antihypertensive agents depends on their capacity to lower systemic BP and also on their specific effects on renal hemodynamics (8). This effect could influence positively or negatively intraglomerular pressure through the facilitation of the transmission of an uncontrolled systemic BP that, as we know, is present in many patients with CKD even while on treatment and/or through the effect opening or closing the efferent arteriole (8). A recently published meta-analysis of 11 randomized controlled trials has assessed the effect of systolic BP (SBP) on the renal outcome in 1,860 patients with non-diabetic renal disease (9). The lower risk for progressive renal disease was observed when SBP ranged from 110 to 129 mmHg. Higher levels of SBP were associated with a sudden increase in renal risk, regardless of the drug that was used. Values of achieved SBP $<$110 mmHg were interestingly associated with an increased renal risk, consistent with the potential negative renal effects of a drastic reduction in renal perfusion pressure when renal vasculature has suffered the consequences of a maintained elevation of BP and nephrosclerosis has developed (10). Independently of the level of BP attained, antihypertensive regimens that include an angiotensin-converting enzyme inhibitor (ACEI) were more effective than regimens without it for slowing the progression of non-diabetic renal disease. Similar data were found in a secondary analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT), the risk for reaching a renal endpoint in diabetic nephropathy is reduced progressively and continuously at lower levels of the achieved SBP. An optimal renoprotective effect was demonstrated for SBP between 120 and 130 mmHg, with no further benefits below 120 mmHg (11). Here again the drug blocking the effects of angiotensin II exhibited an effect beyond that of BP control obtained by other means. However, two prospective studies (12,13) have shown that a strict BP control to values below 130/80 mmHg does not seem to protect GFR beyond the effect of a control below 140/90 mmHg.

It can then be concluded that the reduction in BP is markedly renoprotective, despite of the type of drug indicated, in both diabetic and non-diabetic renal disease. A strict BP control, independently of how it was obtained, can also be accompanied by a relevant antiproteinuric effect (14).

RECENT TRIALS FOCUSING ON RENAL OUTCOMES

Renin–angiotensin–aldosterone system blockade is strongly recommended by most recent guidelines as the initial regimen of choice for renoprotection based on the results of several clinical trials and meta-analyses that have, with hardly any exception, revealed larger reductions in proteinuria as well as a diminished velocity of progression to the development of renal endpoints with RAAS lockade as compared with other antihypertensive regimens in both diabetic and non-diabetic nephropathies (1–3,14). As an example, the previously mentioned meta-analysis conducted by Jafar et al. (9) suggests that ACE inhibition was associated with overall relative risk reductions of 30–40% for doubling of serum creatinine and/or ESRD in non-diabetic nephropathy, with the greater benefits being seen in patients with heavier proteinuria. Such data indicate that the greater renoprotection that is observed with RAAS blockade is mediated by BP-independent mechanisms.

Similar positive results with suppression of the RAAS, beyond BP control, were seen in the patients included in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and IDNT studies (15,16). These two studies included patients with overt diabetic nephropathy, and two angiotensin receptor blockers (ARBs), losartan and irbesartan, were compared to placebo and placebo or amlodipine, respectively. Data from the RENAAL trial showed that changes in albuminuria in the first 6 months of therapy were approximately linearly related to the degree of long-term renal protection: every 50% reduction in albuminuria in the first 6 months was associated with a 45% reduction in the risk for ESRD during later follow-up (17). A secondary analysis of the IDNT study demonstrated that the risk for renal failure was reduced for increases in proteinuria in the first year of the study (18).

The advantage of RAAS suppression was also demonstrated for the prevention of the development of overt diabetic nephropathy in the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA) study (19). This study showed that treatment with the ARB irbesartan was more effective than placebo in preventing the development of macroalbuminuria and also in favoring regression to normoalbuminuria in microalbuminuric patients with type 2 diabetes, despite a similar BP control.

The possibility that dual RAAS blockade, combining an ACEI and an ARB, was superior to either monotherapy alone, was tested with positive results in the Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting-Enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE) trial (20). This study included patients with non-diabetic CKD and proteinuria and the combination of losartan and trandolapril was more positive than either therapy alone. Similar results have been obtained in a similar study with the combination of candesartan and enalapril (21). These data indicate that a better degree of suppression of the RAAS is obtained with the combination but leave open the possibility that doses higher than those normally used for each component could be equally positive as the combination at lower doses (22). In this sense, recently published data have shown that up-titration of the dose of an ARB improves its capacity to diminish albuminuria (23,24). Up-titration of the dose of an ARB is important because the only head-to-head comparison between an ACEI and an ARB, performed in the Diabetics Exposed to Telmisartan And enalaprIL (DETAIL) study (25) for the long-term renal outcome in mostly microalbuminuric type 2 diabetics, showed that telmisartan (40–80 mg/day) offered comparable renoprotection to enalapril (10–20 mg/day).

The capacity of RAAS suppression for the primary prevention of development of microalbuminuria in type 2 diabetics was recently tested in the Bergamo Nephrologic Diabetic Complications Trial (BENEDICT) study (26). Trandolapril alone or in combination with verapamil was significantly better than placebo or verapamil alone to prevent the development of microalbuminuria. The capacity of an ARB with a similar purpose is being tested in the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study (27).

Preliminary studies in humans recently reviewed (28) have shown encouraging data on the role of aldosterone blockade in the prevention of CKD progression. Aldosterone has been

shown to play non-hemodynamic deleterious effects on the kidney and the CV system while contributing to raise systemic and intraglomerular pressure. Clinical studies are warranted to address, in a more definitive way, the safety and efficacy of aldosterone antagonism in CKD and ESRD.

TRIALS NOT FOCUSED ON RENAL OUTCOMES

As previously commented, the capacity of renal function abnormalities to predict CV events and death in patients with arterial hypertension and established CV disease raised the interest to investigate, in *post-hoc* analysis, the evolution of renal function, determined exclusively as estimated GFR or creatinine clearance in different trials including hypertensive patients, patients with HF and also post-MI patients. Data from these trials must be received with some caution because trials devoted to CV disease frequently exclude patients with renal disease and do not provide adequate information on the renal function of enrollees (29). In fact, a recently published meta-analysis including both trials primarily devoted to renal disease and primarily devoted to CV disease has come to question the value of suppression of the RAAS beyond BP control in order to protect renal function (30). The use of adequate dosages of an ACEI or an ARB and for the adequate length of follow-up is essential in order to conclude on beneficial or detrimental actions related to their effects. An accurate analysis of the studies included in the meta-analysis shows that in those not primarily devoted to renal function this was not the case, in particular when Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), that mostly drove the result of the meta-analysis due to the high number of patients included, is considered (31). With respect to the time of follow-up, it is well recognized that, only in the presence of albuminuria, short follow-up periods of 2–5 years are adequate to show potential differences in renal protection (32). Preliminary data with longer follow-up periods indicate that suppression of the RAAS is required for a better renal protection (33).

Even so, data from trials devoted to hypertension and to renal disease have come to clarify the positive role of calcium antagonists in renal protection when used either alone or in combination with drugs suppressing the RAAS (34). It has also been shown that patients with hypertension or established CV disease and CKD seem to be particularly good responders to the suppression of the RAAS (35,36) and to the administration of a statin (37) and aspirin (38).

EVIDENCE WITH OTHER THERAPIES AND RENAL OUTCOMES

Individuals with CKD usually present with multiple other risk factors for CV disease, and the risk attributable to CKD or to the presence of the other factors is totally independent one from the other (39). An integral CV protection is required in patients presenting with CKD (5).

Drugs other than antihypertensives can also present positive effects on renal function as well as on BP control. This is the case for the effects of statins and thiazolidinediones on albuminuria and on BP (40–43).

In summary, a strict BP control, an adequate suppression of the RAAS, and an integral protection of the increased global CV risk are required in every patient presenting with any stage of CKD.

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NON-PHARMACOLOGICAL INTERVENTIONS 28

Wolfgang Kiowski, Jens Jordan

INTRODUCTION

Lifestyle modifications, in particular dietary and non-pharmacological measures, are commonly recommended by experts and clinical guidelines both for the prevention as well as therapy of hypertension (1–7). Such approaches clearly are of great potential importance in a disease with a very high prevalence [27% of the US population has blood pressure (BP) ≥140/90 mmHg] (Lichtenstein 20). Accordingly, this chapter discusses the most commonly advocated measures and evaluates the data upon which these recommendations rely, both with respect to the prevention of hypertension, as well as their potential for reducing BP in patients with hypertension.

WEIGHT REDUCTION

A healthy body weight is currently defined as a body mass index (BMI) of 18.5–24.9 kg/m^2, and a BMI of ≥30 kg/m^2 represents obesity. In the United States, only one-third of the adult population has normal body weight and one-third are obese (1,8). Similarly, in the United Kingdom, approximately 50% of the adult population are either overweight or obese (BMI ≥ 25 kg/m^2), a dramatic increase from 1980 when 6% of men and 8% of women were obese (9). Along with the increase in overweight and obesity is a proportional increase in co-morbidities and cardiovascular risk factors, e.g., type 2 diabetes mellitus and dyslipidemia. Moreover, obesity is an independent risk factor for cardiovascular morbidity and mortality (10,11) and, in a recent study of 527,265 U.S. men and women, all-cause mortality among participants who were overweight at the age of 50 years was 20–40% higher than that among participants who had a BMI of 23.5–24.9 kg/m^2 at that age (12). The risk among obese subjects was two to at least three times that of participants with a BMI of 23.5–24.9 kg/m^2. Alarmingly, the prevalence of gross obesity (BMI ≥ 40 kg/m^2), which brings about the most severe health complications, increased from 0.78% in 1990 to 2.2% in 2000 in the United States (13). Not only overweight itself but the pattern of fat distribution also seems to be of importance with central adiposity, reflected by an increased waist-to-hip ratio, or more simply defined by an increased waist circumference (14), carrying a significant greater risk for stroke, ischemic heart disease and all-cause mortality and the development of diabetes mellitus compared to peripheral adiposity (15). Differences in waist-to-hip ratio between men and women have been proposed as an explanation for the higher incidence in myocardial infarctions in men (16). This association between visceral fat and cardiovascular risk may be stronger in older as compared to middle-aged men, although in another study the amount of visceral adipose tissue was an independent risk factor for myocardial infarction in elderly women but not men (17).

However, obesity is more than a co-morbid condition because it can cause or worsen arterial hypertension in susceptible individuals. In many populations, BP is positively correlated with BMI (18). For each 1 kg/m^2 increase in BMI, BP increased by 1.47/1.13 mmHg. It has been estimated that overweight and obesity may account for up to one-third of the hypertension prevalence (19). However, the risk for developing hypertension is particularly high in individuals with abdominal fat distribution (20). The beneficial effect of weight loss on metabolic disease, such as new onset diabetes, is undisputed. In the following section, we present data regarding the influence of weight loss on BP control.

Weight loss appears to prevent new onset arterial hypertension. Stamler et al. (21) randomized subjects with high-normal BP to either "nutritional-hygienic intervention" or no intervention. Subjects in the intervention group lost 2.7 kg body weight during the study. During 5 years of follow-up the incidence of hypertension was 8.8% in the intervention and 19.2% in the control group. In the larger Trials of Hypertension Prevention, Phase I (22), men and women, aged 30–54 years, with high normal diastolic BP were randomized to weight reduction, sodium reduction, stress management, or no intervention over 18 months. Subjects in the weight reduction group lost 3.9 kg weight and BP decreased by 2.9/2.3 mmHg. Weight loss had a more pronounced effect on BP in subjects with more severe adiposity (23). The findings were replicated in The Trials of Hypertension Prevention, Phase II (24). Importantly, subjects who lost at least 4.5 kg after 6 months and maintained their weight reduction over 30 months had the greatest decrease of BP in that trial and a relative risk for the development of hypertension of 0.35 (25).

Several studies suggest that weight loss achieved through caloric restriction has a beneficial effect in hypertensive patients. In the Trial of Antihypertensive Interventions and Management (TAIM), patients with mild hypertension at 110–160% of ideal weight were randomized to nine drug/diet treatment groups with patients receiving either placebo, chlorthalidone (25 mg), or atenolol (50 mg), combined with a usual, a weight loss, or a low sodium/high potassium diet (26). In the weight loss group, body weight decreased by 4.7 kg after 6 months with a concomitant 8.8 mmHg diastolic BP decrease. In the Trial of Non-pharmacologic Interventions in the Elderly (TONE) (27) elderly hypertensive patients on a single antihypertensive drug were randomized to reduced sodium intake, weight loss, both combined, or usual care. In this study, moderate weight loss decreased the need for antihypertensive therapy by approximately 30%. Furthermore, weight loss improves the response to antihypertensive medications (26,28).

A BP-reducing effect of weight loss is supported by meta-analyses of randomized controlled trials. In the analyses by Neter et al. (29), BP decreased by 1.05/0.92 mmHg per kilogram of weight loss. The response was even larger in patients on antihypertensive medications. Another meta-analysis included weight loss studies lasting ≥2 years (30). When surgical interventions were excluded, a 10 kg weight loss led to a BP decrease of 4.6/6.0 mmHg. The BP reduction was less than expected in patients undergoing bariatric surgery. The results of these two meta-analyses are summarized in Figure 28.1.

Many patients are unable to maintain a weight loss through lifestyle intervention in the long term. Therefore, the long-term effect of weight loss through lifestyle interventions on BP is not well supported by actual data. The beneficial BP response to weight loss through bariatric surgery abates over the years. Despite these issues, it is undoubted that weight reduction is a safe and effective measure to improve overall cardiovascular and metabolic risk in hypertensive patients.

The prevention and treatment of obesity cannot, however, be left solely to health professionals. Action is needed by government, the food industry, and society as a whole. The potential for the prevention and treatment of overweight and obesity is indicated by the finding that between 1977 and 1996, food portion sizes and energy intake in the United States increased between 15% and 50% (31) and that fast-food frequency was directly associated with changes in body weight and with insulin resistance during a follow-up of 15 years (32). In addition, energy expenditure needs to be encouraged (33). In those patients, in whom weight loss cannot be achieved by lifestyle modification and diet, the role of currently available drug therapy, e.g., orlistat, sibutramine (34) and rimonabant (35) needs to be better defined.

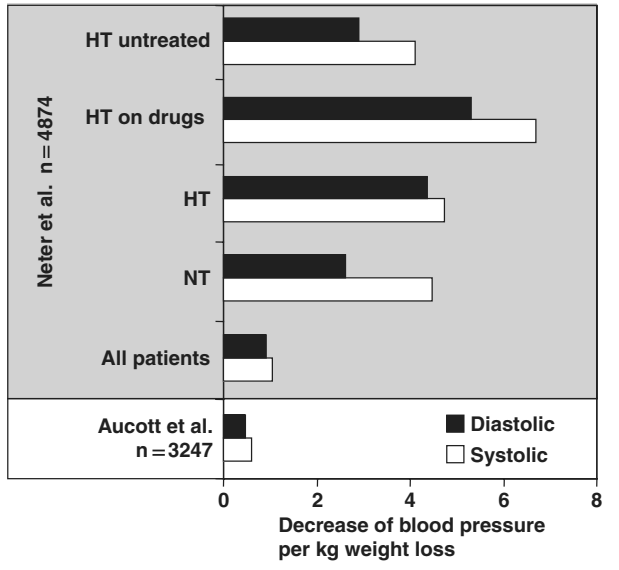

Fig. 28.1 Changes of BP after weight loss. Results were obtained from two meta-analyses based on either 25 randomized controlled trials (29) or on seven randomized controlled or prospective studies (30). As can be seen, BP reductions per kg weight loss in the analysis by Neter et al. were greater in HT subjects (50% of the population) and particularly so in treated HTs (24% of the population). Overall, BP reduction was much smaller in the analysis of Aucott et al. The reason for this discrepancy is not clear but may be related to inclusion of studies with at least 2 years of follow-up as compared to a minimum of 8 weeks in the analysis of Neter et al. *Abbreviations*: BP, blood pressure; HT, hypertensive; NT, normotensive.

DIETARY SODIUM REDUCTION

The notion that dietary salt intake has a significant impact on BP goes back to a paper by Ambard and Beaujard in 1904 (36). Subsequent studies suggested a linear relationship between salt consumption and hypertension prevalence in various populations (Figure 28.2) (37). However, the relationship between sodium excretion and BP was more variable in the Intersalt study (38). On the other hand, the Multiple Risk Factor Intervention Trial (MRFIT) suggested an important relationship between BP and sodium intake in participants on and off antihypertensive medications (39). The heterogeneity in the data may be explained in part by differences in salt sensitivity of BP between subjects (40,41). Not every patient will have a beneficial BP response to sodium restriction.

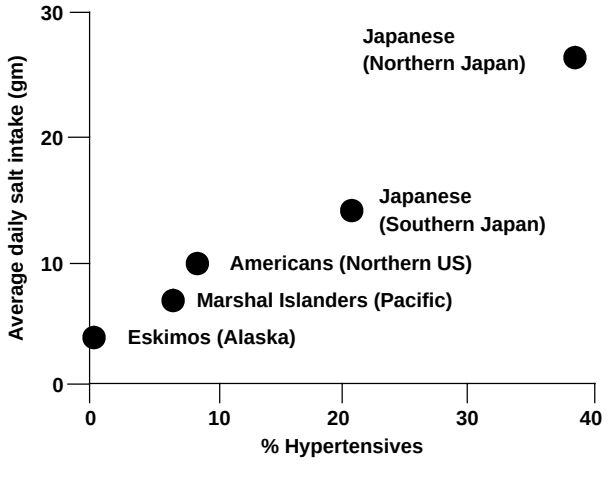

Fig. 28.2 Correlation between sodium intake and blood pressure based on various populations. *Source*: From Ref. 37.

Several studies on sodium restriction have been conducted in normotensive subjects. In the Hypertension Prevention Trial, subjects with diastolic BPs between 78 and 89 mmHg were randomly assigned to no dietary counseling or to one of four dietary intervention groups including reduced calories, reduced sodium, reduced sodium and calories, or reduced sodium and increased potassium (42). After 3 years, mean BP was reduced in all four intervention groups. In Trials of Hypertension Prevention, Phase I, sodium restriction lowered BP by 1.7/0.9 mmHg (43). The response to sodium restriction was less consistent in Trials of Hypertension Prevention, Phase II (24) but sodium restriction reduced the incidence of hypertension (relative risk 0.80). In the recent dietary approach to stop hypertension (DASH)-sodium trial (44), participants were randomized to either a typical U.S. diet or the DASH diet (45). Within the assigned diet, high (150 mmol/day), intermediate (100 mmol/day, and low (50 mmol/day) levels of sodium were given for 30 days each. As shown in Figure 28.3 for subjects assigned to the control diet, reduction of sodium intake from the high to the intermediate level reduced systolic BP by 2.1 mmHg and by an additional 4.6 mmHg during further reduction to low sodium intake. Likewise, diastolic BP decreased not only when switching from high to intermediate sodium intake, but also when decreasing sodium intake further to an average of 60 mmol/day. African-American subjects showed an even greater response.

Over the years, several meta-analyses assessed the effect of sodium restriction on BP in normotensive subjects (46–49). The inclusion criteria differed between analysis as did the results. The decrease in BP for a 100-mmol/day reduction in daily sodium excretion (6 g of salt) ranged between 1.0/0.1 mmHg (46) and 3.57/1.66 mmHg (48). More intense sodium restriction for a medium of 8 days lowered BP by 1.2/0.26 mmHg (significant for systolic pressure only) (47). In a meta-analysis of trials with follow-up of at least 6 months, urinary sodium excretion decreased by an average of 34 mmol/day with concomitant BP reduction by 1.1/0.5 mmHg that was significant for systolic BP (49).

Clinically, studies on sodium restriction in hypertensive patients are particularly relevant. In the TONE trial, older hypertensive patients were randomized to reduction in salt intake or no intervention (50). During a mean follow-up of 27.8 months, urinary sodium excretion and BP decreased by 40 mmol/day and 4.3/2.0 mmHg, respectively. With sodium restriction, more patients remained free of antihypertensive therapy. In the DASH-sodium trial (44), 41% of the participants were hypertensive. Systolic BP decreased approximately 2 mmHg when sodium intake was reduced from 150 to 100 mmol/day. BP decreased further when sodium intake was reduced to 50 mmol/day. African-Americans and older subjects appear to be more susceptible to sodium restriction.

The meta-analyses discussed above (46–49) and a more recent analysis (51) evaluated BP response to dietary sodium restriction in hypertensive subjects. In one analysis, sodium restriction by 95 mmol/day led to 3.7/ 0.9 mmHg BP reduction (significant for systolic pressure). Older subjects showed a greater response. With slightly more intense sodium restriction BP decreased by 3.9/1.9 mmHg (47). He and MacGregor (48) estimated that 100 mmol/day reduction in sodium intake would lower BP by 7.1/3.9 mmHg in hypertensive patients.

Together, the data suggest that even substantial reductions in sodium intake that are difficult to sustain in real life have a marginal effect on BP in unselected normotensive subjects. Hypertensive patients appear to have a greater benefit (Figure 28.4) (52), particularly older subjects and African-Americans. Given the large variability in salt sensitivity, subgroups of patients that have not been defined yet may show an even greater reduction in BP.

Concerns have been raised regarding potential long-term adverse effects of low sodium intake as both low urinary sodium excretion (53) and a high renin-sodium profile were independently associated with the risk of myocardial infarction in hypertensive patients (54). Decreasing sodium intake increases plasma renin proportional to the degree of reduction in urinary sodium excretion and, although not significant, also increased plasma total and low-density cholesterol

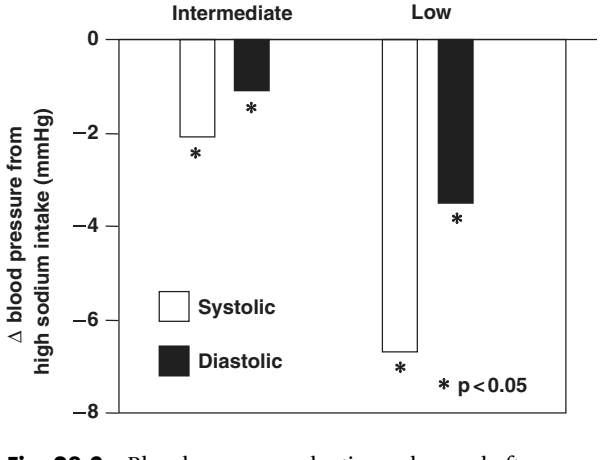

Fig. 28.3 Blood pressure reductions observed after going from high sodium intake (150 mmol/day) to intermediate (100 mmol/day) or low (50 mmol/day) intake. Based on data from the DASH sodium trial. It is obvious that blood pressure is reduced substantially when going from 100 to 50 mmol of sodium intake per day.

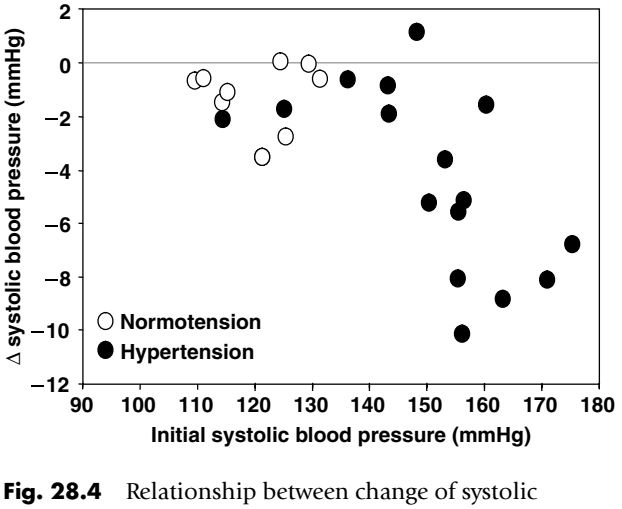

Fig. 28.4 Relationship between change of systolic blood pressure and baseline systolic blood pressure in a meta-analysis of controlled trials of reduced sodium intake and blood pressure. The figure shows that hypertensive subjects have a greater blood pressure reduction than normotensives, but it also shows that those who have the highest blood pressures to start with will still be hypertensive. *Source*: From Ref. 52.

(47), findings compatible with potential adverse long-term effects on cardiovascular morbidity and mortality. However, a long-term follow-up study over ≥13 years in 803 men in London found no significant relation between plasma renin activity and coronary events (55), either in normotensive subjects nor in men with hypertension. Thus, it is unknown whether or not long-term sodium restriction has a beneficial effect on cardiovascular morbidity and mortality.

POTASSIUM INTAKE

Cross-sectional and interventional studies determined the effect of potassium intake on BP. In INTERSALT (38), 50 mmol/day increased potassium intake was associated with 3.6/1.87 mmHg BP reduction. In a study of 20,921 Dutch men and women, BP and dietary potassium were inversely correlated (56). Other studies replicated the statistical correlation at least in men (57,58). Potassium intake was inversely related to the development of hypertension, both, in men (59) and in women (60). However, the relationship disappeared after adjustment for dietary fiber and magnesium intake.

Intervention trials did not show a consistent and sustained BP reduction with potassium supplementation. For example, in the Trials of Hypertension Prevention, Phase I investigation, potassium supplementation reduced diastolic BP at 3 but not at 6 months follow-up despite a persisting increase in urinary potassium secretion (61). Increased dietary potassium reduced the need for antihypertensive therapy in a small trial with 47 hypertensive patients (62) but the finding was not confirmed in a larger trial (63). Potassium supplementation may decrease BP in patients with diuretic-induced hypokalemia (64). A mild reduction in BP with increased potassium intake has been observed in some (65) but not all meta-analyses (51).

Taken together, increased potassium intake may elicit a mild BP reduction. The response may be more pronounced in hypertensive subjects and in those of African descent. The data has to be interpreted with caution because few larger and long-term intervention trials have been conducted so far. A potentially relevant association between low potassium intake and increased stroke risk independently of BP should be followed up (66).

DIETARY CALCIUM

Epidemiological data provide inconsistent data regarding the influence of dietary calcium intake on BP. Some studies showed positive correlations between calcium intake or urinary calcium excretion and BP (67–69), while others showed the opposite (60). Pooled analysis of data from suitable epidemiological studies suggested a rather small reduction in BP with increased calcium intake on BP.

Several meta-analyses have been performed investigating the effects of either increased dietary calcium intake or calcium supplementation on BP (70–72). For example, one analysis showed a 0.89/0.18 mmHg BP reduction per gram of calcium intake per day (71). Pregnancy-associated hypertension and its complications and their relationship to calcium intake have received special interest as an early study suggested a reduced rate of hypertensive disorders with calcium supplementation. The findings were not confirmed in a larger trial (73).

Increased calcium intake may lead to a minimal reduction in BP and cannot be recommended for BP control on a population or individual level.

MAGNESIUM AND BP

Epidemiological evidence supports a role of magnesium intake on BP regulation. Increased magnesium intake was associated with reduced BP and attenuation of a BP rise during follow-up in individual studies (56,60) and in a meta-analysis (74). However, interventional trials have largely failed to show a BP-lowering effect of increased magnesium intake (75,76). The evidence in favor of a causal association between magnesium supplementation and BP reduction is weak. Larger and longer duration trials would be needed to assess the true effect of magnesium supplementation on BP and cardiovascular outcomes.

VITAMINS

Several cross-sectional epidemiological surveys have suggested a role of vitamins in the regulation of BP. In the largest analysis of 15,317 men and women in the United States (77), serum levels of vitamins A and E were positively and significantly associated with both systolic and diastolic BPs. Alpha-carotene and beta-carotene were inversely and significantly associated with systolic and vitamin C associated with diastolic BP. A meta-analysis of 18 trials investigating the relationship between vitamin C and BP (78) suggested an inverse association between higher vitamin C intake or plasma vitamin C levels and BP.

Galley et al. (79) randomized subjects to 8 weeks placebo or antioxidant treatment (zinc, ascorbic acid, alpha-tocopherol, and beta-carotene daily). The authors attributed a slight reduction in systolic BP with antioxidant treatment to increased nitric oxide availability. The SU.VI.MAX trial in 5086 subjects assessed the effects of antioxidant vitamins and trace elements at nutritional doses on risk for developing arterial hypertension over a 6.5-year period (80). The intervention was ineffective. Moreover, antioxidant vitamins had no effect on cardiovascular morbidity and mortality in several outcome trials (81–84).

DIETARY FIBER INTAKE

Several large cross-sectional analyses suggested that dietary fiber intake may influence BP and the risk of hypertension. In men with a fiber intake of <12 g/day, the relative risk of hypertension was 1.57 compared with an intake of >24 g/day (59). Fiber intake was not related to development of hypertension in women but was inversely related to BP in women developing hypertension during follow-up (60). A recent meta-analysis summarized the results of 25 randomized controlled trials in which a change in fiber intake was the only significant intervention (85). Overall, increased dietary fiber intake was associated with a non-significant −1.15 mmHg change in systolic BP and a significant −1.65 mmHg reduction in diastolic BP. Clinically relevant BP reductions were observed in hypertensive patients (−5.95/−4.2 mmHg) and in trials lasting ≥8 weeks. Because increased dietary

fiber intake may have additional health benefits, it can be recommended for most patients.

DIETARY PATTERNS

So far, we presented the evidence for the importance of single dietary components. Obviously, it may be difficult to precisely define the role of a single nutrient in a diet for BP control. It may be easier to evaluate the effects of specific dietary patterns with complex changes in dietary components. Vegetarian or vegan diets, the Mediterranean-style diet, and the DASH diet have received considerable attention.

VEGETARIAN AND VEGAN DIETS

Vegetarian diets are characterized by high intake of fiber, calcium, potassium, magnesium, polyunsaturated, and monounsaturated fatty acids and a lower, or in case of a strictly vegan diet, absent intake of animal protein and saturated fats. Compared with non-vegetarians, vegetarians and vegans tend to have lower BP and lower incidence of arterial hypertension (86). The differences in age-adjusted BP between meat eaters and vegans were 4.2/2.8 mmHg in men and 2.6/1.7 mmHg in women. BP reduction was largely explained by differences in BMI in that study. Interventional trials support the idea that vegetarian diets reduce BP (87,88). Adherence to a vegetarian or vegan diet decreases the risk for new onset arterial hypertension and moderately decreases BP in subjects with high normal BP or mild arterial hypertension.

MEDITERRANEAN DIET

The traditional Mediterranean diet is characterized by a high intake of vegetables, fruits and nuts, and cereals, and a high intake of olive oil but a low intake of saturated lipids. Furthermore, the diet includes moderately high intake of fish (depending on the proximity of the sea), a low-to-moderate intake of dairy products (and then mostly in the form of cheese or yogurt), and low intake of meat and poultry. Regular but moderate ethanol quantities are ingested primarily in the form of wine. Adherence to this type of diet has been associated with lower total mortality (89,90), reduced complications after myocardial infarction (91), and a lower prevalence of obesity (92). Reduction in BP may contribute to the cardiovascular benefit (93). In an interventional trial, patients assigned to 3 months of a Mediterranean diet showed reduction in BP by −5.9/−7.1 mmHg compared with patients assigned to a low fat diet (94). Thus, a Mediterranean type of diet seems appears to have a beneficial effect on BP. More importantly, the diet may reduce morbidity and mortality in patients with established cardiovascular disease.

DIETARY APPROACH TO STOP HYPERTENSION DIET

Building on evidence from previous trials investigating single nutrients, DASH tested the combined effects of nutrients that occur together in food (45). The trial was designed as an 11-week feeding program with meals prepared for the 459 patients with mild, untreated hypertension by a research kitchen. Subjects then were randomly assigned to one of three diets for an 8-week intervention period. The nutrient composition of the control diet was typical of the diets of a substantial number of Americans. The fruits-and-vegetables diet was rich in potassium and fiber but otherwise similar to the control diet. The DASH diet was rich in fruits, vegetables, and low-fat dairy products with reduced saturated and total fat (Table 28.1). The sodium content of each diet was similar at approximately 3 g/day and weight and alcohol intake were kept constant. At the end of the trial, the DASH diet lowered BP by −5.5/−3.0 mmHg while the fruits and vegetables diet lowered BP to a lesser extent (−2.8/1.1 mmHg). The BP effect of the DASH diet was more pronounced in hypertensive subjects and in African-Americans. Efficacy of a DASH diet in reducing BP has been confirmed in subsequent studies.

REDUCTION IN ALCOHOL CONSUMPTION

Cross-sectional studies documented increased BP and a higher incidence of hypertension with higher levels of alcohol intake (95,96). In a large surveys in 30,000 subjects (97), BP increased by 0.9/0.6 mmHg per daily drink in men and 2/1 mmHg in women who consumed two or more drinks. Interestingly, alcohol ingested in moderate amounts may be associated with reduced BP (98), thus suggesting a J-shaped association between alcohol intake and BP (Figure 28.5). A J-shaped association was, however, not observed in all surveys and racial differences may exist as linear relationships of BP and alcohol consumption were repeatedly reported in Japanese studies (99).

A number of studies investigated the effects of reduction of alcohol intake on BP. Moderation of alcohol consumption

Table 28.1 The dietary approaches to stop hypertension (DASH) eating plan

Food group (examples or comments)	Recommended no. of daily servings
Grains (whole wheat bread, oatmeal)	7–8
Vegetables (tomatoes, potatoes, carrots, beans, spinach, peas, squash)	4–5
Fruits (bananas, grapes, oranges, apricots, melons)	4–5
Low-fat dairy products [fat-free (skim) or low-fat (1%) milk, yogurt, cheese]	2–3
Meats (primarily poultry or fish; select lean meats and prepare by trimming fat and broiling, roasting or boiling; remove skin from poultry)	≤2
Nuts, seeds, dry beans (peanuts, walnuts, almonds, sunflower seeds, lentils)	4–5/week
Fats and oils [soft margarines, vegetable oil (e.g., olive, corn, canola, or safflower)]	2–3
Sweets (maple syrup, sugar, jam, jelly, hard candy, sorbet)	5 ×/week

Details of the DASH Eating Plan including information on serving sizes are available at http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/index.htm.

reduced BP in healthy normotensive men (100). In heavy drinkers with arterial hypertension, reduction in alcohol consumption reduced BP by 14/7.5 mmHg at 2 years follow-up while BP remained unchanged in the control group (101). However, in another randomized trial, reduction in weekly alcohol consumption from 432 to 230 g at 6 months decreased BP only by 2/1.9 mmHg (102).

One meta-analysis revealed a dose-dependent reduction in BP with reduction in alcohol consumption (103). A 79% reduction in alcohol consumption from a baseline of 3 to 6 to 1 to 2 drinks/day was associated with 3.3/2 mmHg reduction in BP. A more recent meta-analysis limited to subjects with BP of at least 140/85 mmHg reported a 3.8-mmHg decrease in systolic BP secondary to reduction in alcohol consumption (51).

In patients with arterial hypertension, moderation in alcohol intake to two drinks per day in men and one to two drinks per day in women is a sensible recommendation. As non-drinkers have a higher risk for cardiovascular events, recommendations to totally abstain from alcohol are difficult to support.

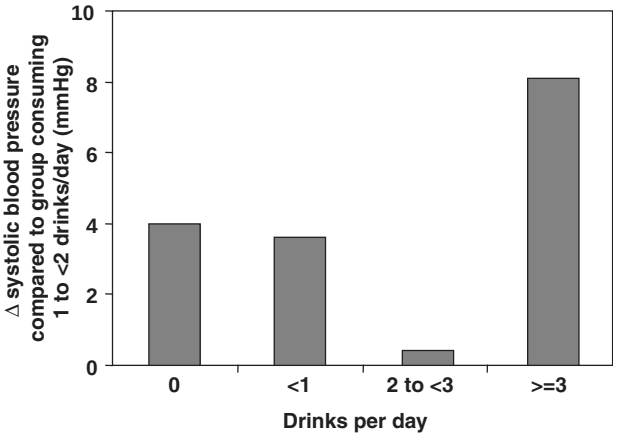

Fig. 28.5 Alcohol consumption and blood pressure. In this study of 316 young men and women, those who drank one to two drinks per day had the lowest systolic pressures. When their blood pressures were taken as reference, those who drank less or not at all and those who drank substantially more (e.g., three or more drinks per day) had higher blood pressures, while those who drank slightly more (e.g., two to three drinks per day) had only marginally higher blood pressures. *Source*: From Ref. 98.

SMOKING CESSATION

Cigarette smoking is one of the most important modifiable risk factors for cardiovascular disease (104). Importantly, smoking is a particularly powerful risk factor in combination with other cardiovascular risk factors. Smoking increases the relative risks for coronary heart disease in hypertensive subjects with low or high cholesterol levels by 3.0 and 9.7 in men and 2.3 and 15.9 in women, respectively (105). However, whether or not smoking increases BP is controversial. Some studies suggested that chronic smokers actually may have similar BPs (106) or, in case of light smokers, even lower BP compared to non-smokers (107). The fact that BP measurements are usually taken in a smoke-free environment may lead to underestimation of BP in smokers given the short-lived effect of smoking on BP and heart rate (108). Indeed, daytime ambulatory BP was increased in smokers whereas office BP was similar in smokers and non-smokers (109). Smoking may diminish the response to antihypertensive therapy (110).

Smoking cessation is difficult, especially in heavy smokers. However, smoking cessation can be recommended in all patients. The risk of experiencing a first myocardial infarction or stroke returns to the level of someone who never smoked within a few years (111) in men and in women (112–114). Smoking cessation is frequently associated with an increase in body weight, which may prevent some patients, particularly younger women, from quitting.

EXERCISE

Epidemiologic studies demonstrated that physical fitness is associated with reduced cardiovascular morbidity and mortality (115–118). For example, in healthy Norwegian men the relative risk of death from any cause was reduced by 46% in those in the highest fitness quartile as compared to the lowest quartile during a follow-up of 16 years (116). Sedentary men who commenced moderately vigorous sports activity had a 23% lower risk of death compared with men who stayed sedentary (119). Although there is less data available in women, a number of reports confirm the beneficial effects of physical fitness and activity on all-cause mortality (120–123). Finally, regular physical activity may be of benefit in preventing stroke in women as well as in men (124,125). Although the exercise level at which these beneficial effects occur is not precisely defined, it appears that moderate activity may be as effective as high levels of activity (119,122,123,126).

While the data convincingly show that regular aerobic exercise confers considerable cardiovascular (and non-cardiovascular) benefit, it should be noted that strenuous physical exercise may trigger an acute myocardial infarction, particularly in subjects who are habitually sedentary (127). It seems prudent conducting an exercise stress test before commencing a training program and to gradually increase exercise intensity and duration over time.

The mechanisms whereby regular physical activity produces its preventive cardiovascular effects have not been fully elucidated. Improvement in lipid profile (128,129), glucose metabolism (130,131), overweight, nitric oxide bioavailability (132,133), and sympathetic nervous activity (134,135) may contribute to the beneficial effect. Moreover, exercise lowered BP, both, in normotensive and hypertensive subjects. For example, in hypertensive subjects, endurance training on a bike three or seven times per week at 70% maximum work capacity for 1 month each reduced BP by 11/9 and 16/11 mmHg, respectively (134). More moderate levels of exercise may also be effective (136). A beneficial effect of exercise on BP is supported by meta-analyses. In a meta-analysis of 72 trials in which exercise was the only intervention, BP decreased on average by 3.0/2.4 mmHg (137). In hypertensive subjects, BP decreased by 6.9/4.9 mmHg. Another analysis summarized studies in which walking was the only intervention (138). Walking decreased BP approximately 3/2 mmHg.

Conventionally, "dynamic" or "aerobic" exercise such as walking, running, swimming and cycling has been the

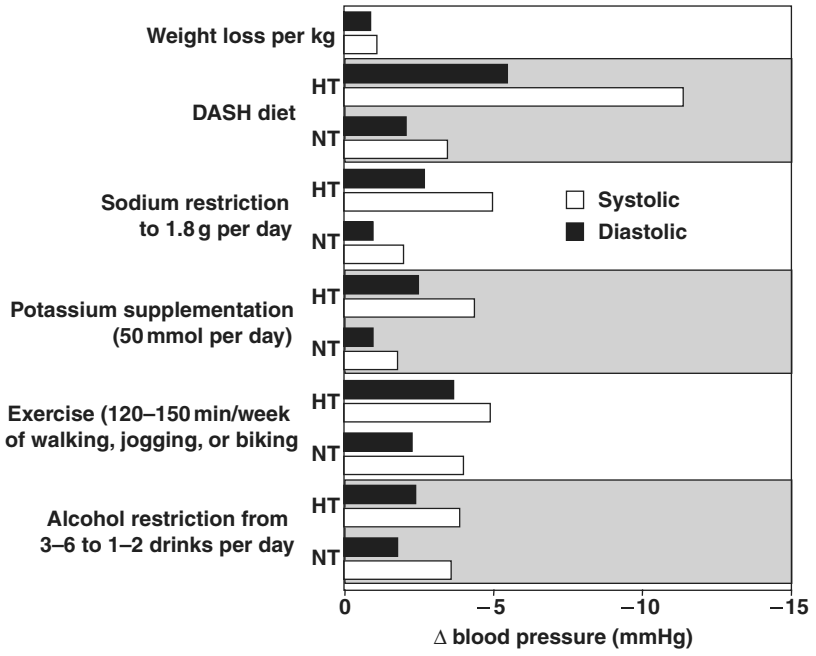

Fig. 28.6 Estimates of blood pressure-lowering effects of commonly recommended non-pharmacological measures to reduce blood pressure. The results are based upon the data presented in this chapter. It should be recognized, though, that blood pressure lowering effects of combinations of these measures are not necessarily additive.

recommended form of physical activity. "Isometric" or "resistance" training such as weight lifting or body building has not been recommended. However, a meta-analysis of nine mostly dynamic resistance training studies showed a significant reduction in diastolic BP by 3.5 mmHg and a non-significant reduction in systolic BP by 3.2 mmHg (137). Furthermore, resistance training improves insulin sensitivity. Contrary to previous recommendations, moderate intensity resistance training may not be contraindicated but data regarding long-term cardiovascular benefit are lacking so far.

CONCLUSIONS

There is abundant evidence that lifestyle changes and dietary measures are effective measures to help prevent the development of hypertension and control BP in patients with hypertension. Figure 28.6 summarizes the evidence for the most commonly recommended non-pharmacological measures. Given the fact that in a recent review in the United States only 4% out of a sample of 153,000 subjects followed a healthy lifestyle, e.g., did not smoke, had a normal weight, ate a diet rich in fruits and vegetables and exercised regularly for five times per week (139), the potential benefit of various interventions discussed above becomes obvious. Lifestyle modification counseling should be offered to all patients with or at risk of hypertension and, particularly in those with additional cardiovascular risk factors. The main challenge remains the optimal implementation of such lifestyle strategies. Apart from advice from healthcare professionals, government legislation and regulation as well as societal change will be necessary to aid patients in choosing and sustaining healthy lifestyle decisions.

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ANTIHYPERTENSIVE DRUG CLASSES 29

Peter A van Zwieten

HISTORICAL BACKGROUNDS

Once hypertension was recognized as a dangerous condition in the 1930s, attempts were made to lower the elevated blood pressure (BP) in hypertensive patients (1). Initially, the problem was approached by dietary measures only, aiming to restrict sodium consumption. The "severe" rice and fruit diet of Kempner displayed modest but significant antihypertensive activity. Although extremely difficult for patients to maintain long term, the rice and fruit diet may be considered as the trigger mechanism that led to the development of diuretics as antihypertensive drugs.

A similar type of initiative may be derived from the application of surgical sympathectomy with the aim to lower elevated BP, which was followed up by chemical sympathectomy by means of ganglion-blocking agents. The ganglioplegics were the first antihypertensive drugs applied in long-term treatment (2).

Attempts to lower BP by means of intravenously administered drugs were also initiated by the infusion of sodium nitroprusside (SNP), a drug that dilates both arterial (resistance) and venous (capacitance) vessels (3). Ganglion blockers, vasodilators, and diuretics were available as antihypertensive drugs toward the end of the 1950s, although these drugs were then by no means applied on a large scale.

The major development of effective and tolerable antihypertensive drugs gained momentum in the 1960s and was pursued in the subsequent decennia. This development, up to our present day, is illustrated by the well-known graph as presented by the late Dr. Franz Gross (4,5) and depicted in Figure 29.1.

We briefly mention a few older categories of antihypertensive drugs. Most of these agents are no more used on a large scale—although effective BP lowering agents, their tolerability is inferior to that of the more modern agents.

VASODILATOR DRUGS

In the 1950s, it was realized that vasodilatation could be a useful principle to lower elevated BP in hypertensives. Most antihypertensive drugs from various categories, as discussed in the present chapter, owe their antihypertensive activity to vasodilatation, in particular at the level of the precapillary arterioles (resistance vessels). However, not all of these drugs are classified as vasodilators. As a matter of semantics, the term vasodilator drug is limited to the following agents: SNP and the nitrates; directly acting agents that activate guanylate cyc1ase, such as hydralazine, minoxidil, and diazoxide; and calcium antagonists (CAs).

α-Adrenoceptor antagonists (α-blockers), angiotensin-converting enzyme (ACE) inhibitors and AT_1-blockers also owe their antihypertensive activity to vasodilatation, but it is unusual to c1assify them as vasodilator drugs. These agents are discussed in different sections of the present chapter.

Sodium nitroprusside, a potent dilator of both arterial (resistance) and venous (capacitance) vessels was the first vasodilator drug infused intravenously with the aim to lower BP in a hypertensive emergency (3). Its vasodilator activity is caused by the release of nitric monooxide (NO). The same holds for nitrates, such as nitroglycerine and isosorbide, used in the treatment of angina pectoris.

Hydralazine and its homologue dihydralazine were the first orally applied vasodilator antihypertensives introduced in the 1960 (6). These drugs activate guanylcyc1ase by a direct action, thus generating cyclic GMP and causing vasodilatation, which occurs predominantly in the resistance vessels. The main problem with these drugs is their concomitant stimulation of the sympathetic nervous system (SNS), causing reflex tachycardia. In many patients they also stimulate the renin–angiotensin system, causing salt and fluid retention thus counteracting the antihypertensive effect. For these reasons, these "directly" acting vasodilators should be combined with both a β-blocker and a diuretic.

Minoxidil, a very potent vasodilator, is sometimes prescribed for patients with resistant hypertension, but the drug is unsuitable for monotherapy and for long-term use. Diazoxide is another potent, directly acting vasodilator, which was sometimes used in hypertensive emergencies.

RESERPINE AND OTHER RAUWOLFIA ALKALOIDS

Plants of the genus *Rauwolfia* contain numerous different alkaloids, which have been used in traditional Indian medicine for antipsychotic purposes. In the 1960s, the antihypertensive

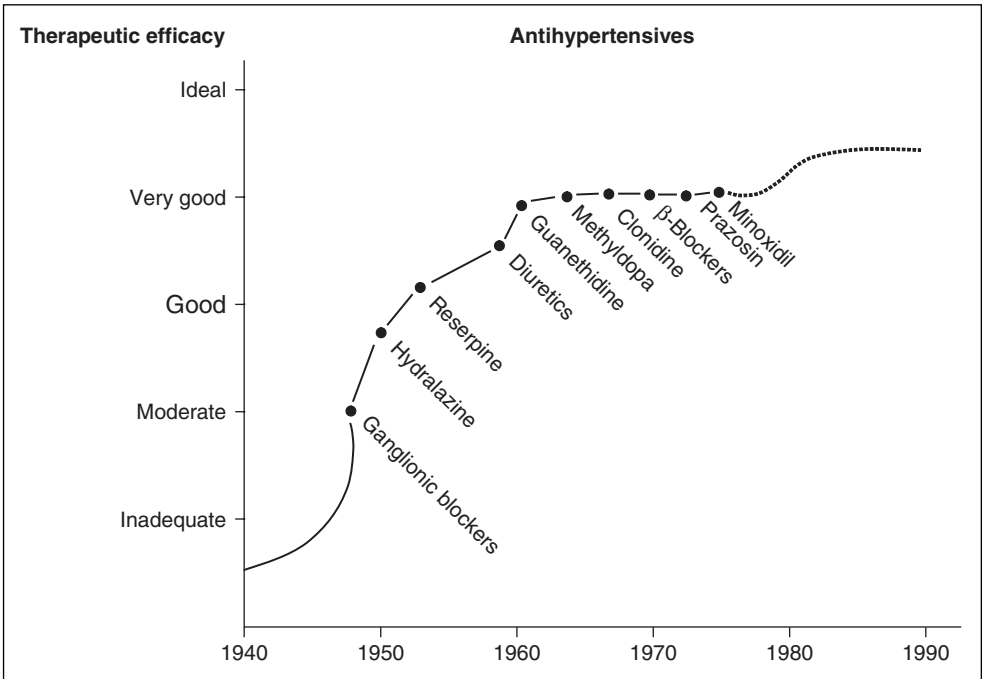

Fig. 29.1 Introduction of various antihypertensive drugs over the past decades and their therapeutic efficacy at lowering of elevated blood pressure. *Source*: From Ref. 4.

activity of these alkaloids was discovered and introduced as a new approach in antihypertensive therapy in the Western world. Reserpine is the best known alkaloid of this type.

By destroying the postganglionic sympathetic neuronal stores of noradrenaline (NA), it causes depletion of the neurotransmitter and impaired activity of the postganglionic neurons (6–8). In addition, reserpine was shown to provoke peripheral sympatho-inhibition via a central mechanism triggered in the brain stem (8). Reserpine is an effective antihypertensive drug. Reserpine has lost a great deal of its importance because of its adverse reactions, but it continues to be used in several developing countries because of its low cost.

VERATRUM ALKALOIDS

Among attempted antihypertensives were Veratrum alkaloids (protoveratrine A and protoveratrine B) because of their sensitizing effect on the baroreceptor system. They cause reflex vasodilatation and bradycardia by stimulating sensory endings in the cardiac atria and, as such, they trigger the Bezold-Jarisch reflex (6). Orthostatic hypotension and the results of cholinergic stimulation (salivation, nausea and vomiting, etc.) may occur as a result of therapeutic doses. Therefore, these drugs have been abandoned. However, the Veratrum alkaloids deserve to be mentioned here because of their interesting mode of action.

GANGLION-BLOCKING DRUGS (GANGLIOPLEGICS)

The ganglion-blocking agents may be characterized as the first deliberately applied antihypertensive drugs. All ganglion-blocking drugs act predominantly at postsynaptic sites in the autonomic ganglia. As competitive inhibitors at the level of the nicotinic cholinergic receptors, they antagonize the actions of the neurotransmitter acetylcholine and, hence, cause sympatho-inhibition and a reduction of elevated BP. Since the same nicotinic cholinergic receptors are present in both sympathetic and parasympathetic ganglia, the inhibition of the effects of acetylcholine also occurs within the parasympathetic ganglia (6).

Ganglion-blocking drugs are potent antihypertensive drugs, as a result of their effects on sympathetic ganglia. This mechanism also explains the severe orthostatic hypotension associated with the use of these agents. Parasympathetic blockade underlies most other side effects of the ganglion blockers, such as relaxation of intestinal smooth muscle, constipation, impaired micturition, and paralysis of accommodation for near vision. Inhibition of perspiration is caused by blockade of the sympathetic ganglia with uniquely parasympathetic neurons.

Pentaquine, originally an antimalarial drug, was the first ganglioplegic agent used in the experimental treatment of hypertension (2,6). Hexamethonium, mecamylamine, chlorisondamine, and trimetaphan were also explored as potential antihypertensive drugs. All of these drugs appeared to be potent antihypertensives, but their severe side effects are such that they can no longer compete with various, more modern antihypertensives, which are effective in lowering BP but much more tolerable.

ADRENERGIC NEURON-BLOCKING AGENTS

These agents, of which guanethidine and bretylium are the prototypes, inhibit postganglionic neurotransmission in the SNS and, hence, reduce elevated BP (6). Although there is no doubt concerning their antihypertensive efficacy, their adverse reactions are such that they can no longer be used in modern antihypertensive treatment.

DIURETICS AS ANTIHYPERTENSIVES

As early as the 1940s the antihypertensive action of the now obsolete mercurial diuretics had been reported, but due to their toxicity these drugs are long gone. The thiazide diuretics, still widely used at present, were introduced into antihypertensive therapy from the 1960s onwards. The background of the antihypertensive use of diuretics was triggered by the BP-lowering effect of severe sodium restriction, such as that evoked by Kemper's rice and fruit diet.

Ever since then, diuretics have been used successfully as first-line antihypertensive drugs. In spite of this, there continues to be some debate concerning their mode of action, which is not known in full detail.

Thiazides are the predominant class of diuretics used as antihypertensives. Loop diuretics, such as furosemide, are also active as antihypertensive, but certainly not particularly suitable for this purpose, because of their potent diuretic action, which is an unnecessary nuisance for hypertensive patients. Thiazide diuretics are therefore preferable in clinical practice, owing to their mild or even absent diuretic action when prescribed in low doses.

THIAZIDE DIURETICS

At a cellular level, the thiazide diuretics are inhibitors of the reabsorption of Na^+-ions in the distal renal tubuli, thus giving rise to volume depletion as the primary mechanism underlying their antihypertensive activity. It seems unlikely, however, that the reduction in extracellular volume can fully explain their long-term antihypertensive effect. With chronic therapy, the plasma volume returns to near pretreatment values in many (but not all) patients, whereas in others it remains contracted to differing degrees. It, therefore, seems likely that other mechanisms besides a reduction in plasma volume are involved as well. A reduction in peripheral, vascular resistance by thiazide diuretics is likely a further mechanism underlying the antihypertensive action of the thiazide diuretics, in particular during long-term therapy. The efficacy and safety of thiazide diuretics have been substantiated by numerous small- and large-scale studies.

Thiazide diuretics are also effective and protective against the complications of hypertension in the elderly, and they continue to be appreciated in first-line therapeutics with elderly hypertensives, also because they are usually well tolerated and cheap (for review, see Refs. 9,10).

The antihypertensive effect of diuretics is relatively mild and depends on the initial BP level. On average, a decrease in systolic and diastolic BP by approximately 10% can be achieved. In normotensive subjects, BP is not usually diminished. It has been recognized that thiazide diuretics are effective in patients with isolated systolic hypertension (ISH), as demonstrated with low-dose chlorthalidone in the SHEP study (11).

Thiazide diuretics can be combined with several types of antihypertensive agents. They enhance the antihypertensive activity of both ACE inhibitors and angiotensin II-receptor antagonists (AT_1-blockers, ARBs).

Hydrochlorothiazide, chlorothiazide, and chlorthalidone are the classical thiazide diuretics. When used in appropriate dosage, these compounds are equi-effective and comparable. For indapamide, modest vasodilator activity has been demonstrated to occur in addition to the diuretic activity (9). The various newer thiazide diuretics do not offer relevant advantages and, thus, hydrochlorothiazide and chlorthalidone remain the drugs of choice.

The metabolic side effects of thiazide diuretics are well known: loss of K^+-ions and hypokalemia, impaired glucose tolerance and reduced insulin sensitivity, dyslipidemia and hyperuricemica.

More recently, it has become clear that thiazide diuretics may be considered as diabetogenic when used long term, in particular when combined with a β-blocker. This combination should therefore be avoided in diabetics and in all patients with a substantial risk to become diabetic.

Furthermore the question arises whether young hypertensives should be exposed to the metabolic risks caused by thiazide diuretics and/or β-blockers for the several decennia of treatment which are ahead.

POTASSIUM-SPARING DIURETICS

Classical potassium-sparing diuretics, such as amiloride and triamterene, are weak natriuretic agents, unsuitable for monotherapy. However, they are frequently added to thiazide diuretics in order to counteract the loss of K^+-ions.

The aldosterone receptor antagonist spironolactone is a weak potassium-sparing diuretic that can be added to thiazide diuretics. Spironolactone somewhat reduces the rigidity of the large conduit vessels (12). For this reason it may be of special interest in the treatment of ISH, frequently established in elderly hypertensives.

The general interest in the pathophysiological role of aldosterone has been greatly stimulated by the recently discovered beneficial effect of spironolactone in congestive heart failure (RAYLES study) (13).

Aldosterone not only causes well-known renal effects (Na^+ and fluid retention, loss of K^+-ions), but also enhances vascular and cardiac fibrotization and collagen synthesis (14). The suppression of the latter effect is believed to be an important component of various beneficial effects of spironolactone, both in the treatment of hypertension and heart failure.

The use of aldosterone antagonists may be improved and stimulated by the introduction of newer compounds that have a much weaker endocrine activity, thus causing less (or no) gynecomastia as a side effect. Eplerenone is an example of one of the newer agents. Its beneficial activity in congestive heart failure was recently demonstrated in the EPHESUS study (15).

SYMPHATHOLYTICS: DRUGS DEPRESSING THE SNS AND ITS INFLUENCE ON THE CARDIOVASCULAR SYSTEM

A causative role of the SNS in the development and maintenance of hypertension is increasingly recognized and demonstrated (16). For this reason the use of drugs that will depress the activity of the SNS and its influence on the cardiovascular system appears to be a logical approach in the treatment of hypertension (17,18).

Virtually all structures, neuronal pathways, and receptors involved in the SNS can now be impaired or blocked by more or less selective pharmacological agents, as depicted in Figure 29.2.

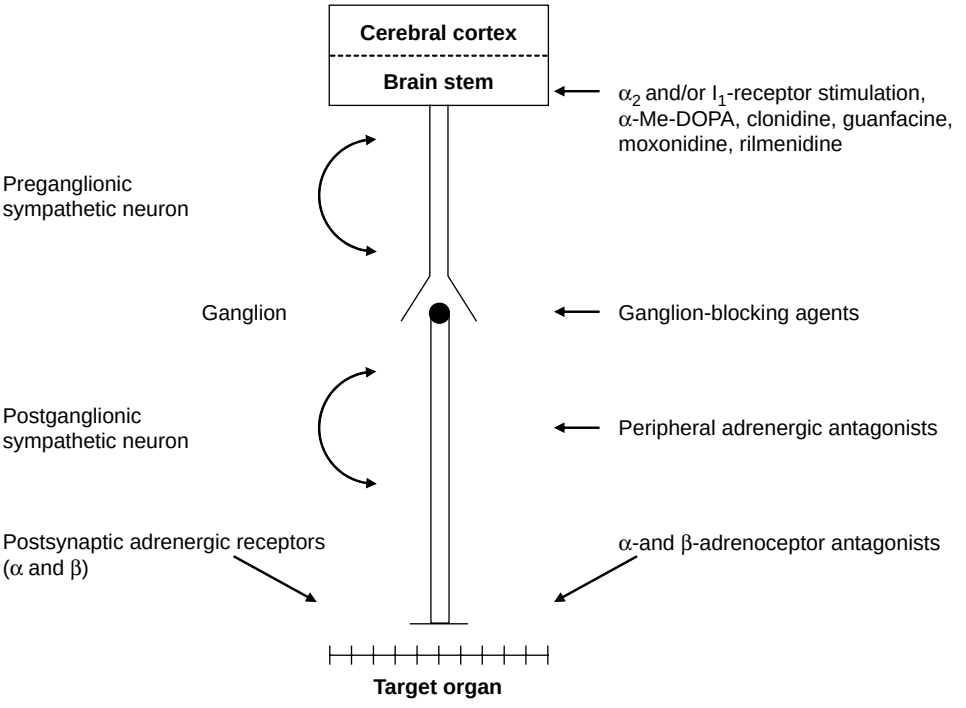

Fig. 29.2 Schematic representation of the influence of various antihypertensive drugs on the different structures in the central and peripheral sympathetic system. Various drugs like clonidine and related agents, as well as α-methyl-DOPA and, to some degree, reserpine, interfere with the central regulation of blood pressure at the level of the brain stem. The ganglion-blocking agents will interrupt sympathetic transmission at the ganglionic level. Various peripheral adrenergic antagonists, e.g., guanethidine and compounds with a similar pharmacological profile, interrupt sympathetic transmission at the postganglionic level. Various α- and β-adrenoceptor antagonists may lower arterial blood pressure because they diminish the activating influence of the SNS on circulation. *Abbreviation*: I, imidazoline.

We already mentioned the older, now obsolete drugs that depress the SNS activity, such as the ganglion-blocking agents, reserpine, and adrenergic neuron-blocking drugs. A few other categories of SNS-depressants have maintained a certain position in the management of hypertension and they deserve to be briefly discussed here.

ALFA-ADRENORECEPTOR ANTAGONISTS (α-BLOCKERS)

Postsynaptic α-adrenoreceptors mediate the vasoconstrictor activity of norepinephrine (the endogenous neurotransmitter) and other sympathomimetic agents. It therefore appears to be a logical approach to block these α-adrenoreceptors by means of an antagonist in order to achieve vasodilatation and a lowering of elevated BP. The subdivision of α-adrenoreceptors into α_1- and α_2-subtypes has taught us that only the selective α_1-adrenoreceptor antagonists are potentially useful in the treatment of hypertension. Non-selective $\alpha_1 + \alpha_2$-blockers such as phentolamine will enhance the release of norepinephrine via α_2-adrenoreceptors at presynaptic sites and hence cause tachycardia (17). Prazosin was the prototype of selective α_1-adrenoreceptor antagonist. Because of its unfavorable pharmacokinetic profile it causes a rapid onset of action and orthostatic symptoms. It has been replaced by the selective α_1-blocker doxazosin which has a better pharmacokinetic profile.

Doxazosin causes dilatation of both arterial and venous vascular beds. It has a slower onset and longer duration of action and is preferable to prazosin. In contrast to most other antihypertensive drugs, the α_1-blockers appear to moderately improve metabolic aspects such as plasma lipid profile and insulin resistance (19).

Doxazosin and other α-blockers have not maintained a strong position in the management of hypertension, probably in part because they have not been subjected to large-scale randomized intervention trials. A few α-adrenoceptor blockers with additional therapeutic components have been developed.

Urapidil, a derivative of uracil, is a hybrid drug with at least two different modes of action combined in the same molecule (which has no stereoisomers). It is a selective α_1-adrenoceptor antagonist that is less potent on a molar base and also somewhat less selective for α_1-receptors than prazosin. In addition, it displays substantial central hypotensive activity, which, unlike clonidine and related drugs, is not mediated by central α_2-adrenoceptors. This central mechanism is caused by stimulation of central serotonergic receptors of the $5HT_{1A}$-subtype. This additional, central mechanism probably explains why urapidil, although a potent vasodilator, does not provoke reflex tachycardia (for review, see Refs. 20,21).

Labetalol is a combined α- and $\beta_1 + \beta_2$-blocker, but its α-component (which would cause vasodilatation) is much weaker than its affinity for β-adrenoceptors (see also section on "β-adrenoceptor antagonists with additional vasodilator properties").

Ketanserin is a selective antagonist of $5HT_2$-serotonergic receptors with additional (although weaker) affinity for α_1-adrenoceptors. Its moderate antihypertensive activity is most likely explained by its α-adrenoceptor affinity. Attempts have been made to imply $5HT_2$-receptor blockade in the antihypertensive activity of ketanserin, but this mechanism has remained highly controversial (for review, see Refs. 22,23).

The more detailed subdivision of α_1-adrenoceptors into α_{1A}-, α_{1B}-, and α_{1D}-subtypes has been followed up by the development of more or less selective antagonists with respect to these receptor subpopulations. However, such newer agents have not offered realistic improvements of antihypertensive drug therapy. For selective α_{1A}-adrenoceptor antagonists, such as tamsulosin, alfuzosin, and terazosin, a moderate selectivity for α_1-adrenoceptors in the prostate has been demonstrated, and these drugs are currently used to improve urinary flow in patients with benign prostate hyperplasia.

BETA-ADRENORECEPTOR ANTAGONISTS (β-BLOCKERS)

β-Adrenoreceptor blockers were initially introduced as therapeutics in the management of certain types of arrhythmia and angina pectoris. In both cases, their beneficial activity is readily explained pharmacologically. In 1969, Prichard and Gillam convincingly demonstrated the antihypertensive efficacy of β-blockers in patients (24), and since then these drugs have been used on a very large scale in the management of essential hypertension. Despite their very well documented and widespread application as antihypertensive therapeutics, the pharmacological explanation of their antihypertensive potency remains unsatisfactory. The following hypotheses have been put forward as explanations of their antihypertensive activity (25):

1. A reduction in cardiac output;
2. Lowering of plasma renin activity (PRA);
3. Central hypotensive activity;
4. Blockade of presynaptic β-adrenoceptors.

None of the various hypotheses proposed can be satisfactorily reconciled with the experimental findings. In spite of this, β-blockers continue to occupy a major position in the treatment of hypertension. In the various guidelines concerning this subject, such as the 1999 World Health Organization–International Society of Hypertension (WHO-ISH), Joint National Committee (JNC) VI, and the European Society of Hypertension and the Europran Society of Cardiology (ESH–ESC) Guidelines 2003 (26), they maintain an important position as first-line drugs. More recently this position had been challenged on the basis of meta-analysis data (27).

The efficacy of β-blockers with respect to the lowering of BP appears to be well and widely established. Doubt has been expressed, however, concerning the prospective activity of these agents against the various complications of hypertensive disease (27). In spite of this it should be realized that β-blockers maintain a very important position and mandatory indication in the treatment of various cardiological disorders, such as angina pectoris, secondary prevention subsequent to an acute coronary syndrome, tachy-arrhythmias, and, as established more recently, congestive heart failure (28).

Most of the adverse reactions toward β-blockers can be derived from their basic pharmacological profile: lowering of heart rate and arterio-venous conduction; negative inotropic activity; cold hands and feet, as a result of vasoconstriction, predominantly mediated by β_2-adrenoreceptors; sleep disturbances, mainly caused by lipophilic β-blockers that penetrate into the brain; bronchoconstriction as a result of β_2-receptor blockade.

Moreover, the metabolic profile of β-blockers is considered to be unfavorable, in particular with respect to insulin resistance/glucose intolerance and dyslipidemia (27). Several variations have been introduced within the spectre of β-blocking agents, such as β_1-adrenoreceptor selectivity, intrinsic sympathomimetic activity (ISA), pharmacokinetic profile, etc.

At present, it is the widely accepted opinion that the following properties will be desirable in the choice of a β-blocker for the treatment of hypertension:

1. β_1-receptor selectivity;
2. Sufficiently long duration of action, allowing once daily administration.

A few examples of β-blockers with some of these particular properties are listed in Table 29.1. As very well-known agents, the β-blockers have been the subject of numerous review papers, chapters, and monographies (for instance, see Ref. 29). The efficacy of β-blockers as antihypertensives substantiates the hypothesis that hypertensive disease is associated with sympathetic activation.

β-ADRENOCEPTOR ANTAGONISTS WITH ADDITIONAL VASODILATOR PROPERTIES

A few β-blockers have been developed that possess vasodilator potency, in addition to their β-blocking activity. From a hemodynamic point of view, this would seem an attractive combination. A well-known example of such compounds is *labetalol*, a non-selective $\beta_1 + \beta_2$-blocker that displays weak α-adrenoceptor antagonistic activity. However, the α-adrenoceptor antagonism appears to wear off in the course of prolonged antihypertensive treatment (30). Nebivolol is a highly β_1-selective blocker, with much weaker vasodilator activity, which is probably triggered by NO (31), and possibly

Table 29.1 Examples (not complete) of a few β-adrenoreceptor antagonists (β-blockers)

Drug	β1-selectivity	ISA	Details
Acebutolol	$\beta_1 > \beta_2$	+	
Alprenolol	$\beta_1 + \beta_2$	+	
Atenolol	$\beta_1 >> \beta_2$	−	
Bisoprolol	$\beta_1 >> \beta_2$	−	
Carvedilol	$\beta_1 + \beta_2$	−	Weak α_1-activity; beneficial in congestive heart failure
Esmolol	$\beta_1 >> \beta_2$	−	Short action
Metoprolol	$\beta_1 > \beta_2$	−	
Labetalol	$\beta_1 + \beta_2 + \alpha_1$	−	Weak α_1-blockade
Nebivolol	$\beta_1 >> \beta_2$	−	Vasodilator (via NO)
Oxprenolol	$\beta_1 + \beta_2$	++	
Pindolol	$\beta_1 + \beta_2$	+++	
Propranolol	$\beta_1 + \beta_2$	−	
Sotalol	$\beta_1 + \beta_2$	−	In addition: class III antiarrhythmic activity

$\beta_1 + \beta_2$ = non-selective; $\beta_1 > \beta_2 = \beta_1$-selectivity.

Abbreviations: ISA, intrinsic sympathomimetic activity; NO, nitric oxide.

also by the moderation of β_3-adrenoreceptors (32). Its position in antihypertensive treatment remains to be established.

Carvedilol is a non-selective $\beta_1 + \beta_2$-blocker with additional weak α-blocking activity. It is an effective antihypertensive but the major interest in this drug concerns the treatment of congestive heart failure. Its beneficial effect on this condition, probably based upon antiarrhythmic activity, has been demonstrated in several double-blind, placebo-controlled studies.

CENTRALLY ACTING ANTIHYPERTENSIVES

The central nervous system (CNS) exerts a very important regulatory function on the peripheral circulation via the autonomic nervous system. It was therefore an obvious idea to attempt to develop drugs that could depress elevated BP via a mechanism primarily located in the CNS, more precisely in the brain stem.

Clonidine, an imidazoline (I_1) derivative developed in the 1960s, was the first drug for which a primarily central antihypertensive mode of action was recognized (33–35). Curiously, clonidine was primarily used as an additive to shaving cream with the aim to evoke piloerection, a process enhanced by α-adrenoceptor stimulation. Another attempt to use clonidine included exploring its potential efficacy as a nasal decongestant, based upon its α-adrenoceptor-mediated vasoconstrictor potency. When applied topically on the nasal mucosa by Dr. Wolff, a scientist of the Boehringer Ingelheim Company (Germany), clonidine caused collapse, due to its potent, hypotensive activity.

Clonidine and related drugs stimulate α_2-adrenoreceptors in the pontomedullary region of the brain stem, thus causing peripheral sympatho-inhibition via inhibitory neurons. Clonidine also stimulates imidazolidine (I_1)-receptors in the rostral ventrolateral medulla (RVLM) thus activating another neuronal pathway that depresses peripheral sympathetic activity. The depressed SNS-activity, triggered via two types of central receptors (α_2 and I_1, respectively) readily explains the potent antihypertensive activity of clonidine and related drugs. These agents are effective antihypertensives with a favorable hemodynamic profile. They appear to counteract left ventricular hypertrophy, brought about by hypertension.

However, their subjective side effects, in particular sedation, dry mouth, and male impotence, have greatly reduced the practical use of such agents in the long-term treatment of hypertension. However, clonidine continues to be useful for the treatment of perioperative hypertension and sympathetic hyperactivation in cardio-anesthesiology and cardiothoracic surgery.

α-Methyl-dihydroxyphenylalanine (α-methyl-DOPA) is in fact an older drug than clonidine, but its central mechanism was elucidated somewhat later. Initially, α-methyl-DOPA's antihypertensive effect was attributed to the so-called "false transmitter theory." This hypothesis was subject to considerable criticism. A few years later (1967, 1968) the central antihypertensive effect of α-methyl-DOPA was discovered (35–37). In fact, the pro-drug α-methyl-DOPA is converted into its active metabolite (α-methyl-NA) which subsequently stimulates central α_2-adrenoreceptors as described for clonidine, thus causing peripheral sympatho-inhibition and a reduction of elevated BP.

The centrally acting antihypertensive agents can no more compete with more modern antihypertensive drugs, mentioned as first choice in various recent guidelines. The centrally acting α_2-stimulants display poor tolerability when compared with β-blockers, diuretics, CAs, ACE inhibitors and AT_1-receptor blockers.

A major further disadvantage of the older centrally acting drugs is the lack of large-scale outcome studies addressing the sequelae of hypertensive disease.

More recently, a new type of centrally acting antihypertensives, the imidazoline (I_1)-receptor stimulants, has been introduced and clinically developed. Moxonidine and rilmenidine are the prototypes of this newer category of centrally acting antihypertensives (for review, see Refs. 38–40). The imidazoline (I_1)-receptor is located in the RVLM. Stimulation of the I_1-receptor causes peripheral sympatho-inhibition and a reduction of BP.

Since moxonidine and rilmenidine display stronger affinity for the I_1- than for the α_2-receptor, it may be hoped that these agents will show a more favorable profile of adverse reactions than clonidine and α-methyl-DOPA. Large-scale intervention studies with the I_1-receptor stimulants have not been performed and their position in the treatment schedule remains unclear.

In spite of these problems and uncertainties, it would seem of interest to further explore and improve the concept of centrally acting antihypertensives, including the possibility of targeting the CNS receptors different from the α_2- and I_1-receptors investigated so far.

CALCIUM ANTAGONISTS (CALCIUM CHANNEL BLOCKERS)

Calcium antagonists are potent vasodilators, as a result of the blockade of the influx of extracellular calcium ions into depolarized arteries via specific calcium channels of the L-type (Figure 29.3).

The chemical structures of the three major subtypes of the CAs are largely heterogenous (Figure 29.4). Verapamil, the first clinically used CA is a phenylalkylamine. Although a vasodilator it is not frequently used as an antihypertensive agent, but it continues to be an important drug in the treatment of certain tachy-arrhythmias and of angina pectoris. More or less the same holds for the benzothiazepine diltiazem.

DIHYDROPYRIDINE CAS

Dihydropyridine CAs, of which nifedipine is the prototype, are the most important category of CAs used in the treatment of hypertension. Dihydropyridine CAs are potent vasodilators. Vasodilatation, predominantly occurring in the resistance vessels, causes a reduction in elevated, peripheral resistance as in essential and other forms of hypertension. Vasodilatation in the arterioles should therefore be considered as the major mechanism of the antihypertensive potency of the hemodynamic effects of the CAs. Effects on the venous system do not play an important role.

From a historic point of view, the question arises whether there may exist any causative relationship between hypertensive disease and the dysfunction of calcium homoeostasis. If such a relationship would indeed exist, the CA might then be regarded as causative therapeutics of hypertension, but such a relationship can no more be defended. Accordingly, mere vasodilatation should be considered as an effective,

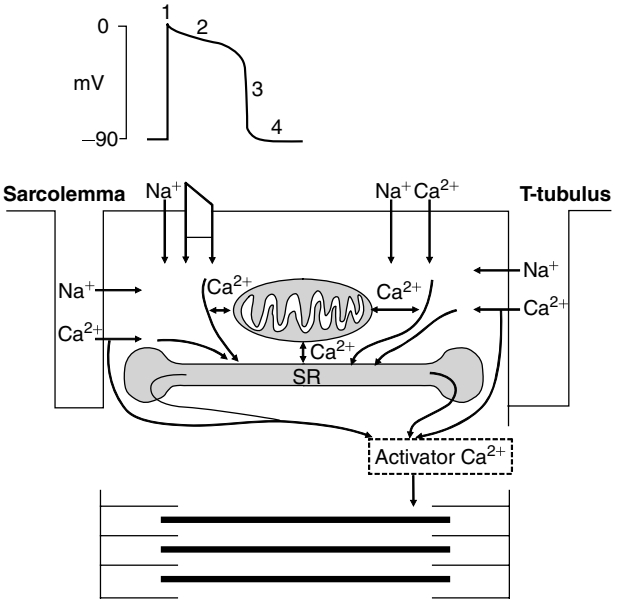

Fig. 29.3 Effect of calcium antagonists (CAs) on a cardiac cell with a typical cardiac action potential (*top*). The calcium (slow) inward current flows during the characteristic plateau phase (phase 2) of the action potential. This calcium influx is selectively inhibited by CA. Activation of the sarcoplasmic reticulum (SR) and other cellular calcium pools occur via Ca^{2+} and Na^{+}, which flow into the cell. The SR and other pools donate activator Ca^{2+}, which stimulate the contractile proteins. The presence of tubular systems (invaginations), characteristic of cardiac tissues, causes considerable enlargement of the cellular surface, thus allowing an effective influx of Na^{+} and Ca^{2+}. Inhibition of the calcium inward flux by a CA causes diminished activation of the contractile proteins.

but not causative, mechanism of the CA as an antihypertensive therapeutic.

The antihypertensive efficacy, safety, and protective effects against the complications ofhypertension have been documented by numerous smaller studies for various CAs. During the last 10 years several controlled, clinical trials have been performed, where CAs were compared with conventional drugs. Studies, such as Syst-Eur, STONE, HOT, INSIGHT, NORDIL, ELSA, etc., have confirmed on an epidemiological scale what was observed in the smaller studies, in particular with respect to the safety of the CA.

The adverse reactions to the dihydropyridine-CAs are also predominantly based upon their vasodilator activity: headache, flush, reflex tachycardia. Edema in the lower extremities is probably caused by direct actions of dihydropyridine-CAs on the local micro- and lymph circulation. It does not reflect the generalized retention of sodium and fluid since it does not very well respond to diuretic treatment (for review, see Refs. 41,42).

NEWER CAS

Various attempts have been made to improve the pharmacokinetic profile and selectivity of the classic CA. Most newer compounds belong to the dihydropyridine CA (Figure 29.4).

A major objection against classic, non-retarded nifedipine is its rapid onset and short duration of action. The rapid vasodilator effect triggers reflex tachycardia, whereas the short action requires three to four daily doses of the drug for adequate control of BP. These deficiencies have been largely overcome by

1. a slow release preparation, in particular nifedipine-GITS;
2. the introduction of lipophilic CAs with a slow onset and long span of action, such as lacidipine, lercanidipine, barnidipine and manidipine.

These newer agents cause little or no reflex tachycardia as a result of their slow onset of action. Their long duration allows once daily dosage per 24 h for the control of BP.

Some of the newer CAs possess a certain degree of vasoselectivity, which means that their vasodilator (therapeutic) potency is not accompanied by relevant cardiodepressant activity. Examples of such agents are most of the aforementioned lipophilic CAs (for review, see Refs. 43,44). Manidipine may be of interest since it displays a certain degree of selectivity for the renal vascular bed.

Although in an early stage, it may be of interest to mention the new dihydropyridine CA that, in addition to its vasodilator effect, may inhibit the release of NA from the sympathetic nerve endings via the blockade of N-type channels on the neuronal membranes. Mibefradil and cilnidipine are examples of such CAs. The relevance of T-channels remains subject to debate (45,46).

Taken together, the CAs, in particular the dihydropyridine CAs, have acquired and maintained an important position in the long-term management of hypertension. They continue to be mentioned as drugs of choice in various guidelines/schedules together with four other categories of first-choice antihypertensives (26).

ANTIHYPERTENSIVE DRUGS AND THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

The involvement of the renin–angiotensin–aldosterone system (RAAS) in hypertensive disease is well established and the system is recognized as an important target of antihypertensive drugs. As shown in Figure 29.5, several components of the RAAS are well-accepted targets for antihypertensive agents, such as ACE inhibitors, AT1-receptor antagonists, and (possibly) renin inhibitors.

RENIN INHIBITORS

Renin is a highly selective enzyme, which catalyses the release of the decapeptide Ang I from the substrate angiotensinogen. As such, it would be a logical target for an enzyme inhibitor, which would then reduce the genesis of Ang I, and consequently also that of Ang II, the major effector of the RAAS. Several renin inhibitors have indeed been developed. Such agents are indeed effective BP-lowering drugs, which owe their antihypertensive activity predominantly to dilatation of the resistance vessels, whereas the heart rate remains unchanged. As is to be expected for such agents, PRA is significantly reduced. This finding represents a major difference with the later discovered ACE inhibitors and Ang

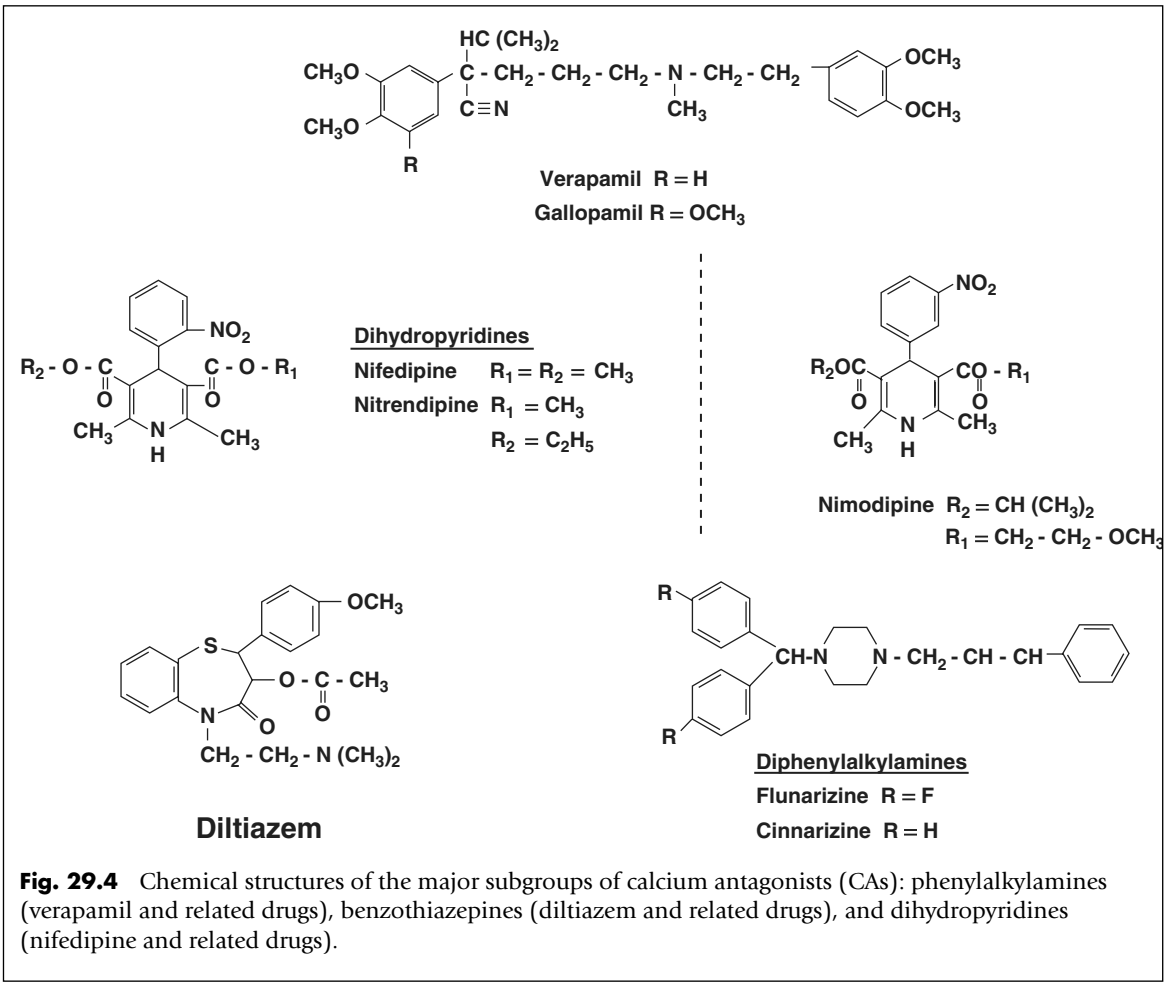

Fig. 29.4 Chemical structures of the major subgroups of calcium antagonists (CAs): phenylalkylamines (verapamil and related drugs), benzothiazepines (diltiazem and related drugs), and dihydropyridines (nifedipine and related drugs).

II-receptor antagonists (AT_1-blockers), which induce an increase in PRA when used in long-term treatment. High PRA values have been repeatedly discussed as a potential risk factor, although this fear has not materialized in the large number of patients treated with ACE inhibitors of AT_1-blockers. In spite of this, the availability of renin inhibitors as potent vasodilator antihypertensives, which simultaneously reduce PRA, would be attractive both clinically and from a scientific point of view.

Numerous attempts have been made to develop renin inhibitors, but without real success, since the experimental compounds so far introduced are rather clumsy molecules with very low bioavailability and they are unsuitable for oral administration (47).

The newer experimental agent aliskiren (48) has shown some more promising results and it appears to be modestly suitable for oral administration, although its bioavailability is still rather low.

ACE INHIBITORS

Angiotensin I-converting enzyme catalyzes the conversion of angiotensin I to the active peptide angiotensin II, the major effector agent of the RAAS. It therefore seems a logical development to inhibit this enzyme by drugs, suppressing the biosynthesis of angiotensin II.

The venom of the snake species *Bothrops jararaca* appeared to contain peptides that inhibit ACE, and they were the basis of chemical research projects aiming at the discovery of selective ACE inhibitors. Captopril, designed to fit upon the active site of the enzyme, ACE, was the first orally active, nonpeptidergic ACE inhibitor. Several other ACE inhibitors were developed and introduced in the drug treatment of hypertension and heart failure.

Most ACE inhibitors so far introduced are pro-drugs, which are converted in vivo into their active component. For instance, enalapril is converted into enalaprilate by hydrolysis of the ester moiety in the enalapril molecule. Captopril and lisinopril are the two ACE inhibitors, which are not pro-drugs. At the clinical level, the question as to whether an ACE inhibitor is a pro-drug or not appears to be irrelevant. The same probably holds for properties such as tissue binding, particularly strong enzyme affinity or the presence or absence of SH-groups. The pharmacokinetic profile of the various ACE inhibitors is decisive for the question as to whether they can be used in a once daily dosage (most compounds) or not.

The ACE inhibitors are now widely used as effective antihypertensives, and there are large-scale studies (CAPP, STOP-2) where their protective action against the complications of hypertension has been documented.

ACE inhibitors are widely used in hypertensive diabetics with the aim to decelerate the development of diabetic nephropathy as reflected by the suppression of microalbuminuria. ACE inhibitors have become the drugs of choice in the treatment of congestive heart failure, a preference which is very well documented by randomized, controlled studies (CONSENSUS, SAVE, SOLVD, AIRE, etc.). ACE inhibitors

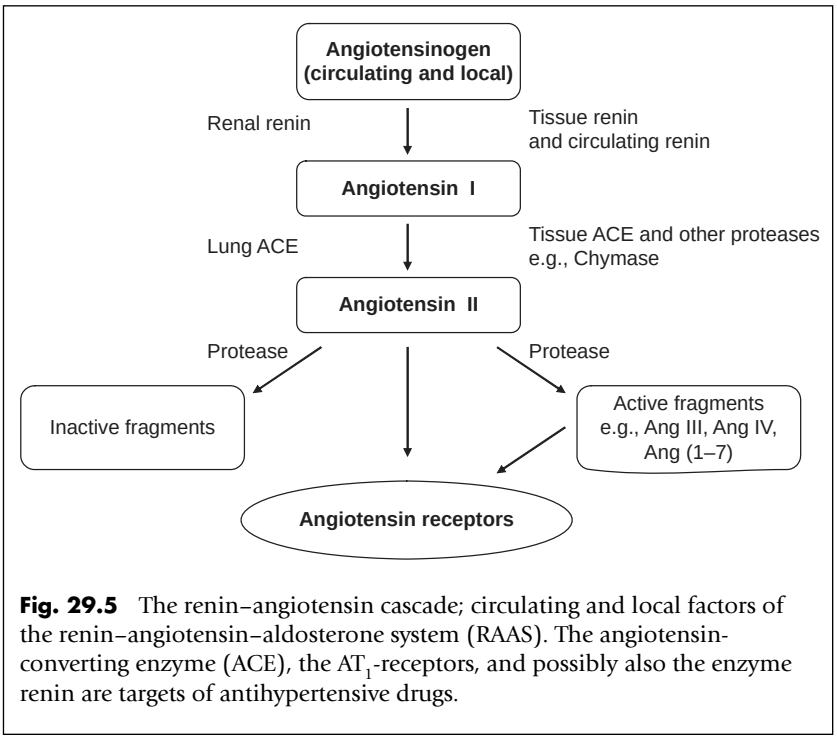

Fig. 29.5 The renin–angiotensin cascade; circulating and local factors of the renin–angiotensin–aldosterone system (RAAS). The angiotensin-converting enzyme (ACE), the AT_1-receptors, and possibly also the enzyme renin are targets of antihypertensive drugs.

may be useful as secondary prevention in post-MI-patients, and there is much interest for their potential ability to improve endothelial dysfunction, as shown for quinapril in the TREND-study. The ACE inhibitors counteract left ventricular hypertrophy.

There is an ongoing debate concerning the question of whether the accumulation of bradykinin, caused by a blockade of the enzyme kinase-II (which is identical to ACE) plays a relevant role in the various beneficial actions of the ACE inhibitors. The ACE inhibitors display a favorable metabolic profile: they reduce insulin resistance, improve glucose tolerance, and appear to reduce the development of new diabetes in hypertensive patients.

The ACE inhibitors are usually well tolerated. Cough is the most frequently reported adverse reaction, which can not only occur rapidly but also after several months of treatment. Angioneurotic edema is a dangerous although very rarely occurring adverse reaction that reflects a most serious allergic response. In patients with congestive heart failure, the hypotensive reaction to an ACE inhibitor can be a problem or even a contraindication.

Taken together, the ACE inhibitors have acquired and maintained a strong position in the treatment of hypertension, congestive heart failure, and in the secondary prevention subsequent to an acute coronary syndrome (for review of the ACE inhibitors, see Refs. 49–51).

ANGIOTENSIN II-RECEPTOR ANTAGONISTS (AT_1-BLOCKERS, SARTANS, ARBS)

The various unfavorable effects of angiotensin II are mediated by receptors, now indicated as AT_1-receptors. It seems logical to block these AT_1-receptors by means of receptor blockers/antagonists for therapeutic purposes.

Since the 1970s, several peptidergic Ang II-receptor antagonists have been synthesized, and some of them have been made available for research purposes, such as saralasin, sarile, and sarmesin. However, the potential therapeutic use of these peptidergic antagonists is greatly hampered by their low oral bioavailability, short duration of action, and partial agonistic activity. Most of these shortcomings have now been overcome by the introduction of more recently developed non-peptidergic, Ang II-receptor antagonists (AT_1-blockers).

In 1982, Furakawa et al. reported in patent literature (52) that certain *N*-benzylimidazoles (S 8307, S 8308) lower BP and antagonize Ang II-induced vasoconstriction in vitro.

Subsequently, a series of potent and orally active, non-peptidergic Ang II-receptor antagonists, based on these lead structures, have been introduced. These compounds proved potentially suitable as antihypertensive drugs for long treatment, owing totheir long duration of action, good bioavailability and lack of intrinsic agonistic activity.

Losartan (Dup 753), synthesized by Timmermans et al., was the first non-peptidergic Ang II-receptor antagonist introduced as an antihypertensive drug (53). Since then, several drugs based upon this principle have been introduced and registered. A biphenyl structure is characteristic for most but not all of the AT blockers thus developed, and many of them contain an imidazole component, which may or may not be condensed with other nuclei (Figure 29.6).

Several but not all of the AT_1-receptor blockers contain a tetrazolium moiety, which is not necessarily essential for the therapeutic potency. Losartan, candesartan, valsartan, eprosartan, telmisartan, olmesartan, and irbesartan are the AT_1-blockers which have been registered in several European countries.

All of these compounds are selective for the AT_1-receptor. Accordingly, the freely accessible AT_2-receptor will be stimulated by high levels of endogenous angiotensin II, brought about by a reflex mechanism associated with vasodilatation and the lowering of elevated BP. Stimulation of the AT_2-receptor is believed to be a favorable phenomenon, causing vasodilatation and an anti-proliferative action on blood vessels. The aforementioned AT_1-blockers are long

acting, thus allowing once daily administration for the control of BP.

The antihypertensive efficacy and the protective action against cerebro-/cardiovascular events of the various AT_1-blockers have been documented by several randomized epidemiological studies, such as LIFE, SCOPE, VALUE, etc. The protective activity against albuminuria/nephropathy has been demonstrated in several studies, such as RENAAL, IDTN, etc.

The beneficial effect of candesartan and valsartan in congestive heart failure was demonstrated in appropriate epidemiological studies, such as CHARM and VAL-HEFT, respectively. Both candesartan and valsartan have been registered for the treatment of congestive heart failure in several countries.

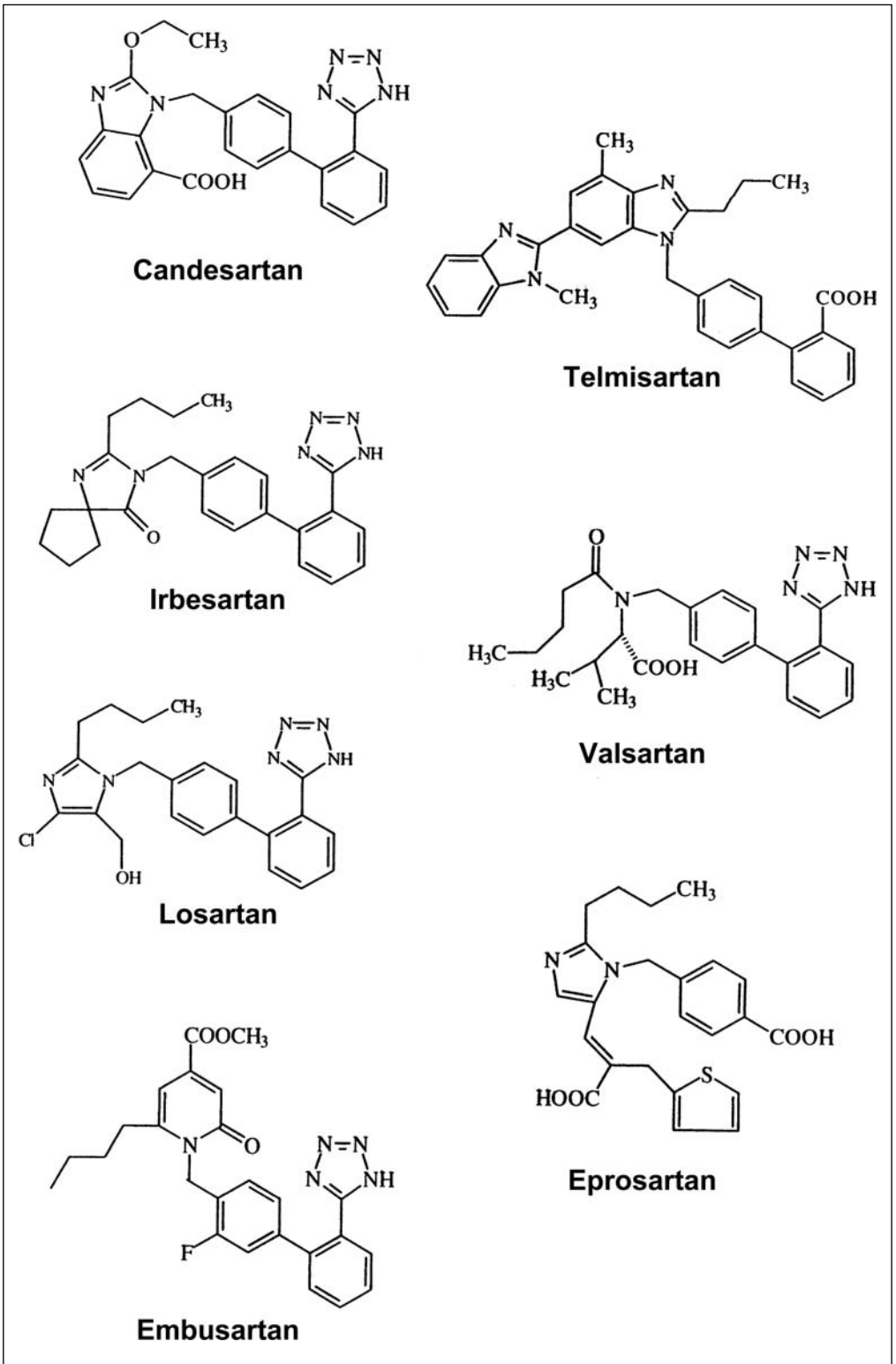

Fig. 29.6 Chemical structures of several angiotensin II-receptor antagonists (AT_1-blockers, sartans, ARBs).

The differences between the various AT_1-blockers now available are not impressive. A few claims put forward for certain individual compounds can be mentioned here.

Losartan: additional uricosuric activity (not a class effect of the AT_1-blockers).
Eprosartan: inhibition of the release of norepinephrine from the sympathetic nerve endings, caused by the blockade of presynaptic AT_1-receptors.
Telmisartan: very long duration of action; potentially favorable metabolic profile, owing to the stimulation of the peroxisome-proliferator-activated receptor subtype γ (PPAR-γ).
Valsartan: very high selectivity for the AT_1-receptor → stronger activation of the AT_2-receptor.

The clinical relevance of these claims remains to be demonstrated by appropriate studies.

A major advantage of the AT_1-blockers is their excellent tolerability. Adverse reactions so far reported appear not to be different from those of placebo. For instance, the AT_1-blockers do not cause cough, in contrast to the ACE inhibitors. Angioneurotic edema has been reported in extremely rare cases for losartan.

AT_1-blockers are now recognized as first-choice drugs, mentioned together with four other categories of antihypertensive agents, in schedules for treatment, such as the ESH–ESC guidelines 2003 (26).

AT_1-blockers can be combined with other types of antihypertensives. The combination AT_1-blocker–thiazidediuretic is a powerful antihypertensive regimen (for review, see Refs. 54–58).

ENDOTHELIN ANTAGONISTS

The endothelins exhibit a number of actions in vivo that suggest a potential role in hypertension, in particular because of their potent vasoconstrictor activity. Antagonists of endothelins are therefore of potential interest as antihypertensive drugs. At least two types of endothelin receptors, ET_A and ET_B, have been identified and a great deal of research activity is being directed toward the development of antagonists of these receptors. Patterned after the design of peptidergic receptor blockers, several non-peptidergic antagonists have now been developed (58).

Combined $ET_A + ET_B$ receptor antagonists (such as bosentan) are now available, as well as selective ET_A of ET_B blockers. Bosentan appears to be an aterial vasodilator. In a randomized study in hypertensive humans bosentan was shown to lower BP with an acceptable hemodynamic pattern and tolerability. A beneficial effect of bosentan in patients with pulmonary hypertension has been documented and bosentan has been registered for the treatment of this condition in several countries (59). The development of more endothelin receptor antagonists may be expected in the near future. Congestive heart failure may be another target for endothelin receptor antagonists.

INHIBITORS OF NEUTRAL ENDOPEPTIDASE AND ACE (VASOPEPTIDASE INHIBITORS)

Atrial natriuretic peptides display potent vasodilator and natriuretic activity. Brain natriuretic peptice is considered as a marker for congestive heart failure: its plasma concentration rises following the progression of the disease, whereas its plasma levels decrease as a result of beneficial intervention. The natriuretic peptides are subject to metabolic degradation by the enzyme neutral endopeptidase (NEP). Conversely, the inhibition of NEP will cause accumulation of the natriuretic peptides and, hence, enhance their potentially beneficial effects.

Experimental inhibitors of NEP have indeed been developed, but they do not cause consistent and useful antihypertensive activity. However, omapatrilate, a drug that simultaneously inhibits NEP and ACE, was shown to be a potent antihypertensive both in animal models and in human hypertensives (60,61). Why this type of drug is such a potent antihypertensive remains a subject of speculation. Omapatrilate has also shown beneficial activity, in small studies, in patients with congestive heart failure. Unfortunately, the side effect profile of omapatrilate was rather unfavorable with a high incidence of angioneurotic edema reflecting a very serious allergic reaction. This adverse reaction was observed in particular in negroid hypertensive patients.

Pharmaceutical industry has introduced the term *vasopeptidase inhibitors* for drugs, which simultaneously inhibit NEP and ACE. However, this term is misleading and incorrect, since vasopeptidase is not a well-defined enzyme.

New examples of the NEP-ACE inhibitors do not necessarily cause the same problems as omapatrilate. However, the enthusiasm for this type of agents has understandably been hampered by the aforementioned disappointing safety profile of omapatrilate and there is not much news in this field.

HYBRID DRUGS

In the preceding paragraphs several drugs with two or even more antihypertensive modes of action have been mentioned. Although potentially of scientific interest, the practical, clinical value of such agents is complex and it is difficult to evaluate which of the mode(s) of action really count. The present tendency to apply combination therapy in hypertension is certainly justified and well-documented by clinical studies (62). If combination therapy is deliberately applied, it will be preferable to prescribe and define the two (or more) components than to use hybrid drugs with dual mechanisms. We limit ourselves here to the enumeration of a few hybrid drugs which are used or were used on a lager scale (see Table 29.2).

CONCLUSIONS AND PERSPECTIVES

Antihypertensive drug treatment has a short but impressive history. Whereas it was not terribly difficult to develop effective BP-lowering agents, it proved much more problematic to find antihypertensives that were well tolerated and did not greatly impair the quality of life of hypertensive patients who should be able to lead normal and active lives. The tolerability of antihypertensive drugs is understandably a very important factor with respect to patient compliance. The issue of tolerability has gradually but greatly improved with the introduction of various older and newer antihypertensive drugs. Furthermore, the protective activity of older and newer antihypertensive drugs against the complications of hypertension (in particular stroke) has been convincingly demonstrated by means of appropriately designed intervention trials.

Table 29.2 Enumeration of hybrid antihypertensive drugs that display two (or more) antihypertensive modes of action

Drug	Modes of action
Indapamide	Thiazide diuretic + vasodilator
Urapidil	α_1-blocker + $5HT_{1a}$-receptor agonist (CNS)
Ketanserin	$5HT_2$-receptor antagonist + α_1-blocker
Labetalol	β_1 + β_2-blocker > α_1-blocker
Carvedilol	β_1 + β_2-blocker > α_1-blocker
Nebivolol	β_1-blocker + vasodilator (via NO)
Clonidine	α_2 + imidazolin (I_1) stimulant (CNS)
Eprosartan	AT_1-blocker + inhibitor of norepinephrine release (via presynaptic AT_1-receptor)
Telmisartan	AT_1-blocker + PPAR-γ agonist
Omapatrilate	Inhibition of NEP + ACE inhibitor

Abbreviations: ACE, angiotensin-converting enzyme; CNS, central nervous system; NEP, neutral endopeptidase; NO, nitric oxide; PPAR-γ, peroxisome-proliferator-activated receptor subtype γ.

It has been recognized that a few homeostatic mechanisms and pathways are the prime targets of current and novel antihypertensive drugs. These systems are the SNS, the RAAS, calcium homeostasis, and the ionic transport mechanisms in the kidneys, respectively. Over the years the importance of the RAAS has gained momentum as a target for antihypertensive drugs.

Further improvements based on the intervention with the aforementioned systems can be thought of, although it will be difficult to beat the more modern antihypertensive agents with respect to BP lowering efficacy and tolerability. It will be difficult to find genuinely novel antihypertensive agents. Nevertheless, in the near future I expect novel drugs to consist of the relatively small organic molecules, which are still simple in comparison with biochemical molecules such as large peptides, enzymes, etc., the targets of the available drugs. One can imagine that the treatment results of developed drugs can be predicted better and optimized by means of pharmacogenomic analysis.

It is my personal opinion that the use of gene therapy in hypertension is still very remote due to the complexity of the genetic pattern of essential hypertension.

Finally, it should be emphasized that the development of antihypertensive drugs has greatly facilitated the detailed analysis of several major regulatory systems in cardiovascular physiology and disease. This development is not sufficiently recognized by the medical profession. Without the various drugs that have been developed, we would not have been able to acquire such a detailed knowledge of the autonomic nervous system, the central nervous regulation of BP, kidney function, calcium homeostasis, and the RAAS (63).

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THERAPEUTIC STRATEGIES 30

Giuseppe Mancia

INTRODUCTION

Unequivocal evidence is available that antihypertensive treatment reduces the elevated incidence of cardiovascular morbid and fatal events associated with hypertension (1,2). Evidence is also available that the degree of benefit largely depends on blood pressure (BP) lowering, per se (i.e., independent of how it is obtained) (3–5) and that treatment optimization requires BP to be lowered to $<$140/ 90 mmHg (6–8) in all hypertensive patients and to $<$130/ 80 mmHg in patients at high or very high cardiovascular risk because of the coexistence of diabetes, a history of coronary or cerebrovascular disease, and possibly multiple risk factors (9). The above means that a great deal of attention must be devoted to strategies that can effectively achieve target BP values in the majority of hypertensive individuals. This chapter reviews these strategies and addresses their advantages and disadvantages.

LIFESTYLE CHANGES

Lifestyle changes should be instituted, whenever appropriate, in all hypertensive patients, as well as in individuals with a BP $<$140/90 mmHg in whom there is a high or very high risk condition, because, under these circumstances, drug-induced BP reductions have been shown to be beneficial (10–13). This is because their implementation may lower BP, reduce the number and doses of the drugs that may have to be subsequently employed, and favorably affect total cardiovascular risk. The lifestyle measures that should be considered are (*i*) smoking cessation, (*ii*) weight reduction in overweight patients, (*iii*) moderation of alcohol consumption, (*iv*) physical activity, (*v*) reduction of salt intake, and (*vi*) increase in fruit and vegetable intake together with a reduction in saturated and total fat intake (9). It should, however not be forgotten that lifestyle measures have never been tested for their activity to prevent cardiovascular complications. Furthermore, their BP lowering effect is small and, for some measures, absent in the long-term, with a high between-patients variability in the response. Salt restriction, for example, lowers BP in a fraction of hypertensive patients, has no effect in an additional fraction, and rarely causes a BP increase due to stimulation of the sympathetic and the renin–angiotensin systems (14). Finally, long-term compliance with lifestyle changes is extremely low (15). Thus, there should be no fideist approach to this strategy. On the contrary, when lifestyle changes represent the main therapeutic option, patients follow-up should be intensified to avoid their living without an adequate BP reduction, and be prepared to timely institute drug treatment when lack of BP control is detected.

MONOTHERAPY WITH PROGRESSIVE INCREASE IN DRUG DOSES

Decades ago, a widespread opinion was to initiate drug treatment with one compound and to progressively increase its dose in case of an insufficient BP lowering effect until BP control was achieved. This strategy is now regarded as obsolete for several reasons. First, the BP lowering effect of some drug classes (e.g., diuretics) does not show a substantial increase above a given dose range. Second, unfortunately this is not the case for side effects which have a close relation with the dose employed for several drug classes, e.g., diuretics, beta-blockers, and calcium antagonists (Figure 30.1) (16). Even when the side-effect to dose relationship is less clear or absent, e.g., for angiotensin receptor antagonists and angiotensin-converting enzyme (ACE) inhibitors (Figure 30.1) (16), a treatment strategy based on a progressive increase in the dose of the initial drug should not be encouraged because, in several instances, this means a substantial increase in cost. Furthermore, even when high doses are used, the ability of monotherapy to effectively reduce BP does not exceed 50% of the hypertensive population, of which no more than 20–25% may attain control (17,18).

SEQUENTIAL MONOTHERAPY

A popular strategy in clinical practice is to switch from one monotherapy to another in the hope to find the monotherapy which controls BP and thus avoid use of multiple drugs. This has a scientific basis because, in a given individual, the antihypertensive response to one class of drugs does not

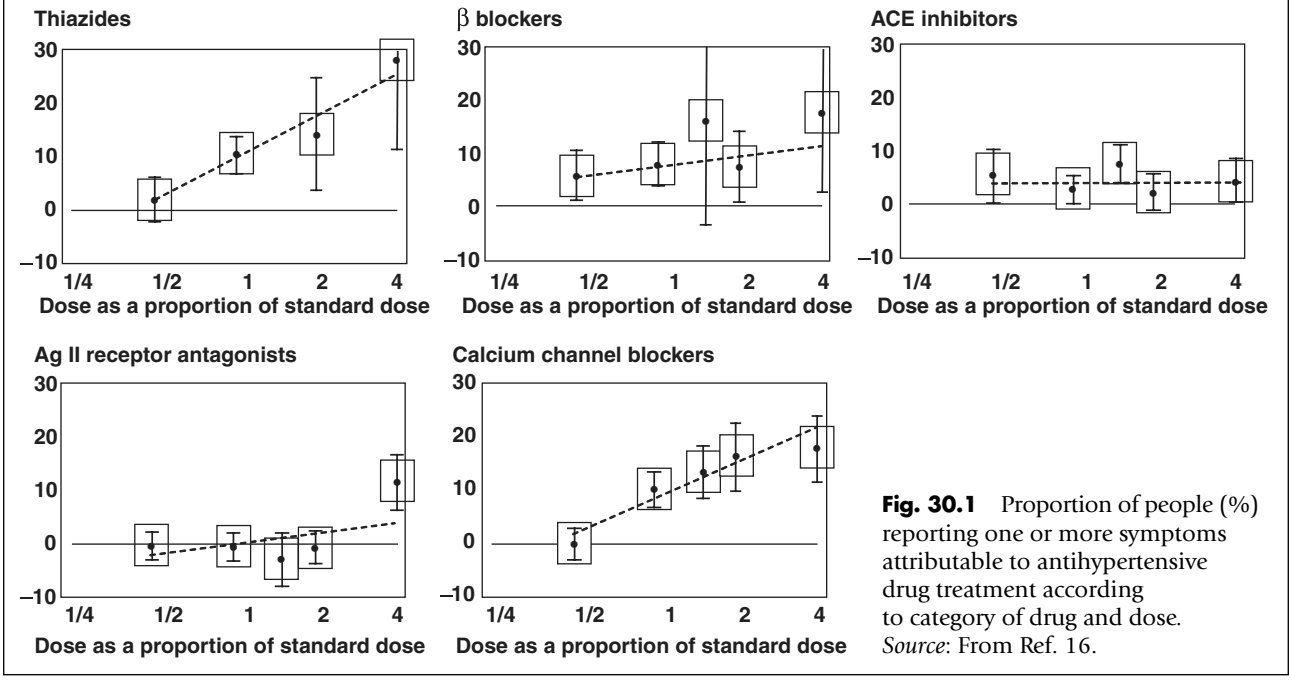

Fig. 30.1 Proportion of people (%) reporting one or more symptoms attributable to antihypertensive drug treatment according to category of drug and dose. *Source*: From Ref. 16.

invariably reflect that to a different class of drugs (19), suggesting that the ineffectiveness of one monotherapy does not preclude an adequate response to another. However, as I have mentioned above, the ability of any monotherapy to control BP is limited, presumably because a single mechanism of action is frequently ineffective against a multiregulated variables such as BP. In addition, it is obvious that, because the full effect of several antihypertensive drugs may become evident only after several weeks, sequential monotherapy is a time-consuming strategy that may prevent identification of successful treatment for months, leading to physician's frustration and loss of patients' confidence, motivation, and compliance. Thus, unless required from the absence of any BP reduction or the appearance of serious side effects, substitution of one monotherapy with another cannot be regarded as the best strategy to control BP in the general hypertensive population.

STEPPED-CARE STRATEGY

The stepped-care strategy consists of an initial monotherapy followed, once the proper dose of the first drug is employed, by the addition of a second, a third, and even a fourth drug, until BP control is achieved. This is recommended by international guidelines because, compared to monotherapy, progression to combination treatment guarantees a much greater BP lowering effect (Figure 30.2) (16) and rate of BP control, with favorable consequences also on the incidence of side effects and the acceptance of prescribed treatment by the patient (20). Recommendations on the initial drugs to be used, as well as on the subsequent combinations between two and three drugs, have changed considerably in the last three decades (21–24). The latest guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) (9) recommend initiating treatment with a thiazide diuretic, an ACE inhibitor, a calcium antagonist, an angiotensin receptor antagonist, or a beta-blocker because, for each of these classes, there is evidence of cardiovascular protection from large-scale randomized trials (1,2,5,25). They also recommend combining drugs (after a full dose of the initial monotherapy has been shown to be ineffective) according to few well defined criteria. First, the drugs to be combined should have different and complementary mechanisms of action. Second, the BP lowering effect of the combination should be greater than that of the combination components, possibly also with a reduction of their side effects. Third, compared to its components, the combination should also have a greater protective effect on hypertension-related organ damage and, at least potentially, on the incidence of cardiovascular morbid and fatal events. With the exception of the last requirement (which is difficult to be investigated and on which evidence is limited), several two-drug combinations meet the above criteria, and their use can thus be recommended. As shown by the tick lines of Figure 30.3 (9) they are the combination of a thiazide diuretic with an ACE inhibitor or an angiotensin receptor

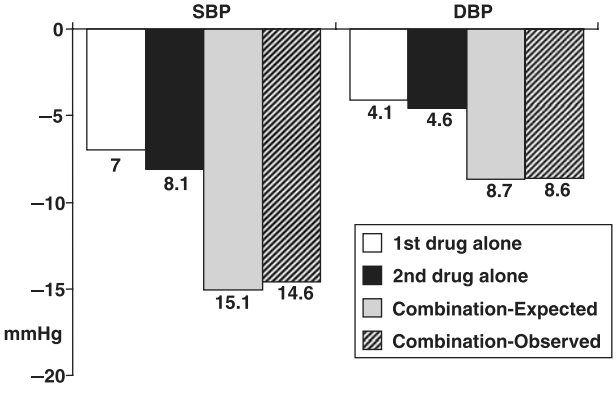

Fig. 30.2 Blood pressure reduction with two different drugs separately administered or combined together in different clinical trials. *Abbreviations*: DBP, diastolic blood pressure; SBP, systolic blood pressure. *Source*: From Ref. 16.

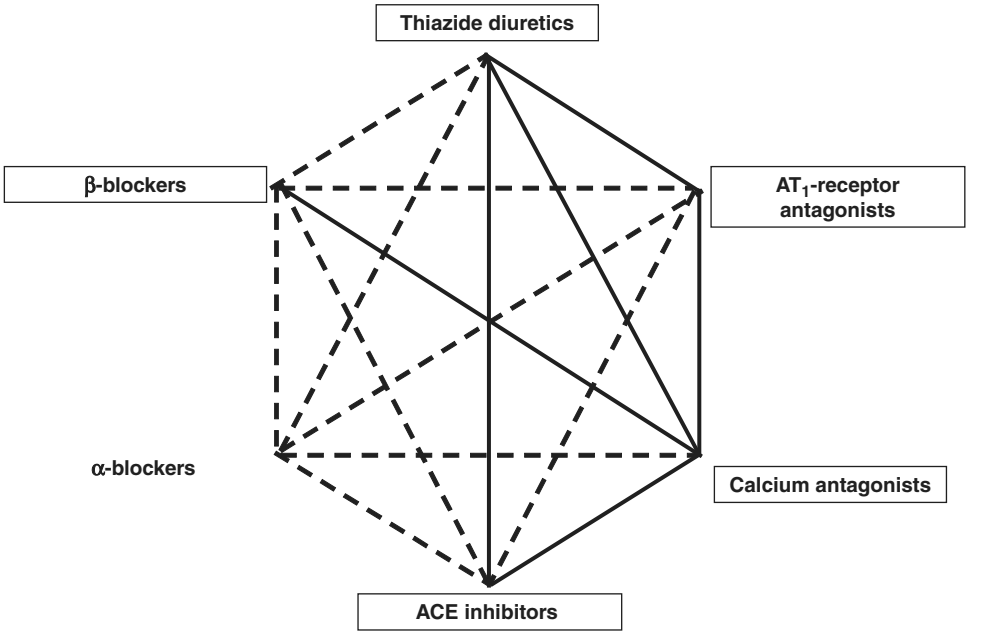

Fig. 30.3 Possible combinations between different class of antihypertensive drug treatments. *Source*: From Ref. 9.

antagonist, a calcium antagonist with an ACE inhibitor and an angiotensin receptor antagonist, a calcium antagonist with a thiazide diuretic, and a beta-blocker with calcium antagonist of the dihydropiridine type. However, other combinations (those indicated in Figure 30.3 by the dashed lines) can also be used and may indeed offer advantages or even be electively required in some clinical circumstances, though less advantageous in others. The time-honored combination of a beta-blocker with a thiazide diuretic, for example, is not recommended in patients with a metabolic syndrome because it may further increase the already high risk of incident diabetes associated with this condition (2,6,27). It can, on the other hand, be profitably employed in hypertensive patients with congestive heart failure, angina pectoris, or a recent history of myocardial infarction (9), i.e., conditions in which beta-blockers have been shown to be protective and the addition of diuretics to the treatment regimen may be important to improve the symptomatic picture or to achieve BP control. The combination of an ACE inhibitor and an angiotensin receptor antagonist, although probably not particularly effective for achieving BP control in the general hypertensive population, may enhance the ability of antihypertensive treatment to reduce proteinuria (28) in patients with renal damage, favorable consequences on renal survival, and cardiovascular risk (29). Although in clinical practice alpha-blockers are now rarely used as first-choice drugs, they can be usefully combined with several other drugs in the attempt to bring BP values down to control, and this has indeed been successfully done in important trials (30). This is the case also for central agents, as well as for drugs such as those opposing the effect of aldosterone, which can exert an independent protective effect in heart failure (31) and help achieve BP control when part of the multidrug treatment regimen in resistant hypertension (32).

Two further aspects of the stepped-care treatment strategies need to be briefly mentioned. First, the importance of combination treatment for achieving BP control cannot be overemphasized because it is also indisputably documented by its exceedingly large use in most recent trials aimed at achieving BP control (Figure 30.4) (35). Secondly, in the stepped-care treatment strategy, the role of combinations of more than two drugs is by no means marginal. This is shown in Figure 30.4, which illustrates that, in several trials, an average of more than two or even three drugs were used. In three or more than three drug combinations, inclusion of a diuretic is often important.

COMBINATION TREATMENT AS FIRST CHOICE

The 2003 ESH–ESC Guidelines (34) recommended considering combinations of two antihypertensive drugs, not only as a step frequently necessary after an unsuccessful monotherapy, but also as an alternative to monotherapy to start antihypertensive treatment. This has been maintained in the 2007 ESH–ESC Guidelines (9) because, although initiating treatment with two drugs may potentially expose the patient to an unnecessary agent, this approach may have several advantages. First, by using a combination as first-step treatment, either combination component can be given in the low dose range, which is more likely to be free of side effects compared to full dose monotherapy, keeping in mind that side effects are the major case of low compliance and withdrawal from treatment (20). Second, as mentioned above, the frustration of repetitively and mainly searching for an effective monotherapy may be avoided. Third, starting treatment with a two-drug combination may allow BP targets to be achieved

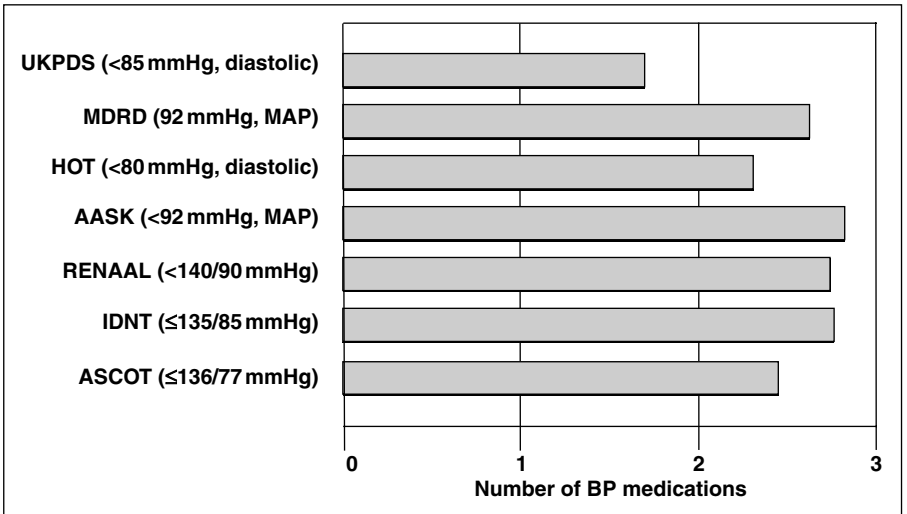

Fig. 30.4 Number of medications required to achieve blood pressure (BP) targets in different clinical trials.

earlier than with monotherapy, which may be of crucial importance in high-risk patients in which even few months of ineffective BP control can lead to an increased incidence of cardiovascular morbid and fatal events (6). The approach proposed by the 2007 ESH–ESC Guidelines (9) is shown in Figure 30.5. Physicians may favor initial monotherapy when hypertension is mild and the total cardiovascular risk not high or very high. They may, on the other hand, decide to use combination treatment as the first step in patients with a marked BP elevation or a high or very high cardiovascular risk. This is justified by the need to obtain a pronounced BP reduction in a relatively short time as well as to hit a low BP target, which is very difficult to achieve with a single drug treatment regimen.

FIXED COMBINATIONS

An issue which has long been debated is whether fixed combinations, i.e., predetermined doses of the combination components in the same tablet, should be preferred to extemporaneous combinations, i.e., separate administration of the combination components. The most obvious merit of extemporaneous combinations is flexibility—that is, the possibility

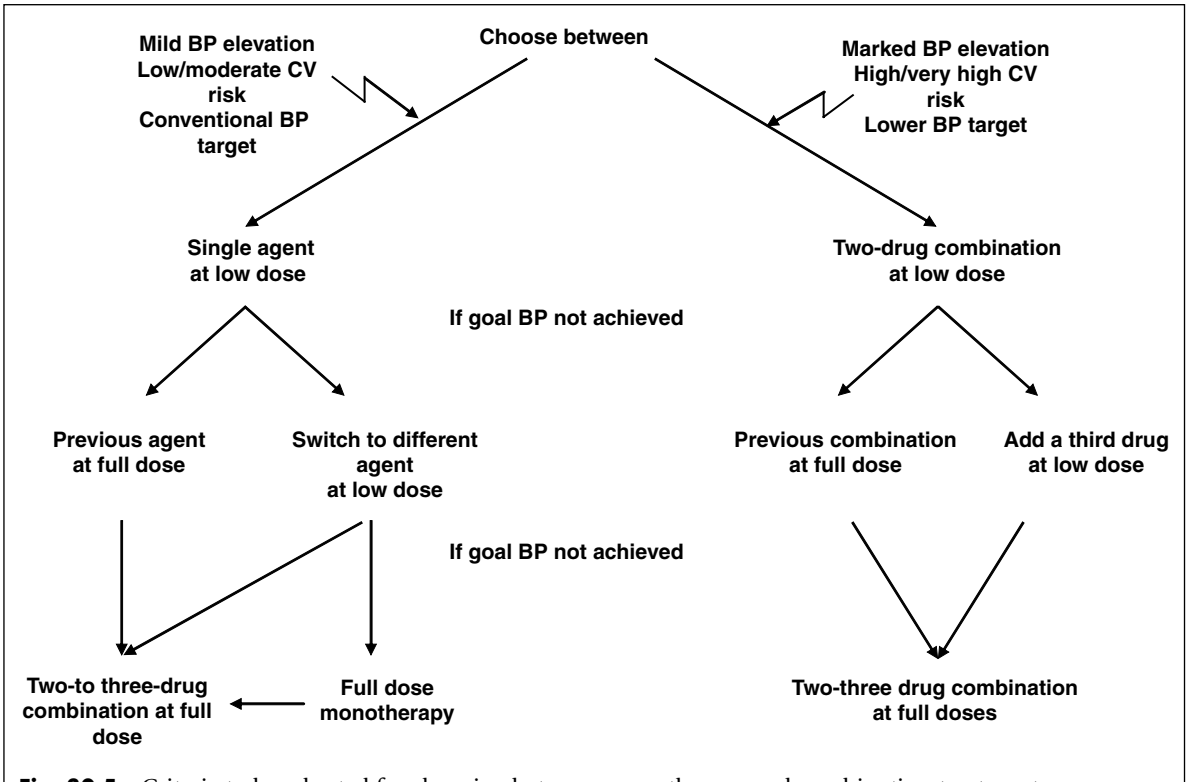

Fig. 30.5 Criteria to be adopted for choosing between monotherapy and combination treatment. *Abbreviations*: BP, blood pressure; CV, cardiovascular. *Source*: From Ref. 9.

of increasing the use of one drug when that of the other is kept unchanged—in relation to the physician's perception of the chance of achieving BP control and cardiovascular protection with no or limited side effects. Furthermore, when drugs are given separately, their role in the appearance of side effects can be more easily detected, and drug substitution more rationally effected. However, fixed-dose combinations reduce the number of tablets to be taken daily, which has a measurable effect on patients' compliance (35). Their level of acceptance by the doctor is also high and this may substantially contribute to improve on a major problem of hypertension treatment today, i.e., low rate of BP control. For some drugs, fixed combinations are now provided at different doses, which can minimize the problem of the reduced flexibility.

SELECTION OF INDIVIDUAL DRUGS OR DRUG COMBINATIONS

Identification of the drug to be used as first-step antihypertensive treatment has always been a debated issue. However, this can now be considered somewhat outdated because, if combination treatment is needed in most patients (and treatment must be continued over life time), which drug is used alone in the first few weeks after treatment initiation is of marginal relevance. The important issue appears more to be which drug(s) should be included in a combination, given that drug classes (and sometimes even drugs within the same class) differ for the frequency of the side effects they may induce, as well as for their effects on risk factors, organ damage, cause-specific events, and protective properties in specific groups of patients. Antihypertensive treatment in specific conditions are described in several chapters of this Manual. Suffice to mention that, according to 2007 ESH–ESC guidelines (9), the general criteria on which to base selection of a given drug or drug combination are the following: First, the previous favorable or unfavorable experience of the individual patient with a given drug class, both in terms of BP effects and tolerability; Second, the effect of drugs on cardiovascular risk factors in relation to the cardiovascular risk profile of the individual patient; Third, the presence of subclinical organ damage, renal disease, cerebrovascular disease, or diabetes, which may be more effectively treated by some drugs than by others; Fourth, the presence of coexisting disorders, because their treatment may interfere with antihypertensive drugs, both pharmacodynamically and pharmacokinetically; Fifth, the cost of drugs, either to the individual patient or to the healthcare provider, although cost considerations should never predominate over the need to give patients the most protective and best tolerated treatment; Finally, physicians should give preference to drugs that effectively reduce BP throughout each 24 h period, because 24-h BP values are prognostically important over and above office BP values (36).

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Special conditions: diagnosis and treatment

SECTION 7

RESISTANT AND MALIGNANT HYPERTENSION 31

Anthony M Heagerty

INTRODUCTION

No manual of hypertension would be complete without a section devoted to resistant and malignant forms of hypertension. While there is a clear overlap between the two entities, in most acculturated societies, malignant phase hypertension is not observed frequently. However, when present, and if untreated, the prognosis is extremely poor, with 50% of individuals dying within 12 months. Both these forms of hypertension require aggressive consideration and management.

RESISTANT HYPERTENSION

The 2003 European Society of Hypertension–European Society of Cardiology Guidelines for the Management of Arterial Hypertension (1) define resistant hypertension as that form of high blood pressure (BP) that exists when it is resistant or refractory to treatment, or when a therapeutic plan that has included attention to lifestyle measures and the prescription of at least three antihypertensive drugs in adequate doses has failed to lower systolic and diastolic BPs sufficiently. In such situations, referral to a specialist should be considered, because persistent hypertension is often recognized to be associated with target organ damage (2). Causes of resistant hypertension are shown in Table 31.1.

One of the most common causes of resistant hypertension is poor compliance or adherence to therapy. In this situation, two options are possible. First, it can be helpful to suspend all drug therapy under close medical supervision and begin again with a new and simpler regime; or, second, arrange a brief admission to hospital to administer therapy under supervised conditions while monitoring BP.

In addition, it is imperative that secondary causes of hypertension are excluded. For example, an occult renal artery stenosis can lead to BP being very refractory to therapy and, although the chances of ameliorating BP are greater in younger patients, it is still possible to reduce treatment load as a result of interventions such as a revascularization procedure, which is often possible using balloon angioplasty and stenting.

In consequence, the key to managing resistant hypertension lies in a careful elicitation of the history, a meticulous examination of the patient, and good investigational backup, primarily to exclude secondary causes of hypertension. However, ultimately, it will be necessary to test whether compliance is good or not. It should be emphasized that the patient's history may well provide the key to the cause: binge drinking of alcohol to excess or the admission to the ingestion of greater than 40 units of alcohol per week, for example, may explain why the BP of an individual is difficult to control. Investigation of secondary forms of hypertension is the focus of Section 12 of this textbook.

MALIGNANT HYPERTENSION

Malignant hypertension embraces a syndrome of severe elevation of arterial BP where diastolic pressure may usually, but does not always, exceed 140 mmHg and has an association with vascular damage that can be manifest on physical examination, particularly in respect of retinal hemorrhages, exudates, and/or papilledema. Some physicians use the term accelerated hypertension when such a syndrome appears but papilledema on retinal examination is absent.

Table 31.1 Causes of resistant and spurious resistant hypertension

Resistant hypertension
Unsuspected secondary cause
Poor adherence to therapeutic plan
Continued intake of drugs that raise blood pressure
Failure to modify lifestyle including weight gain and heavy alcohol intake
Volume overload due to inadequate diuretic therapy
Progressive renal insufficiency
High sodium intake
Spurious resistant hypertension
Isolated office (white coat hypertension)
Failure to use large cuff on large arm

Papilledema is swelling of the veins, which normally are approximately twice the thickness of arteries. In the development of papilledema, the next step is blurring of the disc margins and then the disc becomes more red than usual (normally the optic disc is paler than the surrounding retina). The edema of the optic nerve causes a funnel-shaped hole in the centre of the nerve (the optic cup), which becomes filled with fluid so that the lamina cribrosa cannot be observed. As edema and congestion continue, small veins rupture, leading to hemorrhages in the layers of the retina. All the nerve fibers in the retina fan outwards from the optic disc so that the hemorrhage between the nerve fibers tend to be linear or, sometimes so-called, flame shaped. This arrangement of the nerve fibers also applies to the macula so that any edema, which collects near the macula appears to radiate from it causing the so-called macula star, which is observed in severe papilledema. If raised intracranial pressure is not relieved, the congestion of the disc remains, and the continued pressure on the optic nerve results in optic atrophy, where the optic disc will become very pale and appear white against the pink background of the retina.

Classification of the fundal changes observed in hypertension was originally described by Keith, Wagener, and Barker in 1939. Grade 1 indicated narrowing of the arterioles (which would either be general or focal in nature), grade 2 indicates arteriovenous nipping, grade 3 is manifest by hemorrhage and exudates, and grade 4 indicates papilledema. The presence of grade 3 or grade 4 changes is associated with a marked reduction in life expectancy (3). This original work, of course, was performed retrospectively and without the intervention of effective antihypertensive treatment programs. Most recently, it has been confirmed that milder retinopathy detected on fundal analysis in hypertensive patients cannot be used to determine prognosis (4). Malignant hypertension or hypertensive crisis where there has been an abrupt increase in BP against a chronic history of hypertension is often seen in a variety of conditions (Table 31.2). Severe or poorly treated essential hypertension is usually the commonest harbinger of malignant phase hypertension. Anecdotally, it has been reported that the majority of such patients have a history of current smoking (5). The prevalence of this condition amongst hypertensive patients has obviously diminished as a result of more efficient treatment programs and, of course, most of the diseases that predispose to this (Table 31.2) are relatively rare. What causes this to be a condition with such a sinister prognosis is the breakdown of autoregulation as a result of the arterial wall being exposed to severe levels of high BP. Indeed it is the fact that the exposure is rapid, sustained, and large that places an intolerable burden on the homeostatic mechanisms designed to resist pressure and autoregulate blood flow to target organs. Pathological studies of the vascular wall demonstrate that there is myointimal proliferation and fibrinoid necrosis. The severity of the proliferative response parallels the severity and, of course, the length of exposure to the high BP (6,7). If the process is protracted, vascular smooth muscle hypertrophy and the deposition of collagen adds to the medial thickening and there is an onion skin appearance of small vessels. The fibrinoid necrosis represents spasm and forced dilatation of small arterioles. The leaking of fluid into the extracellular space is associated with small hemorrhages and, of course, target organ damage.

The particular condition that is most dangerously associated with malignant phase hypertension is hypertensive encephalopathy. This is associated with reversible alterations in neurological function and can include headache, disturbed mental status, and visual impairment, which typically can be described as seeing a chequerboard in front of the eyes, with obscuration of vision, and seizures. The risk of developing significant cerebrovascular accident is large. There are pathological findings of micro-infarction and particulate hemorrhages. Once again, this is almost certainly a result of the breakdown in cerebral autoregulation.

Also associated with this condition is a deterioration in renal function, which has been described as being prognostically important, with more severe forms of renal failure being associated with reduced life expectancy, despite the prompt and effective management of hypertension. In some patients, there is irreversible renal damage, necessitating renal assistance, including dialysis on a permanent basis.

Malignant phase hypertension is also associated with hemolysis, red blood cell fragmentation, and evidence of disseminated intravascular coagulation. Such hemolytic anemia is associated with an elevated serum creatinine, suggesting that this process may actually accentuate renal dysfunction. The management of hypertensive encephalopathy and malignant phase hypertension in general must be regarded as that of an emergency, and hypertensive emergencies and urgencies are the specific subject of Chapter 32 of this manual.

Table 31.2 Causes of malignant hypertension or hypertensive crisis

Renovascular hypertension
Parachymal renal disease (chronic)
Scleroderma or other collagen vascular diseases
Use of certain drugs, particularly sympathomimetic agents (such as cocaine, amphetamines. or LSD)
Withdrawal from antihypertensive agents, usually centrally acting drugs such as clonidine
Ingestion of tyramine containing foods, tricyclic antidepressants, or other sympathomimetics, combined with monoamine oxidase inhibitor therapy
Pre-eclampsia or eclampsia
Pheochromocytoma
Acute glomerular nephritis
Head injury
Renin secreting or aldosterone secreting tumors
Vasculitis
Autonomic hyperactivity in Guillain–Barré syndrome or other spinal chord problems

PROGNOSIS OF MALIGNANT HYPERTENSION

The presenting features and natural history of 100 consecutive patients referred with malignant hypertension have been reviewed (8). Most had essential hypertension, although, at that time, the sophistication of searching for secondary causes might be regarded as less than at present. Complications were common, with 33% having vascular and 40% having renal involvement. However, following the institution of effective management programs, the incidence of such initial problems declined over 10 years. Overall survival was reduced compared with the general population, being 82% at 5 years and 67% at 10 years compared with 94% and 84% respectively. This was largely influenced by patients with impaired renal function at presentation. Therefore, when target organ damage is minimal at diagnosis, the long-term prognosis is good. Also, survival is better and reflects not only improved BP control but also good identification of secondary causes and more widely available services, such as renal dialysis and transplantation. Two other studies reinforce that the major reason for poor prognosis is inadequate BP control (9,10). In support of this is a report indicating that BP on treatment was a significant factor influencing outcome (11).

RECENT DEVELOPMENTS IN MALIGNANT HYPERTENSION

1. A recent report from Spain has studied 48 points with malignant hypertension and found that the DD genotype of the angiotensin-converting enzyme is more frequently found (12). Whether this predisposes hypertensive patients to develop the malignant phase of this condition is uncertain.
2. Hemodynamic studies have now confirmed that cerebral autoregulation is impaired in malignant hypertension, and parenteral therapy does not reverse this, indicating that improvement may require a protracted period of good BP control (13).
3. Malignant hypertension can be managed with oral medication if BP is lowered within a few days. If there is evidence of target organ damage, such as in aortic dissection, parenteral therapy will be required (see Chapter 32).

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HYPERTENSIVE EMERGENCIES AND URGENCIES 32

Cesare Cuspidi

INTRODUCTION

Hypertensive emergencies are characterized by a severe increase in systolic and/or diastolic blood pressure (BP) associated with signs or symptoms of acute organ damage (i.e., cardiovascular, renal, and central nervous system). These conditions require an immediate BP reduction (not necessarily a normalization), in order to protect vital organs function; this is usually obtained by the intravenous administration of antihypertensive agents (1,2). The most common clinical presentations of hypertensive emergencies include acute left ventricular failure, acute aortic dissection, acute coronary syndromes, hypertensive encephalopathy, acute brain infarction or intracerebral hemorrhage, pheochromocytoma crisis, and eclampsia (Table 32.1A).

Hypertensive urgencies, at difference from emergencies, are characterized by a severe elevation in BP (>180/120 mmHg) without symptoms or signs of acute target organ involvement. For an adequate treatment of these conditions, a BP lowering within 24 h by the administration of oral agents is required; intensive-care monitoring is usually not needed (3).

Over the last decades, the treatment of arterial hypertension in developed countries has drastically reduced the number of cases of severely uncontrolled BP and, consequently, the likelihood of developing hypertensive emergencies and urgencies. In particular, it has been estimated that approximately 1% of patients may develop a hypertensive crisis during their lives (4), the annual incidence of hypertensive emergencies being about 1–2 cases per 100,000 patients (5). Significantly higher rates have been recently reported in ethnic minorities (i.e., African Americans) and in low socio-economic strata as well as in developing countries (6,7). The management of hypertensive crises remains an important challenge for physicians operating in general as well as in specialistic settings. It should be remarked that, in most instances, severe BP elevations do not represent true hypertensive crises, and a rapid BP reduction in these conditions may represent an unwarranted risk. Chronic asymptomatic severe hypertension, acute BP elevations associated with anxiety or panic attacks, and pseudo-hypertension in the elderly constitute some examples of clinical conditions which do not require an aggressive antihypertensive treatment (Table 32.1B).

CLINICAL ASSESSMENT

An early triage is essential to timely diagnose and effectively treat a patient with a suspected hypertensive urgency/emergency and to reduce the cardiovascular morbidity and mortality.

The initial evaluation of a severely hypertensive patient should include a complete history collection and detailed physical examination performance (8). Duration and degree of pre-existing hypertension, any evidence of target organ damage, such as previous cardiac and cerebrovascular diseases, details of antihypertensive therapy, compliance with medications, and use of over-the-counter preparations (i.e., sympathomimetic and corticosteroid drugs) or illicit drugs (i.e., cocaine) should be promptly ascertained. A variety of symptoms suggesting an acute end-organ involvement should be carefully considered, such as chest pain (myocardial infarction or ischemia, thoracic aortic dissection), back pain (thoracic aortic dissection), dyspnea (acute pulmonary edema), neurological symptoms, such as delirium, nausea, vomiting, seizures, or altered consciousness (hypertensive encephalopathy, ischemic or hemorrhagic stroke). Physical examination should preliminarily assess a full set of vital signs, such as BP, respiratory rate, heart rate, and oxygen saturation. BP should be checked in the sitting and standing position (if possible) with an appropriate size-cuff in both arms (a significant difference should raise the suspicion of aortic dissection) and in a lower limb if peripheral pulses are markedly reduced. A fundoscopic examination may be extremely useful to distinguish a true hypertensive emergency, characterized by the presence of hemorrhages, exudates, and/or papilledema, from a hypertensive crisis without target organ damage (Figure 32.1). Cardiovascular examination should be focused on the search of cardiac murmurs due to aortic insufficiency associated with dissection or to mitral regurgitation of ischemic origin, as well as of signs of heart failure (tachycardia, third heart sound or gallop, crackles in the lung fields, raised jugular pressure). In addition, auscultation of renal bruits or palpation of abdominal masses may provide clues for secondary forms of hypertension, such as renovascular hypertension or polycystic kidney disease. Neurological examination should define the level of consciousness and detect focal signs of ischemic or

Table 32.1A Hypertensive emergencies
Hypertensive encephalopathy
Hypertension associated with acute cerebrovascular disease
Hypertension associated with pulmonary edema
Hypertension associated with acute coronary syndromes
Hypertension associated with dissecting aortic aneurysm
Pheochromocytoma
Hypertension associated with acute renal failure
Eclampsia
Microangiopathic anemia

hemorrhagic stroke. Immediate investigations should include determination of blood electrolytes, creatinine, urea nitrogen, cell count and smear (to exclude a microangiopathic hemolysis), urinalysis, as well as an electrocardiogram and chest X-ray. Further investigations should be rapidly performed on a clinical basis (i.e., head computed tomography in patients with neurologic symptoms, chest computed tomography or magnetic resonance scan in individuals with unequal pulses and/or evidence of an enlarged mediastinum).

The differential diagnosis between hypertensive emergencies and urgencies is based on the clinical evidence of an acute end-organ involvement more than on the degree of BP elevation, per se (Table 32.2) (9). Severe BP elevations in the absence of acute neurological, vascular, and cardiac damages do not represent an immediate risk for patients and can be managed with orally administered antihypertensive agents without hospital admission (10). As an example, a young asymptomatic man, with BP values of 230/130 mmHg and no evidence of compromised end-organs, should not be hospitalized if his follow-up as outpatient is feasible after the institution of an oral treatment. In contrast, a 70-year-old man presenting with pulmonary edema and BP values of 180/100 mmHg constitutes a hypertensive emergency and requires a prompt hospitalization for the initiation of parenteral therapy.

MANAGEMENT: GENERAL PRINCIPLES

Hypertensive emergencies should be treated in intensive care units, where all the potential factors causing BP elevations, such as hypoxia, hypercapnia, pain, and anxiety, as well as the effects of the administration of intravenous antihypertensive drugs, are simultaneously controlled. Two important issues in the early management of hypertensive emergencies are represented by how fast and how much BP is lowered.

Table 32.1B Hypertensive urgencies
Severe uncomplicated essential hypertension
Severe uncomplicated secondary hypertension
Postoperative hypertension[a]
Hypertension associated with severe epistaxis
Drug-induced hypertension
Rebound hypertension (i.e., sudden withdrawal of clonidine)
Cessation of prior antihypertensive therapy
Severe hypertensive crises related to anxiety, panic attacks or pain

[a] At times may become a true hypertensive emergency.

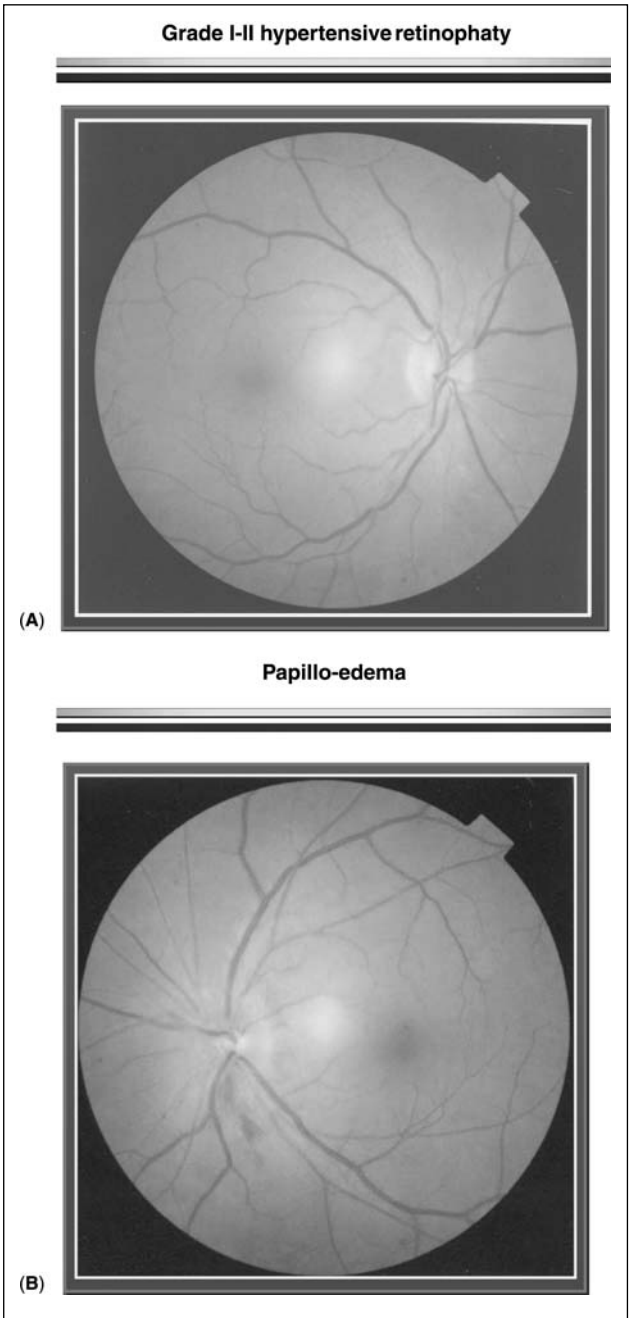

Fig. 32.1 (A) Mild hypertensive retinopathy (arteriolar narrowing and arteriovenous crossing) in a 37-year-old patient with an asymptomatic, severe elevation in blood pressure (230/130 mmHg). **(B)** Advanced hypertensive retinopathy (papilledema and flame-shaped hemorrhages) in a 65-year-old patient seen in the emergency room for a severe elevation in blood pressure (240/140 mmHg), associated with headache, mental confusion, and dyspnea.

Normalization of BP is usually not recommended and, with some exceptions, should not be the aim of therapy, as a sudden BP fall may cause acute hypoperfusion of vital organs and serious ischemic accidents, such as myocardial ischemia or infarction, hemiplegia, or acute renal failure. Older patients with long-lasting hypertension and preclinical organ involvement (i.e., left ventricular hypertrophy, atherosclerosis, and/or arteriolar remodeling) are particularly exposed to these

Table 32.2 Acute target organ damage in hypertension

Target organ	Complications
Brain	Hypertensive encephalopathy Cerebral infarction Cerebral hemorrhage Advanced retinopathy
Heart	Acute coronary syndromes Acute heart failure
Aorta	Aortic dissection
Kidney	Acute renal failure
Placenta	Eclampsia

complications as the lower limit of the autoregulation curve is shifted to the right.

Several clinical considerations may influence the choice of drugs, route of administration, dosage and target BP (11). First of all, it should be emphasized that among the multiple therapeutic options available at present for the treatment of hypertensive emergencies, the appropriate treatment is dictated more by the features of the acute syndrome and by the patient's characteristics than by a body of scientific evidence. To date, indeed, controlled trials assessing the optimal treatment of hypertensive emergencies are not available, due to the difficulties of designing such studies in an extremely heterogeneous population. Thus, the management of hypertensive emergencies should be tailored on the individual patient, in particular on the specific organ at risk (12).

The treatment goal is to progressively reduce mean arterial BP by no more than 20–25% or diastolic BP down to 100–110 mmHg within a period of a few minutes up to 2 h. Patients with extra-cerebral acute organ damages, such as aortic dissection or acute pulmonary edema, would benefit from a more aggressive and rapid BP reduction. In contrast, in patients with acute cerebrovascular damages, the goal pressure should be attained more slowly, within a period of hours, with a careful monitoring of the neurological status.

It should be remarked that the oral or intravenous bolus administration of some agents can cause a drastic BP decrease, depending on the intravascular volume status and prior antihypertensive therapy. For these reasons, it is safer to reach target BP by a constant infusion of intravenous agents rather than by intermittent administrations of intravenous boluses or oral/sublingual drugs (i.e., nifedipine). Thus, the ideal drug for the management of hypertensive emergencies should be fast-acting, easily titratable, rapidly reversible, and safe. Although no single agent is provided of these characteristics, a certain number of effective parenteral drugs are currently available (Table 32.3). The choice between a single drug or a combination therapy may depend on the clinical characteristics of the patient. If a volume overload is present, as in hypertension states related to renal parenchymal disease, acute glomerulonephritis, or associated with left ventricular failure, the early use of diuretics is usually indicated. Diuretic treatment, in turn, is contraindicated in conditions characterized by a reduced intravascular volume (accelerated hypertension, prior use of large doses of diuretics).

Sodium nitroprusside can be safely administered in the majority of hypertensive emergencies, including, acute pulmonary edema and hypertensive encephalopathy. This drug is a potent short-acting arterial and venous dilatator, which induces a simultaneous reduction in cardiac pre- and after-load, and has an extremely rapid onset of action (within a few seconds after the infusion has started), requiring a continuous intra-arterial BP monitoring. A complication of this drug is the thiocyanate toxicity (nausea, vomiting, lactic acidosis, and altered mental status), which occurs when this agent is administered for several days, especially in subjects with renal or hepatic dysfunction. In patients with intracerebral hemorrhage, caution should be used because of the potential antiplatelet effect and intracranial pressure increase. Other useful options in many instances are represented by the intravenous administration of beta-blockers (labetalol and esmolol), calcium-channel antagonists (nicardipine), and fenoldopam mesylate, a peripheral dopamine-1-receptor antagonist (DA1). Fenoldopam is highly specific for DA1 and is 10-fold more potent than dopamine as a renal vasodilator; its antihypertensive action results from the combined natriuretic and direct vasodilatory effect, in particular on intrarenal arteries. These pharmacodynamic characteristics make fenoldopam the agent of choice in hypertensive emergencies associated with renal dysfunction. Angiotensin II-converting enzyme (ACE) inhibitors, diuretics, nitroglycerine, and hydralazine may represent valuable alternative drugs; caution should be used with ACE inhibitors, as they may cause precipitous fall in BP in the presence of hypovolemia or unrecognized renal artery stenosis.

At variance from acute hypertensive syndromes, patients presenting with severe hypertension without symptoms or signs related to target organ dysfunction can be managed as outpatients by the administration of oral agents aimed at lowering BP within 24 h. A number of oral agents may provide a prompt reduction of BP within 30 min to a few hours; dosing recommendations, onset, and duration of action of these drugs are reported in Table 32.4. No data are currently available about the protective effect of a rapid BP reduction in this clinical setting; on the contrary, growing evidence indicate that an aggressive approach, causing a precipitous and unpredictable BP fall, may be harmful, especially in patients with multiple risk factors (13). A general agreement exists that a comprehensive approach to hypertensive urgencies is based on: (*i*) a careful assessment of organ damage; (*ii*) oral administration of single or combination therapy aimed to reduce BP within 24–48 h; and (*iii*) referral to a primary care provider for a follow-up.

SPECIFIC SETTINGS

Myocardial ischemia or myocardial infarction may be associated with hypertension, which usually results from a preexisting high BP exacerbated by pain and agitation. In this setting, intravenous nitrates are useful in reducing systemic vascular resistances, as well as left ventricular preload, and in improving coronary perfusion (Table 32.5). Addition of beta-blockers may contribute to a substantial fall in BP and reduce myocardial oxygen consumption. Effective BP control is mandatory in patients candidates to thrombolysis, as this procedure is allowed only when BP is below 180/100 mmHg.

Aortic dissection is the most dramatic and rapidly fatal complication associated with hypertensive emergencies. Acute BP reduction is essential to reduce shear forces on damaged aorta. The aim of treatment is to decrease systolic BP as rapidly as possible down to 100–110 mmHg and simultaneously control tachycardia resulting from the sympathetic activation. The combined therapy of a beta-blocker and a vasodilator

Table 32.3 Parenteral drugs for hypertensive emergencies

Drug	Dose	Onset	Duration[a]	Adverse effects
Sodium nitroprusside	0.25–10 μg/kg/min	Immediate	2–3 min	Hypotension, vomiting, cyanate toxicity
Glyceril-trinitrate	5–100 μg/min	1–3 min	5–15 min	Headache, vomiting, tachycardia
Labetalol	20–80 mg bolus, 1–2 mg/min infusion	5–10 min	2–6 h	Bronchospam, vomiting, bradycardia
Esmolol	80 mg bolus, 150 μg/kg/min infusion	6–10 min	15–30 min	Asthma, bradycardia
Furosemide	40–60 mg bolus	5–10 min	1–2 h	Hypotension, hypokalemia
Enalaprilat	0.625–1.25 mg bolus	15–20 min	4–6 h	Hypotension, renal failure
Nicardipine	5–15 mg/h	5–10 min	2–4 h	Headache, tachycardia
Fenoldopam	0.1–0.6 μg/kg/min	5–10 min	10–15 min	Hypotension, headache
Phentolamine	5–10 mg/min	1–2 min	5–10 min	Tachycardia, orthostatic hypotension
Hydralazine	10–20 mg bolus	10 min	2–6 h	Tachycardia, angina pectoris
Urapidil	20–60 mg bolus	3–4 min	6–10 h	Sedation

[a] After discontinuation.

(nicardipine or sodium nitroprussiate) is the treatment of choice in these cases (14).

The acute cardiogenic pulmonary edema necessitates rapid and specific interventions, including ventilation and reduction of left ventricular preload and afterload. The first-line treatment of this condition is based on intravenous administration of nitrates and loop diuretics. If this approach is not effective, vasodilators, such as urapidil, nicardipine, or sodium nitroprusside, are also indicated.

BP elevations commonly accompany ischemic stroke, in previously hypertensive and in normotensive subjects. Stroke-related hypertension has been hypothesized to result from the lesions in cerebral areas causing an impaired neurogenic control of cardiovascular system. A general consensus exists that mild to moderate BP elevations do not require any treatment, as BP spontaneously declines to pre-stroke values within 3–4 days after an acute ischemic stroke (15,16). Management of severe hypertension still remains a controversial issue. The American Heart Association recommends that treatment with intravenous labetalol or nicardipine should be started when BP values are above 220/120 mmHg; the target BP should be a 10–15% lowering of BP (17). In patients candidates to treatment with intravenous tissue plasminogen activator BP should be maintained below 185/110 mmHg.

The aim of the acute management of BP elevation in the setting of intracranial bleeding is to prevent rebleeding and reduce edema formation. Patients with intracerebral or subarachnoid hemorrhage and BP values exceeding 180/105 mmHg may benefit from a careful and gradual 20–25% reduction in BP (18). Nimodipine, a dihydropiridine calcium blocker, has been shown to improve neurological outcome in patients with subarachnoid hemorrhage, due to its antagonistic effects on cerebral vasospam (19).

Hypertensive encephalopathy is a potential lethal complication of severe or abrupt BP elevations. Symptoms include severe headache, vomiting, visual disturbances, confusion, and focal or generalized seizures (20). The pathophysiology of this condition is still controversial and is related by some authors to the formation of localized or widespread cerebral edema as a result of the hyperfiltration induced by an excessive increase in blood flow at high pressure (21). Other authors, however, ascribe encephalopathy to cerebral ischemia resulting from arteriolar spasm (22). Fundoscopic examination searching for papilledema, exudates, and hemorrhages plays a key role in the diagnostic work-up (23). Hypertensive encephalopathy may occur not only in patients with prior hypertension, but also in previously normotensive subjects developing a sudden and dramatic increase in BP. A variety of clinical conditions may predispose to hypertensive encephalopathy, namely acute glomerular nephropathy, eclampsia, trombocitopenic thrombotic purpura, pheochromocytoma, erythropoietin, and immunosuppressive drug administration (24). In patients presenting with hypertensive encephalopathy, mean BP should be reduced by 20% within the first hour. Sodium nitroprusside is the drug of choice because of its rapid onset of action and short half-life, which allow an effective BP control, and the lack of adverse effects on cerebral blood flow. Intravenous labetalol, nicardipine, and hydralazine may also be useful in the treatment of hypertensive encephalopathy, although their use is less characterized than that of sodium nitroprusside.

Hypertensive emergencies due to catecholamine excess are generally characterized by an abrupt increase in the

Table 32.4 Oral drugs for hypertensive urgencies

Drug	Initial dose	Onset	Duration[a]	Adverse effects
Captopril	25–50 mg	15–45 min	6–8 h	Renal failure in bilateral artery stenosis
Labetalol	200–400 mg	30–120 min	2–12 h	Orthostatic hypotension, bronchoconstriction
Clonidine	0.150–0.300 mg	30–60 min	8–16 h	Hypotension, dry mouth
Prazosin	1–2 mg	60–120 min	8–12 h	Syncope (first dose), orthostatic hypotension, tachycardia
Nicardipine	20–40 mg	30–60 min	8–12 h	Headache, tachycardia, flushing
Amlodipine	5–10 mg	60–120 min	12–18 h	Headache, tachycardia, flushing

[a] After discontinuation.

Table 32.5 Drugs of choice and relative contraindications for hypertensive emergencies

Condition	Drug(s) of choice	Relative contraindications/cautions
Acute pulmonary edema	Nitroglycerin + loop diuretic Nitroprusside + loop diuretic	Beta-blockers, verapamil
Acute coronary syndromes	Nitroglycerin + beta-blocker Nitroprusside + beta-blocker	Hydralazine
Hypertensive encephalopathy	Nitroprusside, labetalol, nicardipine	Centrally acting sympatholytic agents
Dissecting aortic aneurysm	Nitroprusside + beta-blocker	Isolated use of pure vasodilators
Intracranial hemorrhage	Labetalol, nicardipine	Nitroprusside with caution, nifedipine
Ischemic stroke	Nitroprusside, labetalol, nitroglycerin	Nifedipine
Adrenergic crisis	Labetalol, phentolamine + beta-blocker	Beta-blocker monotherapy
Acute renal impairment	Fenoldopam, nicardipine	Diuretics with caution
Eclampsia	$MgSO_4$, hydralazine, methyldopa	Nitroprusside
Subarachnoid hemorrhage	Nimodipine	Nitroprussiate with caution

alpha-adrenergic tone. These conditions include the hypertension rebound following the withdrawal of centrally acting antihypertensive drugs (i.e., clonidine), pheochromocytoma, cocaine intoxication, abuse of sympathomimetics, and postoperative hypertension (25). The clinical presentation may simply consist in an acute rise in BP; organ damage requiring a rapid treatment may be an accompanying feature. Intravenous labetalol appears to be effective in most of these situations (26). Pheochromocytoma crisis can also be managed with an intravenous alpha-blocker (phentolamine) as a first-line drug, followed by a beta-blocker, if severe tachycardia or ventricular ectopy are present.

Like emergencies, hypertensive urgencies recognize distinct pathophysiological mechanisms, clinical presentations, and require specific therapeutic strategies. Anxiety, panic attacks, and pain are common causes of acute and transient BP elevations; the appropriate therapy in these settings is the administration of anxiolytic or analgesic agents. Perioperative hypertension, refractory nose bleeding, and hypertension crises associated with catecholamines excess represent selected urgencies that may require a prompt treatment with intravenous rather than oral administration of antihypertensive drugs and a careful follow-up by a continuous non-invasive BP monitoring (27).

CONCLUSIONS

Patients presenting with true hypertensive emergencies should be promptly diagnosed and treated in a closely supervised inpatient setting, as an immediate BP reduction with titratable intravenous antihypertensive drugs is mandatory in order to arrest the progressive organ damage. Therapeutic protocols and target BP in the single patient should be based on the clinical presentation and a prompt diagnostic work-up aimed to identify the type and extent of the acute target organ damage.

Differentiation between hypertensive emergencies and urgencies is related more to the presence of acute organ involvement than on BP elevation, per se. Hypertensive urgencies include a wide array of situations in which an acute target organ damage is absent; in most instances, these conditions can be treated outside the intensive care units with oral antihypertensive medications over a period of 24–48 h.

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SECONDARY HYPERTENSION: DIAGNOSIS AND TREATMENT 33

Peter W de Leeuw

INTRODUCTION

In the majority of hypertensive patients, no particular cause for elevated blood pressure (BP) is apparent. In such cases, hypertension is labeled as "primary" or "essential," even when some pathophysiological mechanism (e.g., sympathetic overactivity, sodium sensitivity) seems to prevail in the pathogenesis of the disorder. The term "secondary hypertension" is reserved for those conditions in which a specific underlying disease is responsible for abnormal BP. Since secondary hypertension is potentially curable, it may be worthwhile to search for such diseases. Accordingly, the clinician needs to remain alert for certain signs and symptoms which could raise suspicion of secondary hypertension. Nevertheless, it is not uncommon to find evidence of secondary hypertension in patients without any clinical clues.

Although one may classify the secondary forms of hypertension according to certain pathophysiological mechanisms (e.g., renin-dependent hypertension, volume-dependent hypertension, endocrine hypertension), it is more common to use a nosological distinction, such as the one presented in Table 33.1. In terms of prevalences, renal parenchymal hypertension, renovascular hypertension, and endocrine (adrenal) hypertension are the most important forms of secondary hypertension (1). Sometimes, however, it may be difficult to highlight only one cause. For instance, in patients with post-transplant hypertension, a rise in BP may be secondary to a combination of renal artery stenosis (RAS), parenchymal damage, and the effects of immunosuppressive therapy.

As both transplant hypertension (Chapter 37) and hypertension due to parenchymal renal damage and end-stage renal disease (Chapter 38) are dealt with in separate chapters, these disorders are not discussed here any further. The same applies to the obstructive sleep apnea syndrome, for which one can find a detailed description in Chapter 4. In the present chapter, we focus on renal and adrenal causes of hypertension, as as on some genetic and exogenous causes.

EVALUATION OF THE HYPERTENSIVE PATIENT

In the work-up of patients with high BP and, in particular, when one wants to explore whether a specific cause can be found, a proper history and physical examination are indispensable. In addition, an array of laboratory techniques is germane to a proper diagnosis.

The latter includes radiological investigations and, to some extent, the use of nuclear medicine techniques. However, there is considerable debate about the selection of tests which need to be applied for establishing secondary hypertension. Several tests which seemed to work well in selected populations have proven to be too unreliable when applied on a larger scale. In addition, some diagnostic procedures are considered to be unjustified because the results of such investigations would either not alter clinical practice or not improve prognosis, even when causal therapy would be initiated. In this regard, a major problem in the critical evaluation of diagnostic tests is the definition of the outcome variable or the gold standard. For instance, tests which are able to detect the presence of RAS do not necessarily provide the evidence that the stenosis is the actual cause of the elevated pressure. On the contrary, RAS may also be secondary to hypertension-related atherosclerotic abnormalities in the renal artery. Even more disturbing is the fact that removal of a true cause of the hypertension does not always lower BP because adaptive mechanisms in the vascular wall may help to sustain hypertension irrespective of the prime mover. Of course, the duration of the hypertensive process is of paramount importance so that removal of abnormalities which have been present for a long time are less likely to cure hypertension. Unfortunately, most investigations which have addressed the accuracy of diagnostic modalities or the evaluation of certain treatments were retrospective. Therefore, with respect to the type of patients selection bias cannot always be excluded. Moreover, when the predictive power of a test has been derived from a population with a high a priori chance of finding the abnormality, the same test

Table 33.1 Secondary forms of hypertension

Renal causes
Renal artery stenosis
Atherosclerosis
Fibromuscular dysplasia
Others (e.g., arteritis, dissection, thrombosis)
Renal parenchymal disease
Unilateral (e.g., reflux, tumor)
Bilateral (e.g., glomerulonephritis, cysts)
Renin secreting tumour
Adrenal causes
Excess mineralocorticoid activity
Primary hyperaldosteronism (Conn's syndrome)
Glucocorticoid-remediable aldosteronism
11-β hydroxysteroiddehydrogenase (11-β OHSD) deficiency
Hyperdeoxycorticosteronism
Excess glucocorticoid activity
Primary overproduction of cortisol (Cushing's syndrome)
Primary overproduction of ACTH (Cushing's disease)
Excess production of catecholamines
Phaeochromocytoma
Other biological causes
Aortic coarctation
Obstructive sleep apnea syndrome (OSAS)
Liddle's syndrome
Acromegaly
Hypothyroidism
Hyperparathyroidism
Exogenous causes
Exogenous administration of glucocorticoids
Excess liquorice (via inhibition of 11-β HSD)
Excess alcohol
Certain medications (e.g., non-steroidal anti-inflammatory drugs, cyclosporine)
Birth control pill

may yield disappointing results in patients with a low prevalence of the same abnormality.

RENOVASCULAR HYPERTENSION

Renovascular disease is one of the more common causes of secondary hypertension. This does not mean, however, that there is a clear relationship between the presence of RAS and an elevated BP. When BP normalizes after mechanical treatment of the stenotic lesion(s), it is very likely that the patient had renovascular hypertension. However, in most cases, hypertension either does not change or, at best, is easier to treat after such a procedure. Under those circumstances, renovascular hypertension may still have been present, but secondary changes in the vasculature prevent BP from falling towards normal levels. Alternatively, renovascular hypertension may have been superimposed on pre-existing essential hypertension. Finally, despite great technical achievements, it is still possible that some procedure-related factors (e.g., undetected dissection) help to sustain renal ischemia rather than ameliorating it. Hence, renovascular hypertension can only be diagnosed retrospectively, and even then in a limited number of patients. In many cases, therefore, the clinician remains in doubt about whether RAS is responsible for hypertension or not.

The two main causes of RAS are atherosclerosis and fibromuscular dysplasia (FMD). Examples of both are presented in Figure 33.1. Both conditions clearly differ with respect to patient characteristics and prognosis. For instance, FMD is considered to be a disease of the young, especially women, with a good chance of recovery after percutaneous dilatation. The latter is supported by data from Alhadad and coworkers who, in a retrospective analysis of 69 patients (mean age 44 years), found that nearly 25% of patients were completely cured, while the remainder showed significant falls in BP and serum creatinine and a reduced need for antihypertensive drugs (2). Whether the concept of FMD occurring mainly in young female patients will hold is debatable, especially since we encounter an increasing number of older and male patients with FMD (3). Surely, if one looks for FMD only in young females, the association becomes a self-fulfilling prophecy, which tends to deny that older women who are first diagnosed with hypertension at a later age may have had the disorder all of their lives. So far, no clues have been identified that are sensitive and specific enough to alert the physician to the diagnosis of FMD. Atherosclerotic RAS, on the other hand, may be suspected in elderly patients, with hypertension and renal dysfunction as key symptoms. Severe or recent onset hypertension, abdominal bruit, male gender, flash pulmonary edema, hypercholesterolemia, loss of renal function after treatment with an ACE inhibitor or an angiotensin receptor antagonist, a history of tobacco use, and atherosclerosis elsewhere in the body are clinical clues which may arouse the suspicion of RAS. Yet, in autopsy studies, a significant number of renal artery lesions has been reported which were apparently not suspected on clinical grounds and which were not associated with hypertension during life. In a general population older than 65 years and without renal disease, a prevalence of 6.8% was noted (4). Clinical prediction rules, such as the one proposed (5) and recently validated (6) by Krijnen et al., may assist the physician in the selection of patients who need to be investigated further, but even then the chance of a positive result is not much greater than 30% (5,6). On the other hand, the incidence of finding a lesion in the renal arteries could be as high as 46% when patients with coronary artery disease are screened (7). So, one should still be cautious to reject RAS in a patient who does not meet any of the above-mentioned criteria.

ROLE OF SCREENING TESTS

To screen patients for RAS, one can perform either an anatomical (imaging) or a functional test. However, none of the tests which have been developed in the past thirty years has proved to be reliable enough. As far as imaging is concerned, only one study has directly compared modern techniques [computed tomography (CT) and magnetic resonance (MR) angiography] with the gold standard of intra-arterial digital subtraction angiography (DSA) in a sufficiently large population of hypertensive patients (3). This study showed that current non-invasive imaging techniques are not sensitive or specific

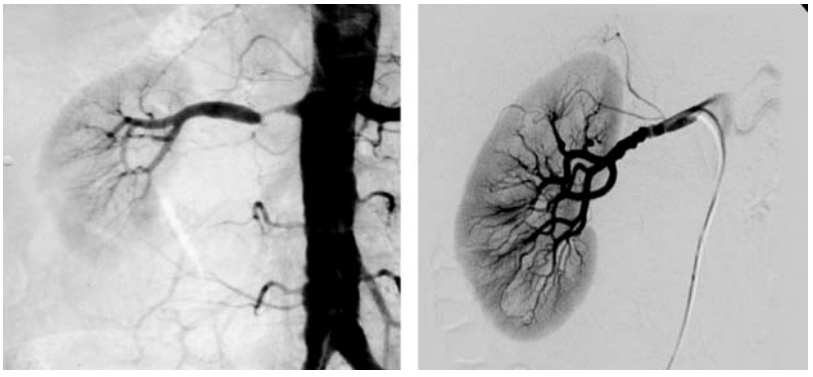

Fig. 33.1 Examples of atherosclerotic renal artery stenosis (*left*) and fibromuscular dysplasia (*right*).

enough to pick up RAS, although sensitivity of these tests may improve in selected groups of patients with a high a priori chance of having the abnormality. Still, imaging techniques provide better results than functional tests (8). Although we are inclined to believe that the lack of accuracy of these tests is due to technical imperfections and/or poor quality of test characteristics, it may simply be that the pathophysiological concepts upon which the tests were based are wrong. For instance, renography, with or without ACE inhibition, has proven to be too unreliable for the diagnosis of (functional) RAS even though the rationale of the test seems sound. Rather than dismissing the test as being inaccurate we may have to conclude that the test result represents a mechanistic phenomenon that we do not yet fully understand.

Several years ago, Radermacher and associates suggested that the renal resistance index, measured by color Doppler ultrasonography can fairly accurately predict the response to renal angioplasty or surgery (9), and thus provide information about the hemodynamic significance of a stenosis. However, this method has not gained widespread acceptance, perhaps because it requires specific operator skills. Therefore, as long as the screening tests do not improve, intra-arterial DSA remains the gold standard to diagnose RAS. CT and MR angiography need to be developed further and tested in large-scale populations. There is little room for functional tests, with the exception, perhaps, of color Doppler ultrasonography.

TREATMENT

Two meta-analyses of randomized controlled trials which compared medical versus mechanical treatment showed only a modest effect of balloon angioplasty (10,11). As illustrated in Figure 33.2, the change in systolic pressure after angioplasty

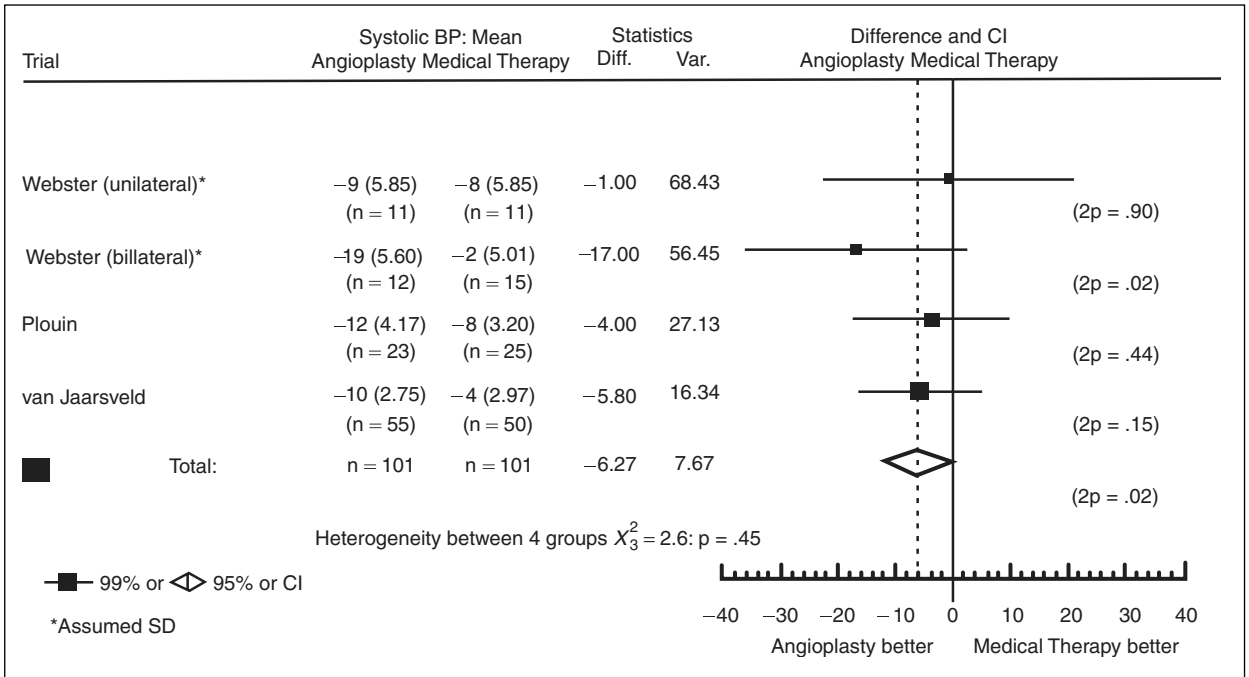

Fig. 33.2 Meta-analysis of randomized trials comparing angioplasty versus medical treatment in patients with renal artery stenosis (11). *Abbreviations*: BP, blood pressure; CI, confidence interval; SD, standard deviation. *Source*: Reproduced from Ref. 11.

is about 6 mmHg more than after treatment with drugs but there is a wide variation in outcome. Nevertheless, there are probably subgroups of patients who would benefit more than others from such treatment (12). Moreover, at present we do not know whether the seemingly disappointing results of angioplasty are attributable to an inherent ineffectiveness of this form of treatment or to inappropriate indications. Since the presence of atherosclerotic RAS is associated with an excessive cardiovascular risk (13), it is also possible that, even if the treatment would improve BP control and renal function, those effects still come too late. Given that revascularization is usually limited to patients with more than 50%, or sometimes even 70% stenosis, it may well be that, by the time this degree of stenosis has been reached, ischemia-induced intrarenal lesions have become irreversible. For the time being, it is wise to select angioplasty only for those patients with RAS in whom hypertension is resistant to treatment or who respond to a lowering of BP with a decline in kidney function. Whether it is ultimately worth diagnosing and treating RAS at all depends entirely upon the results of major outcome trials like the CORAL study (14).

RENAL HYPERTENSION

In many series, renal parenchymal disease ranks number one as source of secondary hypertension. When hypertension is associated with renal parenchymal disease, the clinician is faced with a dilemma. Indeed, renal damage often develops as a result of high BP and this may, in itself, aggravate hypertension. On the other hand, primary kidney disease can be responsible for the development of hypertension. Thus, in a given case, it may be very difficult to determine whether the kidney is cause or culprit of the hypertensive process. Only when it is possible to make a definite histological diagnosis of primary renal disease (e.g., IgA nephropathy) the sequence of events may become clear. The reader is referred to the appropriate chapters elsewhere in this book for a more detailed description of renal hypertension.

A particular case of kidney-derived hypertension is a renin-secreting tumor (15,16), which may either be a Wilm's tumor or a juxtaglomerular cell tumor (reninoma). The latter usually arises in young patients and is associated with elevated levels of renin and aldosterone and hypokalemia. Diagnosis is difficult because hyperreninism is not always detected by renin assays, and imaging techniques often fall short because the tumor may be too small. Based on only limited experience in the literature, CT scanning is the method of choice to visualize such a neoplasm. Ablation of the tumor is the preferred treatment but, if necessary, one can also lower BP by administering an ACE inhibitor or an angiotensin receptor antagonist.

ADRENAL CORTICOID HYPERTENSION

In some cases, hypertension is caused by overproduction of adrenal corticoid hormones. These may be glucocorticoids, as in Cushing's syndrome, or mineralocorticoids, as in Conn's syndrome. The enhanced production of steroids stems from a single tumor (adenoma) or from bilateral, often hyperplastic, nodular tissue. Rarely, a carcinoma is involved. These abnormalities have to be differentiated from the monogenetic forms of hypertension (e.g., Liddle's syndrome) in which hypertension develops as a result of enhanced renal tubular sodium reabsorption. The latter, however, are related to altered biochemical mechanisms and are not related to autonomous adrenal tissue.

The cornerstone of the diagnosis is the demonstration of overproduction of steroid hormones. Detailed descriptions of the various diagnostic tests can be found elsewhere (17). Imaging procedures must follow rather than precede biochemical testing. Once hormonal excess has been shown unequivocally, the question arises whether this is due to an unilateral solitary adenoma or to micro-adenomatous or hyperplastic tissue (which is usually, although not universally, bilateral). There is little doubt that CT and MR imaging are most suitable to detect adrenal masses. Even small lesions can be picked up this way. One should realize, though, that these modern imaging techniques may also discover other (variant) types of abnormalities. It remains necessary, therefore, to match the images with the results of (dynamic) hormonal testing. For instance, when in primary hyperaldosteronism bilateral lesions are found on CT a proper differentiation between adenoma and hyperplasia is not always possible without additional investigations such as adrenal sampling (18,19). Moreover, CT or MR studies will be less conclusive with adenomas smaller than one centimeter in diameter.

Primary hyperaldosteronism must always be considered when a hypertensive patient presents with hypokalemia, although this abnormality is not a prerequisite. Recent data suggest that the aldosterone-to-renin ratio as a proxy for aldosterone biosynthesis is elevated in a substantial proportion of hypertensive patients (20), but not all of these have primary hyperaldosteronism. Therefore, confirmatory tests (oral or intravenous sodium loading) remain necessary. When, in the case of positive test results, both CT and MR imaging fail to show abnormalities, one may consider performing adrenal scintigraphy before adrenal venous sampling is contemplated. The imaging agent NP-59 (6-β-[^{131}I]-iodomethyl-19-norcholesterol) is the preferred compound to use in hyperaldosteronism (21). In most cases of small lesions, scintiscans can differentiate between adenoma and hyperplasia (22). Also, when the clinical diagnosis is Cushing's syndrome, and radiological techniques fail to identify adrenal disease, NP-59 scanning may be helpful (21). Although adrenal venous sampling probably has greater diagnostic accuracy, the procedure is difficult and not without risk in unexperienced hands.

GENETIC ABNORMALITIES LEADING TO 'ADRENAL' HYPERTENSION

Some genetic abnormalities may lead to a form of hypertension in which mineralocorticoid mechanisms are involved. These include glucocorticoid-remediable aldosteronism (GRA), apparent mineralocorticoid excess (AME), and hyperdeoxycorticosteronism. In GRA, aldosterone excess is due to the chimeric 11β-hydroxylase/aldosterone synthase gene, which causes undue stimulation of aldosterone synthase in the zona fasciculata. In this condition, potassium levels often remain normal (23). When a diagnosis of primary hyperaldosteronism has been made on the basis of a raised plasma aldosterone and a suppressed renin, one can confirm the presence of GRA by the finding of overproduction of the cortisol C-18 oxidation products (18-oxotetrahydrocortisol and 18-hydroxycortisol) in urine and their ratio relative to tetrahydroaldosterone.

In AME, the mineralocorticoid properties of cortisol underlie hypertension. Due to deficiency of the 11-β hydroxysteroid-dehydrogenase (11-β OHSD) enzyme, the cortisol-cortisone shuttle at the level of the mineralocorticoid receptor in the distal renal tubules does not work properly. As a result, cortisol levels build up in the kidney and displace aldosterone from its receptor. Sodium retention with hypertension and hypokalemia ensue. In this case, both renin and aldosterone are low (secondary to sodium retention), but, in the urine, an increased ratio of cortisol metabolites (tetrahydrocortisol plus 5α-tetrahydrocortisol) over cortisone metabolites (tetrahydrocortisone) will be found. A ratio of approximately one-to-one is normal, but if it exceeds seven-to-one a diagnosis of AME seems certain.

Increased production of deoxycorticosterone (DOC) occurs primarily in congenital adrenal hyperplasia, where deficiency of either 11β-hydroxylase or 17α-hydroxylase impairs cortisol production. DOC-producing tumors and primary cortisol resistance are also associated with elevated DOC concentrations, but these conditions are relatively rare. Due to its agonistic activity on the mineralocorticoid receptor, DOC causes a form of low-renin, low-aldosterone hypertension with hypokalemia. Except for the abnormalities at physical examination, one finds increased levels of DOC and adrenal androgens in 11β-hydroxylase deficiency, but low levels of androgens in 17α-hydroxylase deficiency. In addition, 11-DOC is high in the former, while corticosterone and 18-hydroxycorticosterone are high in the latter. Table 33.2 summarizes the most important laboratory features that may help in the initial work-up of patients with a suspected adrenal form of hypertension.

Except for the syndromes mentioned above, a gain-of-function mutation has been described for the mineralocorticoid receptor causing a volume-dependent form of hypertension (24). This abnormality, however, seems to be extremely rare.

TREATMENT

As far as therapy is concerned, laparoscopic adrenalectomy is the treatment of choice in cases of an aldosterone or cortisol producing adenoma (17). When surgery is contraindicated or when bilateral hyperplasia (idiopathic hyperaldosteronism) exists, patients with aldosterone excess may be treated with an aldosterone antagonist, such as spironolactone or eplerenone. Cushing's disease (pituitary-dependent hypercortisolism) requires transsphenoidal adenectomy. When surgery fails, radiotherapy or, even better, gamma-knife radiosurgery is the preferred treatment.

Patients with GRA should preferably be treated with dexamethasone (0.125 to 0.5 mg) per day although there is a risk that signs of Cushing's syndrome develop. When that happens, it is best to switch to aldosterone antagonists. The latter are also preferred in patients with AME. In cases of DOC excess, glucocorticoid replacement therapy will ameliorate clinical symptomatology. Importantly, spironolactone is contraindicated in patients with the gain-of-function mutation in the mineralocorticoid receptor (24).

PHEOCHROMOCYTOMA

Although a diagnosis of pheochromocytoma may be suspected in any patient with typical symptoms or a positive family history, the tumor may be found by accident. Unfortunately, no single test is sensitive and specific enough to either confirm or rule out the diagnosis (25). Probably, the best test is to measure plasma metanephrines. Normal plasma concentrations of these metabolites virtually exclude the diagnosis of pheochromocytoma, whereas normal plasma concentrations of catecholamines and normal urinary excretion of metanephrines do not (26,27). However, plasma metanephrines are difficult to measure and assays are not available in every laboratory. Thus, most of the time, one has to rely on the determination of urinary (fractionated) metanephrines and plasma or urinary catecholamines. Moreover, elevations in plasma metanephrines may still be false-positive, particularly in patients using tricyclic antidepressants or phenoxybenzamine (28). Because false-negative test results can also occur, one occasionally has to turn to the clonidine suppression test (25). Normally, plasma norepinephrine falls by more than half, but failure to do so strongly suggests the presence of a pheochromocytoma.

In cases of suspected pheochromocytoma, scanning with [^{131}I]-meta-iodobenzyl-guanidine (MIBG) is necessary (29). There is some debate about whether MIBG-scanning should be done irrespective of the results of CT or MR. Indeed, since pheochromocytoma may be localized extra-adrenally, there is a case for applying MIBG-scanning on a wider basis. Before a pheochromocytoma can be removed by the surgeon—and, again, this can be done via laparoscopic techniques—one must be sure that the patient has had adequate treatment with alpha-blocking drugs. In this regard, most centers still prefer phenoxybenzamine, even though there is very little evidence that this agent is entirely safe. In fact, it produces an irreversible alpha-blockade, which may be cumbersome in the immediate postoperative period when hypovolemia may contribute to a substantial fall in BP.

Table 33.2 Laborarory features of various forms of corticoid-related hypertensive disorders

	Serum potassium	Renin	Aldosterone	Other biochemical features
Primary hyperaldosteronism (e.g., adenoma)	Low	Low	High	
Glucocorticoid-remediable hyperaldosteronism	Normal or low	Low	High	Increased urinary excretion of 18-oxotetrahydrocortisol and 18-hydroxycortisol relative to that of tetrahydroaldosterone
Apparent mineralocorticoid excess	Low	Low	Low	Increased urinary excretion of tetrahydrocortisol plus 5α-tetrahydrocortisol, relative to that of tetrahydrocortisone
Deoxycorticosterone	Low	Low	Low	Increased plasma concentration of deoxycorticosterone; additional abnormalities depending on the nature of the defect

OTHER CAUSES OF HYPERTENSION

Among the other biological causes of hypertension, as mentioned in Table 33.1, are aortic coarctation, the obstructive sleep apnea syndrome (discussed in Chapter 4), Liddle's syndrome, and several endocrine disturbances.

A relatively infrequent hypertension-related disorder is aortic coarctation. Although this abnormality may occur at any level of the thoracic or abdominal aorta, it is most often found just beyond the origin of the left subclavian artery (preductal coarctation) or distal to the insertion of the ligamentum arteriosum (postductal coarctation). The pathogenesis of hypertension in aortic coarctation is still a matter of dispute (30). One of the various theories states that distal hypoperfusion leads to ischemia of the kidneys and a situation that is comparable to bilateral RAS. Firm evidence for this hypothesis, however, is still lacking. Today, children are usually diagnosed at an early age. Although operative repair of the abnormality may normalize BP, exercise-induced hypertension and an elevation in the average systolic 24 hour BPs are still often observed (31).

Liddle's syndrome is due to a mutation in the subunits of the renal tubular epithelial sodium channel. It causes enhanced sodium reabsorption, volume-dependent hypertension with hypokalemia, and suppressed levels of renin and aldosterone. Genetic analysis is necessary to confirm the diagnosis, and amiloride is the preferred drug to initiate treatment. Hypertension may also form part of the symptom complex of some endocrine disorders, such as acromegaly, hypothyroidism, and hyperparathyroidism. In these cases, the underlying disease usually is obvious, and generally BP will normalize after causal therapy.

EXOGENOUS CAUSES

A variety of stimulants and drugs either have a direct effect on the vasculature or interfere with BP regulating mechanisms. For instance, the semi-synthetic mineralocorticoid fludrocortisone raises BP in a similar manner as the naturally occurring steroids. Whenever hypertension complicates fludrocortisone therapy, the risks associated with continuing such treatment must be balanced against the consequences of the underlying disorder for which the drug was given. In most instances, it will not be possible to withhold the mineralocorticoid.

Glucocorticoids increase arterial pressure at high dosages, but the effects of low dosages are disputed. Moreover, it is very difficult to separate true glucocorticoid effects from those related to sodium retention (i.e., mineralocorticoid effects). The situation is even less clear in the case of semi-synthetic glucocorticoids, because these drugs can raise BP without any significant effect on volume homeostasis (32). Indeed, it is doubtful whether the effects of corticosteroids on BP can be explained solely by classical glucocorticoid or mineralocorticoid mechanisms, and this notion has led some investigators to believe that these compounds may have a separate hypertension-inducing action (33). With regard to the management of steroid-induced hypertension, the obvious recommendation is to minimize the use of steroids and to avoid, as far as possible, dosages of steroids that are equivalent to prednisolone $>$20 mg/day. It is not clear whether any particular type of antihypertensive drug is preferable in the treatment of patients with steroid-induced hypertension. Given the many potential pathogenetic factors that are involved, it is likely that drugs from all of the available classes will be useful.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs) produce their anti-inflammatory effect by inhibiting prostaglandin synthesis. Because they are vasodilators, prostaglandins have an important role in maintaining vascular tone, notably when pressor systems are activated (e.g., during volume depletion). In addition, prostaglandins have natriuretic effects. Blocking the production of prostaglandins will, amongst other effects, result in some increase in vascular resistance and BP, and in a tendency to retain sodium. The latter may be augmented by concurrent renal vasoconstriction. The risks of hypertension as an adverse effect of NSAIDs have been extensively reviewed (34–36). In the event of suspected NSAID-induced hypertension, the first step should be to withdraw the offending agent. If this does not resolve the hypertension, the obvious next step is to administer a diuretic, although all other classes of drugs may be tried.

ANTIDEPRESSANTS

Tricyclic antidepressants may also increase BP and heart rate. Hypertension may particularly develop in patients who are treated with venlafaxine, a nonselective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor (SSRI). In placebo-controlled studies with this drug, significant increases in diastolic BP were observed, the mean increase being 7 mmHg after six weeks of treatment (37). However, the incidence of BP rises seems to be low at dosages $<$200 mg/day (37) and is clinically significant only at dosages $>$300 mg/day (38). When hypertension develops in patients receiving a tricyclic antidepressant or venlafaxine, consideration should be given to switching the patient to fluoxetine, a selective SSRI that is considered to be relatively well tolerated. Although fluoxetine has also been implicated in the development of hypertensive episodes (39), sustained hypertension manifests itself in less than 2% of patients during short-term treatment (40). The available data indicate that fluoxetine-related hypertension may not be attributable to the drug itself, but rather to an interaction between fluoxetine with a monoamine oxidase inhibitor (MAOI) when these drugs are administered either concurrently or in close temporal proximity (41,42).

Monoamine oxidase inhibitors may themselves induce a hypertensive state (43), and the risk becomes greater when an MAOI is used in combination with another agent that augments central serotonin and/or noradrenaline levels. In addition, the interaction between MAOIs and sympathomimetic agents (both α- and β-adrenoceptor agonists) is potentially dangerous (39). In this respect, it does not seem to matter whether monoamine oxidase type A or type B is blocked.

It is most likely that the hypertension associated with antidepressant usage is caused by the central accumulation of neurotransmitters, such as serotonin or noradrenaline, which enhance sympathetic outflow. Thus, besides stopping the causative agent, an appropriate way to treat this form of hypertension is to administer an antiadrenergic agent.

OTHER DRUGS

Many other drugs have been associated with the development, or worsening, of hypertension. These include anesthetics, cyclosporin, epoietin (recombinant human erythropoietin), sympathomimetics, and alkylating agents (39). In addition, unexpected pressor responses may occur after the administration of nonselective β-blockers (44) or clonidine (45,46). Although the clinical importance of this phenomenon has not been established, it may be expected to occur more frequently in older patients. Finally, over-the-counter drugs, such as the appetite suppressant phenylpropanolamine, may cause hypertension as an adverse effect, although the incidence of adverse reactions to these drugs have been reported to be relatively low in people aged >50 years (47). Although many other sympathomimetics are available over-the-counter, for example, as an ingredient in oral and nasal common cold remedies, it is not well known how often these formulations are associated with hypertensive reactions.

CONCLUSIONS

Given the many abnormalities that may give rise to an increase in BP, it is perhaps surprising that hypertension is still "essential" in most patients. Although renovascular and renal abnormalities seem to be the most frequent causes of secondary hypertension, it is possible that some causes, such as those related to pharmacological agents, are overlooked. Therefore, a carefully taken history and examination of each patient remain mandatory.

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HYPERTENSION IN DIABETES MELLITUS 34

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INTRODUCTION

Even if diabetes mellitus constitutes a serious public health problem in its own right, studies have shown that it is the clustering of risk factors in patients with diabetes that will jointly further increase the risk for complications, e.g., for cardiovascular disease (CVD) (1). Hypertension is more than twice as common in diabetic people as in the general population, affecting 10–30% of type-1 diabetic patients and 60–80% of those with type-2 diabetes. Hypertension is also present in 20–40% of people with impaired glucose tolerance (IGT).

The association between hypertension and impaired glucose metabolism/diabetes mellitus has long been recognised (2). In 1923, the Swedish physician Eskil Kylin described a syndrome of diabetes, hypertension, and hyperuricaemia (3), which are now regarded as aspects of the broader Metabolic syndrome that has been linked to insulin resistance (4). The relationship between diabetes and hypertension is, however, complex. Both conditions are common, and so they are sometimes likely to be associated only by chance. However, in some instances, they may have a common cause. Hypertension can develop as a consequence of diabetic nephropathy, while some drugs used to treat hypertension can induce hyperglycaemia and new onset diabetes, e.g., high-dose thiazide diuretics and beta-receptor blockers (5).

Hypertension is also a risk factor for microvascular complications, such as nephropathy and retinopathy. The management of hypertension in diabetes has been widely debated, and treatment strategies and appropriate drug therapy has still to be agreed. During the last two decades, several large-scale trials have added considerably to the evidence base, demonstrating convincingly the benefits of lowering blood pressure (BP) but also how difficult it can be to achieve this in clinical practice. One recommendation should therefore be to follow mean BP levels in cohorts of treated patients, ideally on a national level (6).

DEFINITIONS OF BP LEVELS

Hypertension is generally defined if above a mean level, after several recordings, of 140/90 mmHg. People with diabetes are still at risk of macrovascular and microvascular complications at BP levels well below these thresholds, and the optimal treatment target range is therefore lower (130/80 mmHg) for all patients that can tolerate such BP reduction.

There are racial and ethnic differences in the prevalence of hypertension which, presumably, are at least partly genetically determined. For example, hypertension and macrovascular disease are less frequent among Native Americans (the Pima Indians) and Mexican Americans (7). There is evidence that the true prevalence of hypertension is increasing in the diabetic population (especially type-2), after allowing for the greater number of cases identified through screening activities, and the lowering of thresholds for treatment of BP (8). The causes probably include the rising prevalence of obesity and longer survival of older people with diabetes. On the contrary, mean BP is decreasing in the population at large, if age-adjusted data are considered (9)

CAUSES AND CONSEQUENCES OF HYPERTENSION IN DIABETES

Essential hypertension and isolated systolic hypertension are both common in the non-diabetic population, especially in the elderly. It is estimated that essential hypertension accounts for about 10% of cases in diabetic people. Other important causes are the hypertension that coexists with insulin resistance, obesity, and glucose intolerance in the Metabolic syndrome (10), or is secondary to diabetic nephropathy.

Hypertension worsens both macrovascular and microvascular complications in diabetes. The effects of BP on the risk of fatal coronary heart disease (CHD) are 2–5 fold greater than in non-diabetic people, and hypertension accentuates the deleterious influence of diabetes on left ventricular mass and function. The risks of nephropathy and end-stage renal failure are also increased 2–3 fold by hypertension.

HYPERTENSION IN THE METABOLIC SYNDROME

This syndrome comprises insulin resistance, glucose intolerance (including type-2 diabetes), a characteristic dyslipidaemia [hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol, and raised low-density lipoprotein (LDL)

cholesterol with an excess of small, dense LDL particles], abdominal obesity, pro-coagulant changes, and hyperuricaemia (10–12). As these abnormalities are all risk factors for atherogenesis, the syndrome is characterised by a marked tendency to macrovascular disease, especially CHD and stroke, when different definitions of the syndrome are more or less predictive (13,14). Insulin resistance has been proposed (4,10) to be the fundamental cause of hypertension and cardiovascular disease, as well as type-2 diabetes. Insulin resistance is partly genetically determined, and acquired factors, such as obesity, physical inactivity, and poor fetal development with catch-up growth during early infancy (15,16), may also contribute. In support of the latter, family studies have revealed a correlation between the BP of the mother and her offspring that appears to be non-hereditary in origin (17). Fetal growth retardation is suggested to programme abnormal development of the vasculature and capillary rarefication, as well as have a negative impact on tissues that regulate glucose homeostasis.

Insulin resistance is closely associated with high BP in both humans and animals. Experimental induction of insulin resistance (e.g., feeding rats with fructose) is accompanied by a rise in BP. An inverse relationship has been demonstrated in humans between BP and insulin sensitivity (18). Various mechanisms have been proposed to explain how insulin resistance and/or the hyperinsulinaemia that accompanies it could increase BP. There is some evidence that insulin is an endothelium-dependent vasodilator, releasing nitric oxide (NO) from the endothelium which relaxes vascular smooth muscle (19). Blunting of this effect, due to insensitivity to insulin's action on the endothelium as well as on metabolically important tissues, could contribute to the increased peripheral vascular resistance, which is the hallmark of hypertension in obesity and type-2 diabetes. Impaired endothelium-mediated vasodilatation is associated with insulin-resistant states, and may play a key role in the initiation and progression of atherosclerosis (20).

On the other hand, insulin also has several actions that tend to raise BP, and there is some evidence that these are accentuated in insulin-resistant states, presumably because sensitivity is preserved to the effects of the raised insulin levels. Insulin acts on the distal renal tubule to retain sodium and water (21)—an effect, which still operates in insulin-resistance subjects (22)—and therefore could contribute to the rise in total body sodium content that occurs in obesity and type-2 diabetes (22,23). Insulin also stimulates the cell-membrane Na^+-K^+ ATPase, which would raise intracellular Na^+ concentrations in vascular smooth muscle and, by increasing cytosolic Ca^{2+} levels, would enhance contractility and the increase peripheral resistance (22–24). Through its effects on the central nervous system, insulin may stimulate the sympathetic outflow. Theoretically, this could also increase BP (23–25). Finally, insulin may stimulate the proliferation of vascular smooth muscle cells, which could lead to medial hypertrophy and increased peripheral vascular resistance (23,25,26).

HYPERTENSION AND DIABETIC NEPHROPATHY

This association is most obvious in young type-1 diabetic patients, in whom the presence of hypertension is strikingly related to renal damage and even minor degrees of proteinuria. BP begins to rise when the albumin excretion rate (AER) enters the microalbuminuric range (>30 mg/24 h) and is usually over the World Health Organization (WHO) threshold (140/90 mmHg) when AER reaches the macroalbuminuric stage (>300 mg/24 h) (26,27). The association may be partly genetically determined. Diabetic subjects with microalbuminuria commonly have parents with hypertension and may also inherit over-activity of the cell-membrane Na^+-H^+ pump (indicated by increased Na^+-Li^+ counter-transport in red blood cells), which would tend to raise intracellular Na^+concentrations, and thus increase vascular smooth muscle tone (27,28).

The basic mechanisms of hypertension include decreased Na^+ excretion with Na^+ and water retention. Peripheral resistance is increased, to which raised intracellular Na^+ will contribute. The role of the renin–angiotensin–alodosterone system (RAAS) is uncertain, as both increased and decreased activity has been reported (28–30). These discrepancies may be explained by differences in diet, treatment, metabolic control, and the type and duration of diabetes. Na^+ retention and hypertension would be predicted to suppress the RAAS, while renin levels may be influenced by other complications of diabetes. Neuropathy can also lower plasma renin, while renin may be raised in retinopathy and advanced nephropathy. Patients with microalbuminuria who are insulin resistant appear to be particularly susceptible to hypertension (31).

IMPACT OF HYPERTENSION IN DIABETES ON TARGET ORGANS

A large proportion of hypertensive diabetic patients show signs of target-organ damage, particularly affecting the cardiovascular system (32). Hypertension, as an independent risk factor for atherogenesis, synergises with the effects of diabetes and significantly increases the development and progression of CHD, cerebrovascular and peripheral vascular disease.

The deleterious effects of hypertension on left ventricular function are also accentuated by the presence of diabetes. These include impaired left ventricular relaxation (33), increased left ventricular mass, and left ventricular hypertrophy (LVH) (34)—the latter being an independent predictor of premature death from CHD. Also, diastolic dysfunction seems to be present in patients with long-standing diabetes complicated by hypertension.

Hypertension predisposes to the development of certain microvascular complications, particularly nephropathy and end-stage renal failure, for which the risk is increased by 2- to 3-fold. It is also a risk factor for retinopathy, as has been confirmed by the beneficial effects of improved BP control in type-2 diabetic patients, reported by the United Kingdom Prospective Diabetes Study (35).

SCREENING FOR HYPERTENSION IN DIABETES

As these two conditions are so commonly associated, diabetic patients must be regularly screened for hypertension and vice versa. Hypertensive patients, especially if abdominally obese or treated with drugs that might further increase hyperglycaemia in patients with the Metabolic syndrome, should be screened for diabetes at diagnosis and during follow-up.

Should hyperglycaemia be detected, potentially diabetogenic antihypertensive drugs should be reduced or changed to others that do not impair glucose tolerance, and normoglycaemia can often be restored.

All diabetic patients should have their BP checked at diagnosis and at least annually thereafter. This is especially important in those with other cardiovascular risk factors, such as nephropathy, abdominal obesity, dyslipidaemia, smoking, or poor glycaemic control in general.

MEASUREMENT OF BP

BP should be measured in the supine or sitting position using an accurate sphygmomanometer and a cuff of appropriate size (i.e., wider for obese subjects with an arm circumference of >32 cm). Systolic and diastolic pressures should be recorded to the nearest 2 mmHg, if using a manual sphygmanometer (Korotkoff I-V). Usual precautions should be taken to ensure reliability and avoid "white-coat" stress effects that can acutely raise BP. Conditions should be quiet and relaxed, and at least two readings should be taken initially and then repeated at regular intervals over weeks to determine the subject's typical values.

BP should also be checked in the upright position (1 min after standing), because there may be a significant postural fall (>20 mmHg systolic) in patients with diabetic autonomic neuropathy, in the elderly, or those treated with vasodilators or diuretics. Marked postural hypotension— which can coexist with supine hypertension—may indicate the need to change or reduce antihypertensive medication, especially if symptoms are provoked. Ambulatory BP monitoring over 24-hours may be useful in many cases to investigate diurnal patterns or to exclude "white-coat" effects. This is so also in patients with early nephropathy who have nearly normal BP during the day but who may be at risk of hypertensive tissue damage because they fail to show the physiological BP dip during sleep (36).

DIAGNOSIS OF HYPERTENSION IN DIABETES

The criteria issued by the European Society of Hypertension (ESH) define hypertension as an office BP exceeding 140/90, and borderline hypertension as being below these limits but above 130 systolic and/or 85 mmHg diastolic (37).

It is clear from numerous epidemiological studies that the this threshold is too high in diabetic subjects because of their additional risk of both macro- and microvascular disease, and that there are definite benefits from treating microalbuminuric subjects whose diastolic pressure is <90 mmHg (37). A consensus would be to aim for a BP of less than 130 mmHg systolic and under 80 mmHg diastolic, if tolerated.

INVESTIGATION OF HYPERTENSION IN DIABETES

Initial clinical investigation of the hypertensive diabetic patient aims to exclude rare causes of secondary hypertension, to assess the extent of tissue organ damage due to hypertension and diabetes, and to identify other potentially treatable risk factors for vascular disease. The major points in the medical history and examination are the following.

Cardiac function. A standard 12-lead electrocardiogram (ECG) may show obvious ischaemia, arrhythmia, or left ventricular hypertrophy; the latter is more accurately demonstrated by echocardiography, which will also reveal LVH or dysfunction. Exercise testing (or stress-echo) testing and 24-hour ECG Holter monitoring may also be appropriate.

Renal function. A fresh urine sample should be tested for microalbuminuria and examined microscopically for red and white blood cells, casts, and other signs of renal disease. Microscopic haematuria can occasionally occur in type-1 diabetic patients in the apparent absence of significant renal dysfunction, but coexistent renal disease must always be excluded. Serum urea, creatinine, and electrolytes (or even cystatin-C) should be checked. If the serum creatinine concentration is raised, measurement of glomerular filtration rate should be considered, ideally using a specific clearance method (e.g., Cr-EDTA, iohexol). Further specialist investigations that may be needed include an isotope renogram and other tests for renal artery stenosis (i.e., angiogram). This complication of renal arterial atherosclerosis may affect up to 20% of older type-2 diabetes and, if bilateral, can lead to severe and sometimes permanent renal impairment if ACE inhibitors are given.

Lipid profile. Fasting serum lipid concentrations should be checked. If total cholesterol or triglyceride levels are found to be elevated after repeated measurements, further investigation of lipoprotein subclasses (LDL, HDL) is recommended. Treatment for hyperlipidaemia should be considered if the total cholesterol is >4.5 mmol/L, the LDL cholesterol level is >2.5 mmol/L, or the LDL/HDL cholesterol ratio is >4 (38). One option is also to determine the apoB/apoA1 ratio, because it is a very important risk marker for myocardial infarction as shown in the INTERHEART study (39).

Other forms of secondary hypertension may be indicated by clinical findings of endocrine or renal disease, significant hypokalaemia (plasma potassium <3.5 mmol/L without previous diuretic treatment), failure of hypertension to respond to standard treatment, or a sudden decline in renal function after starting treatment with ACE inhibitors, suggestive of renal artery stenosis.

MANAGEMENT OF HYPERTENSION IN DIABETES

Data from randomised trials have increasingly shown the benefits of tight BP control in patients with type-2 diabetes (40). Current guidelines have therefore emphasised the screening, evaluation, and vigorous treatment of elevated BP if combined with diabetes (37,38,41–43), especially systolic BP.

Strict BP control is the primary goal of treatment—less than 130/80 mmHg—for all patients who can tolerate this without suffering side-effects, such as orthostatic reactions, or compromising arterial circulation in critical vascular beds. Management begins with lifestyle modification, but few patients respond to this alone, and most will require more than one antihypertensive drug to control BP adequately (44,45).

LIFESTYLE INTERVENTION

This should include weight reduction or weight stabilisation in the obese, sodium restriction, diet modification, and

regular physical exercise of moderate intensity (40–60 min, 2–3 times a week). Dietary intake of saturated fat has been associated with impairment in insulin sensitivity (46) and should therefore be reduced. Alcohol should be restricted to 3 and 2 units/day in men and women respectively, but omitted altogether if hypertension proves difficult to control. In some cases of therapy resistance, the true contributing factor is poor compliance caused by alcohol over-consumption.

Smoking causes an acute increase in BP and greater variability overall (47). Smoking cessation is especially important, as smoking not only accelerates the progression of atherosclerosis, but also impairs insulin sensitivity (48) and worsens albuminuria (49). Treatment with nicotine supplementation for 4–6 weeks (chewing gum or patches) or drugs such as bupropion or varenicline may be useful. When adopted by the patient, lifestyle modification can be very effective and facilitate the effectiveness of concomitant drug therapy (50).

ANTI-HYPERTENSIVE DRUG THERAPY

Several drugs are available to lower BP, but some are better suited than others to the particular needs of diabetic people because of their favourable or neutral effects on glucose metabolism. Most patients (at least two-thirds) will require combinations of antihypertensive drugs to control BP. Accordingly, the clinician must be able to use a wide variety of antihypertensive drugs and to choose combinations for pharmacological synergy. Combination therapy usually means that lower dosages of individual drugs can be used, thus reducing the risk of their adverse effects.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme (ACE) inhibitors may be used in most cases of diabetic hypertension, even in cases where the RAAS in general is not activated; instead, the drugs may interfere with local angiotension action in specific target tissues. When used alone, however, these agents have a limited hypotensive action in many patients of African decent, who tend to have suppressed RAAS activity.

ACE inhibitors have no adverse metabolic effects, and may also improve insulin sensitivity (51). Even hypoglycaemia has been reported (52). These drugs are particularly beneficial in diabetic nephropathy, by reducing albuminuria, and possibly delaying progression of renal damage (53). Their antiproteinuric effect may be due specifically to relaxation of the efferent arterioles in the glomerulus (which is highly sensitive to vasoconstriction by angiotensin II), thus reducing the intraglomerular hypertension that is postulated to favour albumin filtration; however, the importance of this mechanism remains controversial (54). ACE inhibitors are also indicated in cardiac failure, in combination with relatively low dosages of thiazide diuretics. A dry cough is reported by 10–15% of patients treated with ACE inhibitors, because these drugs also interfere with the breakdown of kinins in the bronchial epithelium. Changing to another ACE inhibitor or an angiotensin II receptor blocker may avoid this problem. ACE inhibitors occasionally precipitate acute renal failure, particularly in the elderly and in subjects taking non-steroidal anti-inflammatory drugs (NSAID) or who have bilateral renal artery stenosis. Other side-effects (rashes, neutropenia, taste disturbance, angioedema) are unusual with the low dosages currently recommended but become more prominent in renal failure. Because ACE inhibitors cause potassium retention, they should not generally be taken together with potassium-sparing diuretics (spironolactone and amiloride) or potassium supplements. Serum creatinine and potassium levels should be monitored regularly, especially in patients with renal failure or renal tubular acidosis, in whom hyperkalaemia can rapidly reach dangerous levels.

The first dose of an ACE inhibitor should be low and taken just before bedtime to minimise postural hypotension, which may be marked in subjects receiving diuretics or on a strict sodium-restricted diet. The same problem may arise in patients with autonomic neuropathy. ACE inhibitors are recommended in patients with left ventricular dysfunction following myocardial infarction. Ramipril has been shown to prevent cardiovascular morbidity and mortality in high-risk diabetic patients, with or without pre-existing ischaemic heart disease (55).

ANGIOTENSIN II RECEPTOR ANTAGONISTS

This promising new class includes drugs which act on the angiotensin II (AT_1) receptor to decrease BP. They are metabolically neutral (56) and, unlike the ACE inhibitors, do not cause cough. They are effective antihypertensive drugs in diabetic patients (57) and have been shown to slow the progression of nephropathy in diabetes patients with varying degrees of albuminuria (58–60). Interestingly, the combination of an ACE inibitor (lisinopril) with an AT_1-antagonist (candesartan) was more effective than either agent alone in lowering BP and urinary albumin excretion in type-2 diabetic patients (61). Data from ongoing large-scale trials are awaited, especially from the ONTARGET trial comparing an AT_1 receptor antagonist (telmisartan) with an ACE inhibitor (ramipril) as well as with the combination of these two agents for cardiovascular events reduction (62).

DIURETICS

Diuretics are often effective antihypertensive agents in diabetes, in which the total body sodium load is increased and the extracellular fluid volume expanded (63). However, diuretics that increase urinary potassium and magnesium losses can worsen hyperglycaemia, as insulin secretion is impaired by potassium depletion and insulin sensitivity in peripheral tissues may also be decreased (64). The use of high-dose thiazide diuretics is reported to increase the risk of non-diabetic hypertensive patients developing diabetes by up to 3-fold (65). This does not seem to occur to the same degree with use of low dosages (66). Potassium depletion is particularly severe with high-dose chlorthalidone, less with furosemide and bendrofluazide, and apparently negligible with indapamide. This mechanism is irrelevant to C-peptide negative type-1 diabetic subjects who are totally dependent on exogenous insulin. Thiazides may also aggravate dyslipidaemia (67), although low dosages probably carry a low risk. These drugs have also been associated with gout and impotence and are generally avoided in middle-aged diabetic men with hyperuricaemia or erectile dysfunction. Diuretics may precipitate hyperosmolar, non-ketotic coma and should be avoided or

used at the lowest effective dose in patients with a history of this complication.

Diuretics have been shown to successfully prevent cardiovascular disease in elderly subjects with type-2 diabetes and systolic hypertension (68). However, one observational study suggested that the use of diuretics increased cardiovascular mortality in hypertensive type-2 diabetics who were still hyperglycaemic in spite of treatment (69). Overall, these drugs are effective and safe when used appropriately at low dosage in diabetic patients, often for combination therapy, sometimes in combination with potassium supplements or potassium-sparing drugs like amiloride. If ineffective, diuretics should be combined with another first-line drug, e.g., an ACE inhibitor or an angiotensin II receptor antagonist, rather than given at increased dosage. Spironolactone is normally not combined with an ACE inhibitor, as this increases the risk of hyperkalaemia. Furosemide is useful in patients with renal impairment (serum creatinine $>150\,\mu$mol/L) or oedema.

Serum urea, creatinine, and potassium should be checked when starting diuretic therapy and every 6–12 months thereafter, as hyperkalaemia can develop, especially in patients with renal impairment.

β-ADRENERGIC RECEPTOR BLOCKING AGENTS

β-receptor blockers may significantly lower BP levels in diabetic patients with hypertension, even though renin release (a major target for these drugs) is commonly reduced in diabetes because of sodium and fluid retention. However, these drugs are often ineffective in patients of African decent who commonly have low-renin hypertension. Another mechanism of action is to reduce BP, heart rate, and cardiac output via interference with β_1 and β_2 receptors in the myocardium and in the vessel wall.

Like diuretics, β-receptor-blockers may aggravate both hyperglycaemia and dyslipidaemia (65). These effects depend on both dosage and the degree of selectivity of the individual drug. The hyperglycaemic effect is attributed to inhibition of β_2-adrenergic-mediated insulin release and decreased insulin action in peripheral tissues. The long-term risks of a non-diabetic person developing the disease may be increased by 6-fold (70) and even more if given together with thiazides why this combination is not recommended (43,65). The metabolic side-effects of β-blockers can be reduced by using low dosages combined with other agents, particularly dihydropyridine calcium antagonists, or by intensifying efforts to decrease weight and improve physical activity.

β-blockers have other side-effects relevant to diabetes. They may interfere with the counter-regulatory effects of catecholamines released during hypoglycaemia, thereby blunting manifestations such as tachycardia and tremor and delaying recovery from hypoglycaemia (71). In clinical practice, however, this rarely presents a serious problem, especially when cardioselective β_1-blockers are used. β-blockers may also aggravate erectile dysfunction, and are generally contraindicated in second- or third-degree atrio-ventricular (AV) heart block, severe peripheral vascular disease, asthma, and chronic airway obstruction. Studies have shown that certain β-blockers (e.g., metoprolol and carvedilol) (71,72) can be used favourably in cardiac failure in patients with diabetes (71).

In the UKPDS, clinical effects of atenolol were comparable to that of the ACE inhibitor, captopril (73). Both non-selective and selective β-blockers are effective in the secondary prevention of myocardial infarction after an initial event in diabetic patients (74). β-blockers in general are useful in patients who also have angina or tachy-arrhythmias.

CALCIUM CHANNEL ANTAGONISTS

These vasodilator agents do not generally worsen metabolic control when used at conventional dosages, although sporadic cases of hyperglycaemia have been reported (75). This may be due to inhibition of insulin secretion (a calcium-dependent process) in susceptible patients, or to a compensatory sympathetic nervous activation (which antagonises both insulin secretion and action) following vasodilatation.

Calcium antagonists exhibit a slight negative inotropic effect and are contraindicated in significant cardiac failure; they often cause mild to moderate ankle oedema. This is due to relaxation of the peripheral precapillary sphincters and raised capillary pressure rather than to right ventricular failure. Because of their potent vasodilator properties, these drugs can cause postural hypotension and can aggravate haemodynamic effects of autonomic neuropathy.

Because of their other cardiac actions, these drugs are particularly indicated in hypertensive patients who also have angina or supraventricular tachycardia (e.g., verapamil). Their vasodilator properties may also be beneficial in peripheral vascular disease. Calcium antagonists are ideally combined with selective β_1-blockers, but the specific combination of verapamil and β-blockers (especially together with digoxin) must be avoided because of the risk of conduction block and asystole. Overall, calcium channel antagonists appear less cardioprotective but better at preventing stroke than either β-blockers or thiazide diuretics (76).

α_1-ADRENOCEPTOR ANTAGONISTS

α_1-blockers can lower BP effectively and also improve dyslipidaemia and insulin sensitivity (77). Doxazosin is normally well tolerated, especially in combination therapy, and side effects include nasal congestion and postural hypotension. Doxazosin has been reported to be inferior to the diuretic chlorthalidone in the prevention of stroke and heart failure (78).

OVERVIEW OF CLINICAL TRIALS FOR HYPERTENSION IN DIABETES

The assumption that improved BP control would improve cardiovascular and other prognoses in type-2 diabetes has been confirmed by the United Kingdom Prospective Diabetes Study (UKPDS) (35). In this landmark study, tighter BP control (averaging 144/82 mmHg) for over eight years led to significant improvements in several outcomes, as compared with less strict control that averaged 154/87 mmHg. The most powerful effects were related to microvascular complications (retinopathy and nephropathy), although significant reductions were seen in the risk of stroke (44%) and heart failure (56%). Myocardial infarction and peripheral vascular disease showed non-significant reductions. Overall, therefore, tight BP control has been proven to provide

substantial benefits for hypertensive diabetic patients. This treatment strategy also seems to be cost-effective (79).

In the Systolic Hypertension in the Elderly Program (SHEP) low-dose, diuretic-based treatment was found to be effective compared with placebo in preventing cardiovascular (CV) complications in elderly patients with type 2 diabetes mellitus ($n = 583$) and isolated systolic hypertension (68). Similarly, the Systolic Hypertension in Europe (Syst-Eur) Trial compared calcium-antagonist based treatment with placebo in elderly patients with isolated systolic hypertension and in a rather large subgroup with type 2 diabetes ($n = 492$). In Syst-Eur, treatment for five years prevented 178 major CV events in every 1,000 diabetic patients treated (80), i.e., approximately six patients had to be treated for five years to prevent one major CV event.

The Hypertension Optimal Treatment Study (HOT) (81) investigated the intensity of antihypertensive treatment using a calcium-antagonist as baseline therapy in hypertensive patients averaging 61.5 years of age and 170/105 mmHg in baseline BP, of whom 1,501 also had type 2 diabetes. In HOT the incidence of major CVD events was lowered from 24.4 to 18.6 and 11.9 events/100 patient-years, respectively, in the randomised tertiles of diabetes patients who had achieved 84, 82 and 81 mmHg, respectively, in diastolic BP. Approximately 20 patients needed to be treated for 5 years to prevent one major CVD event when BP was further lowered from 84 to 81 mmHg in these patients.

The Captopril Prevention Project (CAPPP) (82) compared the effects of an ACE inhibitor with diuretic/beta-blocker treatment in middle-aged hypertensive patients of whom 572 had type-2 diabetes at baseline; there were fewer CV events on captopril and fewer hypertensive patients developed type-2 diabetes on ACE inhibitor compared to "standard therapy". In the Swedish Trial in Old Patients with Hypertension-2 (STOP-2) study all patients were above the age of 70 years, and as many as 719 of them had type-2 diabetes at baseline; however, CV mortality was the same on standard therapy, ACE inhibition, or calcium-antagonist treatment (83).

Also, nearly normotensive subjects with diabetes may sometimes benefit from the use of drugs with BP lowering properties. The results of the Heart Outcomes Prevention Evaluation (HOPE) Study and the Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO) HOPE substudy (84) showed that treatment with the ACE inhibitor ramipril compared with placebo significantly lowered the risk of CVD events (by 25%) and overt nephropathy in people with type-2 diabetes with a previous CVD event or at least one other risk factor, including 56% with a history of hypertension. Uncontrolled diabetic hypertensives (BP >160/90 mmHg) were however not randomised. HOPE was not a hypertension trial, but gives an argument in favour of blockade of the RAAS in cardiovascular risk patients with diabetes.

In the Losartan Intervention For Endpoint Reduction (LIFE) trial (85), a subgroup of 1195 patients with diabetes, hypertension, and signs of LVH on electrocardiograms were randomised to either a losartan-based or atenolol-based treatment. Mortality from all causes was 63 and 104 in losartan and atenolol groups, respectively; RR 0.61 (0.45–0.84), $p = 0.002$. In the The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (86) a subgroup of 12,063 patients (36%) with diabetes were randomised to treatment with chlorothalidone, amlodipine, or lisinopril. There were no differences in the primary composite CV outcome between these three drugs, used in a very heterogenous study population according to ethnicity.

A similar result of equity between treatment arms for the primary composite cardiovascular end-point was found in the Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) based on a sub-analysis of 1,302 patients with hypertension and diabetes at baseline randomised to either a calcium antagonist or conventional therapy (beta-blockers or thiazide diuretics) (87).

In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, 15,245 patients, aged 50-years or older, with treated or untreated hypertension, and high risk of cardiac events participated in a randomised trial based on valsartan or amlodipine. The primary endpoint was defined as a composite of cardiac mortality and morbidity. Patients were followed up for a mean of 4.2 yr. BP was reduced by both treatments, but the effects of the amlodipine-based regimen were more pronounced, especially in the early period. The primary composite endpoint occurred in 810 patients in the valsartan group (10.6%, 25.5 per 1,000 patient-years) and 789 in the amlodipine group (10.4%, 24.7 per 1,000 patient-years; hazard ratio 1.04; $p = 0.49$). Valsartan treatment reduced new onset diabetes with 23%. The main outcome of cardiac disease did not differ between the treatment groups and not for patients with diabetes (88).

The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) trial was a prospective, randomised controlled trial in 19,257 patients with hypertension who were aged 40–79 years and had at least three other cardiovascular risk factors. Patients were assigned either amlodipine adding perindopril as required (amlodipine-based regimen) or atenolol adding bendroflumethiazide and potassium as required (atenolol-based regimen). The primary endpoint was non-fatal myocardial infarction (including silent myocardial infarction) and fatal CHD. The study was stopped prematurely after 5.5 years' median follow-up and accumulated in total 106,153 patient-years of observation. Though not significant, compared with the atenolol-based regimen, fewer individuals on the amlodipine-based regimen had a primary endpoint (429 vs. 474; unadjusted HR 0.90, 95% CI $0.79-1.02$, $p = 0.1052$), fatal and non-fatal stroke (327 vs. 422; 0.77, $0.66-0.89$, $p = 0.0003$), and all-cause mortality (738 vs. 820; 0.89, $0.81-0.99$, $p = 0.025$). The incidence of developing diabetes was less on the amlodipine-based regimen. The amlodipine-based regimen prevented more major cardiovascular events than the atenolol-based regimen, and this was the same also for patients with established diabetes (89).

Recently, new evidence has been published based on data from another large-scale intervention study (ADVANCE) aiming at controlling BP in patients with type 2 diabetes (90). In this multicenter, international study, the effect of the routine administration of a fixed ACE inhibitor–diuretic combination on serious vascular events in patients with diabetes was assessed, irrespective of initial BP levels or the use of other BP lowering drugs. After a six-week active run-in period, 11,140 patients with type 2 diabetes were randomized to treatment with a fixed combination of perindopril and indapamide or matching placebo, in addition to current therapy for CVD risk factor control. The primary endpoints were composites of major macrovascular and microvascular events, defined as death from cardiovascular disease, non-fatal stroke or non-fatal myocardial infarction, and new or worsening renal or diabetic eye disease. After a mean of 4.3 years of follow-up, 73% remained on randomized treatment. Compared with

patients assigned placebo, those assigned active therapy had a mean reduction in BP of 5.6/2.2 mmHg. The relative risk of a major macrovascular or microvascular event was reduced by 9% [861 (15.5%) active vs. 938 (16.8%) placebo: HR, 0.91; 95% CI, 0.83–1.00, p = 0.04]. The separate reductions in macrovascular and microvascular events were similar but were not independently significant (macrovascular 0.92; CI, 0.81–1.04, p = 0.16; microvascular 0.91; CI, 0.80–1.04, p = 0.16). The relative risk of death from cardiovascular disease was reduced by 18% [211 (3.8%) active vs. 257 (4.6%) placebo: 0.82; CI, 0.68–0.98, p = 0.03] and all-cause mortality was reduced by 14% [408 (7.3%) active vs. 471 (8.5%) placebo: 0.86; CI, 0.75–0.98, p = 0.03]. There was no evidence that the effects of the study treatment differed by initial BP level or concomitant use of other treatments at baseline (90). The ADVANCE trials thus gives evidence for the current BP goal of below 130/80 mmHg in patients with type 2 diabetes.

TREATMENT STRATEGIES

In general, lifestyle modification should be tried initially for a few months or so, but if severe hypertension (diastolic >110 mmHg) or signs of hypertensive tissue damage are present, drug therapy should be started immediately. Initially, monotherapy with one of the first-line drugs suggested below should be used, the choice being influenced by other factors such as coexistence of angina, LVH, heart failure, or nephropathy.

HYPERTENSION IN TYPE-1 DIABETES

ACE inhibitors are especially suitable if the patient has albuminuria or more advanced stages of diabetic nephropathy. Diuretics, calcium antagonists, and β_1-selective blockers (as second line) are equally useful alternatives with regard to BP reduction.

If renal function is moderately impaired (serum creatinine values >150 μmol/L), thiazide diuretics become less effective and loop diuretics should be used instead. However, in established renal failure (serum creatinine >500 μmol/L), furosemide may be toxic and dialysis must be started. In some patients, hypoglycaemia attacks may be masked by use of β-blockers.

HYPERTENSION IN TYPE-2 DIABETES

BP control is generally more important than the choice of individual drugs. First-line antihypertensive drugs suitable for use in diabetic patients are ACE inhibitors and AT_1 receptor antagonists (ARB) to block RAAS, but also low-dose diuretics (e.g., in combination with agents that block the RAAS), cardioselective β-blockers (UKPDS), and calcium-channel antagonists (44). Drugs can be selected for their beneficial effects on coexistent problems, e.g., angina or arrhythmia (β-blockers, calcium antagonists), heart failure (ACE inhibitors, ARB, certain β-blockers), previous myocardial infarction (ACE inhibitors, β-blockers), or nephropathy (ACE inhibitors, ARB).

Ramipril has strong evidence-based support for its use in type-2 diabetic patients because of their high cardiovascular risk (84). β-receptor blockers (in combination with low-dose aspirin) are indicated as secondary prevention for patients who have suffered a myocardial infarct, as long as no serious contraindications are present. Low doses of thiazide diuretics are useful in elderly diabetic patient, as this class of drugs has proven efficacy in preventing stroke and all-cause mortality in elderly hypertensives, also with diabetes (83). Indapamide is well-tolerated and with no metabolic side effects. Spironolactone may also be of value, especially for elderly, obese, female patients with hypertension and hypervolaemia with a low-renin profile. α_1-receptor blockers may be used as part of combination therapy, especially in patients with dyslipidaemia (high triglycerides and low HDL-cholesterol levels) and prostatic hyperplasia.

COMBINATION THERAPY

Combination therapy is needed in most diabetic patients (especially those with type 2 diabetes) to achieve satisfactory BP control (44,90). It is often better to use low-dose combinations than to increase dosages of single agents, as side effects are commonly dose-dependent. Potassium-sparing agents (spironolactone and amiloride) should not be combined with an ACE inhibitor because of the increased risk for hyperkalaemia.

Certain combinations of antihypertensive drugs have proved very safe and effective in low to moderate doses, e.g., ACE inhibitor/ARB + low-dose thiazide diuretic; calcium antagonist + ACE inhibitor; selective β_1-blocker + calcium antagonist; or β-blocker + α_1-blocker.

SPECIAL CONSIDERATIONS IN ETHNIC GROUPS

Hypertension in diabetes represents a serious medical problem in many ethnic groups, such as African-Americans. In non-Caucasian patients, β-receptor blockers and ACE inhibitors are often less effective at lowering BP, because the RAAS is already less active. Diuretics and calcium antagonists are often drugs to be preferred, particularly in African-Americans (91).

CONCLUSIONS

The general consensus for treatment of hypertension in type-2 diabetes is now aggressive BP lowering (<130/80 mmHg), usually based on poly-pharmacy with synergistic drug combinations. This should be part of an overall ambitious risk factor control, also addressing smoking, dyslipidaemia, and hyperglycaemia (38). Treatment with an ACE inhibitor has been shown effective in preventing macro- and microvascular events in high-risk diabetics with controlled hypertension.

Based on evidence (40,44,45,90), the following conclusions can be made:

1. Patients with type 2 diabetes should be aggressively treated for hypertension when BP is above 140 and/or 90 mmHg, aiming at BP <130/80 mmHg.
2. These patients usually need two or more drugs/combination therapy to reach the BP target, especially for systolic BP.
3. Although ACE inhibitors have been proven cardiovascular protective and some angiotensin-II receptor blockers nephroprotective, there is no consensus on the "drug of choice" for all hypertensive type-2 diabetic patients.
4. Most studies support the notion that BP reduction, per se, is more important than individual properties of specific drugs in most cases.

5. Blockade of the RAAS seems to be an appropriate choice for being one of the partner drugs in offering combination therapy to hypertensive patients with diabetes or glucose intolerance.
6. New antihypertensive drugs are constantly being introduced and should be tested for both efficacy and tolerability. In addition, certain novel anti-diabetic drugs (e.g., thiazolidinediones) appear to lower BP as well as blood glucose (92,93).

In the future, the application of cardiovascular genomics may substantially change the approach to treating hypertension in diabetes (94), with the possibility of tailoring antihypertensive treatment according to the genotype of the individual patient. In addition, further large-scale studies with large numbers of hypertensive type 2 diabetic patients will be published over the next few years (62). This will greatly reinforce the evidence-based approach to the treatment of this high-risk group. Finally, new clinical and experimental investigations can hopefully shed new light on hypertension in diabetes being an example of early vascular ageing, as shown by for example telomeric attrition (95,96), and how to prevent this process.

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HYPERTENSION IN CHILDREN AND ADOLESCENTS 35

Empar Lurbe

INTRODUCTION

During the last few years, there has been a renewed interest in measuring blood pressure (BP) in children and adolescents after recognizing that not only can secondary hypertension be present in childhood, but that essential hypertension can be too, especially in adolescents. Elevated BP is clearly established as a risk factor for the development of cardiovascular disease morbidity and mortality (1), and it is known that elevated BP in childhood and adolescence often tracks into adulthood (2).

DEFINITION OF HYPERTENSION

Of all that is known about the levels and distribution of casual BP in childhood and adolescents, two facts are well accepted: BP increases during growth and maturation, and adolescence is a fast growth period during which body mass and BP change rapidly (2). 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.

In 1977, the first age-related norms for BP in children were developed by the Task Force for Blood Pressure in Children, a group sponsored by the National Heart, Lung, and Blood Institute and by the National Institutes of Health (3). In 1987, a revision of the standards evaluated data from more than 70,000 Caucasian, African-American, and Mexican-American children (4). Age-specific percentile curves of BP measurements for boys and girls ranging in age from birth to 18 years were created. In addition, these revised standards defined the proper techniques for measuring BP in infants, children, and adolescents. All measurements used in constructing the Task Force's tables were made with a standard mercury sphygmomanometer placed on the child's right arm, using a cuff size that covered 80% to 100% of the circumference of the arm. In 1996, the Task Force became aware of the importance of considering age and height together when defining reference values (5). This approach avoids misclassifying children at the extremes of normal growth, since tall children will not be misclassified as hypertensive, and very short children with high normal BP or even hypertension will not be missed. In children of the same age, the upper limit of systolic BP normality for the 3rd percentile of height is 8 to 9 mmHg lower than those values for the 90th percentile. At the same time, the Task Force redefined diastolic BP as the fifth, rather than the fourth, Korotkoff sound for children in all age groups. No changes to the standards for systolic BP (SBP) and diastolic BP (DBP) for infants younger than 1 year were reported in the 1996 update.

In 2004, The Fourth Report of the Task Force (6) was released. In it, normal BP is defined as systolic and diastolic BP lower than the 90th percentile for age, sex and height. Hypertension is defined as average SBP and/or DBP greater than or equal to the 95th percentile for age, sex and height on three or more occasions. Average SBP and/or DBP levels that are ≥90th but <95th had been designated as prehypertension. As with adults, it is now recommended that children and adolescents with BP levels ≥120/80 mmHg, even if below the 90th percentile, should be considered prehypertensive as well. The classification of hypertension in children and adolescents is shown in Table 35.1.

Two additional points of interest were included in the most recent Task Force Report. First was the introduction of comments concerning oscillometric devices for measuring BP. The BP tables are based on auscultatory measurements; therefore, the preferred method of measurement is auscultation. Oscillometric devices are convenient and minimize observer error, but they do not provide measurements that are identical to auscultation. Therefore, to confirm hypertension, BP in

Table 35.1 Classification of hypertension in children and adolescents

	SBP or DBP Percentile
Normal	<90th percentile
High-normal (Prehypertension)	≥90th to <95th percentile ≥120/80 even if below 90th percentile in adolescents
Stage 1 hypertension	95th percentile to the 99th percentile plus 5 mmHg
Stage 2 hypertension	>99th percentile plus 5 mmHg

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.
Source: From Ref. 6.

children should be measured with a standard clinical sphygmomanometer using a stethoscope placed over the brachial artery pulse.

Second, there was a recommendation for using ambulatory BP, Table 35.2. BP variability and observer bias limit the reliability of office measurements that have the potential for inaccuracies (7). Automated techniques of BP measurement may overcome these limitations, therefore ambulatory BP monitoring became an established instrument for the diagnosis of hypertension in children and adolescents (8).

When using ambulatory BP measurements, simultaneous measurements of office and ambulatory BP delineate four conditions. In normotensive and hypertensive children, both the conventional and the daytime ambulatory BP are consistently normal or elevated, respectively. White-coat hypertension, also known as isolated clinic hypertension, is the transient elevation of a patient's BP in response to the observer measuring the BP (9,10); there is a normal daytime ambulatory BP in the presence of an elevated conventional one. In adults, 37% of patients with white coat hypertension evolved to persistent hypertension over a period of follow-up as brief as 0.5 to 6.5 years (11). The opposite phenomenon, masked hypertension or isolated ambulatory hypertension, consists of an elevated daytime or awake ambulatory BP, but a normal conventional BP measurement (12,13). In adults, masked hypertension is associated with increased left ventricular mass (14) and a worse cardiovascular prognosis (15).

In the largest pediatric study to date, Sorof et al. reported in children referred for evaluation of hypertension that the frequency of white coat hypertension by ambulatory BP monitoring was 35% (40/115) for all patients referred for evaluation and 22% (11/51) for patients with confirmed clinic hypertension (16). Although these results suggest that the phenomenon of white coat hypertension does occur commonly in children, it should be emphasized that white coat hypertension may not be an entirely benign condition and in fact may represent a pre-hypertensive state. There are currently no data on the long-term follow-up of children found to have white coat hypertension on initial assessment.

Recently, in one study carried out in 592 healthy Spanish children and adolescents (17), 535 youth were normotensive using both office as well as daytime ambulatory BP measurement (90.4%), while 45 had masked hypertension (7.6). Compared to normotensive controls, participants with masked hypertension had a higher ambulatory pulse rate, were more obese and were 2.5 times more likely to have a parental history of hypertension. Among 34 patients with masked hypertension (median follow-up 37 months), 18 became normotensive, 13 had persistent masked hypertension, and 3 developed sustained hypertension. Patients with persistent masked hypertension or who progressed from masked to sustained hypertension had a higher left ventricular mass index, and there was a higher percentage with left ventricular mass index above the 95th percentile than there was for normotensive controls.

Masked hypertension had a higher ambulatory pulse rate than did normotensive subjects, were more obese and were more than twice as likely to have a parental history of hypertension. These three characteristics, alone or in combination, predict the development of hypertension and increase cardiovascular risk later in life. Tachycardia and high body-mass index are usually accompanied by the stimulation of the sympathetic nervous system, which together with the elevated daytime BP and obesity might underlie the development of left ventricular hypertrophy in youths with masked hypertension even before these proceed to sustained hypertension (18,19). Approximately 50% of this population with persistent masked hypertension had a positive parental history of hypertension. This is in agreement with previous epidemiological studies, which have demonstrated that children with a positive familial history of hypertension had a higher BP than those without such a history (20). This association was even more pronounced when parents became hypertensive early in their life (21). In children and adolescents, masked hypertension is a precursor of sustained hypertension and left ventricular hypertrophy. This condition warrants follow-up and, once it becomes persistent, is an indication for BP lowering treatment.

Apart from the ability of ambulatory BP monitoring to obtain more accurate and reproducible BP values (22), another advantage of this method is the assessment of BP during sleep and, therefore, the estimation of circadian variability (23). There is a physiological nocturnal fall of BP during sleep in response to the reduction of sympathetic tone. Patients with 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 (24,25).

Table 35.2 Ambulatory blood pressure monitoring (ABPM) in children and adolescents

Useful in the evaluation of
White-coat hypertension
Apparent drug resistance
Drug-induced hypotension
Provides additional BP information in
Chronic kidney disease
Diabetes
Autonomic dysfunction
ABPM should be performed by clinicians experienced in its use and interpretation.

Source: From Ref. 6.

PREVALENCE

The prevalence of hypertension in children is reported to be 1% (4). In recent years, the prevalence in school-aged children appears to be increasing, perhaps as a result of the increased prevalence of obesity. The majority of these children have mild hypertension, most often primary. A small group of children have much higher BPs, usually due to a secondary cause.

Hypertension in children and adolescents depends on the demographic characteristics of the subjects analyzed, age, sex, body weight as well as ethnicity. Prevalence increases in parallel with age; the highest prevalence is in older children and boys have a larger prevalence than do girls in all the screening studies. Body weight has the greatest impact on the rate of hypertension. The role of ethnicity in the different prevalences observed—a higher BP in Hispanic and African-Americans, and a lower one in Asians when either is compared to Caucasians—has been a motive for controversy (26). In a study carried out in a school-based screening, however, ethnic

differences in the prevalence of hypertension were not significant after controlling for overweight. The prevalence increased progressively as the body mass index (BMI) percentile increased from 2% in a BMI percentile below the 5th to 11% in those children in a percentile above the 95th (27).

Besides the characteristics of the subjects, the number of BP measurements is crucial in the prevalence of hypertension. Two studies, by the Task Force in 1987 (4) and by Sinaiko in 1989 (28), found the prevalence of hypertension in the general population to be only 1%. In a study published in 2001 (29), using the Task Force standards of 1996 (5), the combined prevalence of systolic and diastolic hypertension in junior high school-aged children did not substantially change from the previously reported level. Statistically, 5% of children had a BP measurement above the 95th percentile during a single office visit. BP however, 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 (30). Consequently, the prevalence of hypertension decreased to 1% after only one repeated examination. The diagnostic algorithm of hypertension is found in Figure 35.1.

ETIOLOGY

Pediatric hypertension is associated with a broad spectrum of diseases that changes from childhood through adolescence. Definable causes of hypertension 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 hypertension in children and adolescents is classified as secondary with a specific cause that may be correctable or as essential and without an identifiable cause (4). The most common causes of hypertension can change during childhood. Essential hypertension is rarely seen in infants and young children, but its prevalence increases significantly in adolescence (31). A good general rule to follow is that the likelihood of identifying a secondary cause of hypertension is inversely related to the age of the child and directly related to the degree of BP elevation. Consequently, the evaluation of children with hypertension, especially young children and those with severe hypertension, should be comprehensive and aimed at identifying known causes of the disease.

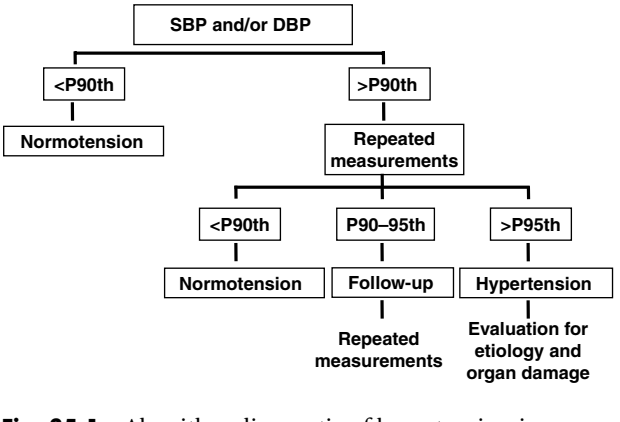

Fig. 35.1 Algorithm diagnostic of hypertension in children and adolescents. *Abbreviations*: DBP, diastolic blood pressure; SBP, systolic blood pressure.

The distribution of definable causes of hypertension is associated with a broad spectrum of diseases and clearly varies with age. Renal parenchymal disorders predominate, accounting for a majority of secondary causes (32). Renal parenchymal disorders with renovascular disease, and coarctation of the aorta account for 70% (33) to 90% (34) of all cases. These figures vary depending not only on the age group, but also on referral centre and referral bias. Additionally, hypertension is often related to prescribed drugs with hypertensive potential. Other infrequent causes of sustained hypertension, tumours and central nervous and endocrine disorders, must be considered once more common causes of secondary hypertension have been eliminated. An emerging cause of secondary hypertension is a single gene mutation that produces large changes in BP (35).

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 hypertension in this age group has not been completely standardized, useful data to this regard has been published (36) and may be used to facilitate the identification of such infants. As in older children, the causes of hypertension 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 and/or the renal arteries probably accounts for the majority of cases of hypertension seen in the typical neonatal intensive care unit (37). 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), hypertension 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 hypertension in this age group, are usually detected within the first decade of life. Late in the first decade and throughout the second, essential hypertension is the most common cause of sustained hypertension, particularly in those children with mild asymptomatic disease (38).

CLUES TO THE INITIAL APPROACH TO DIAGNOSIS OF SECONDARY HYPERTENSION

When confronted with an infant, child, or adolescent with hypertension, 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 hypertension 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 (Figure 35.2). Afterwards, a careful selection of the necessary test often shortens the diagnostic process. Based on

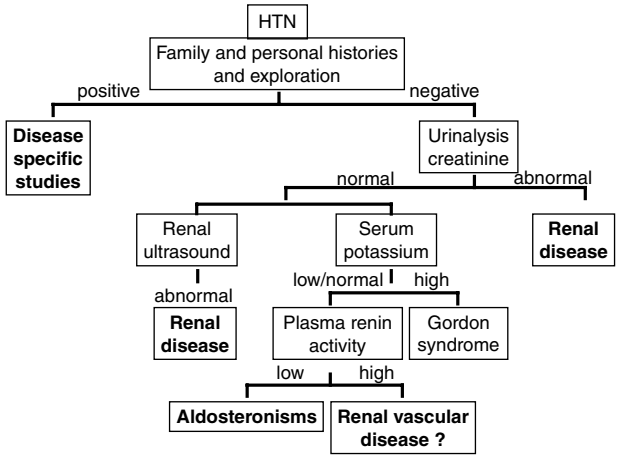

Fig. 35.2 Initial approach to the diagnosis of secondary hypertension (HTN) in children and adolescents.

these, the evaluation of the hypertensive child in current clinical practice generally focuses on the search for an underlying renal parenchymal lesion, vascular anomaly, catecholamine secreting tumour or surreptitious pharmacological agents. In addition to these etiologies, clinicians ought to be aware of several hypertensive syndromes that are inherited as single mendelian traits. The most common causes of hypertension, according to age group, are shown in Table 35.3.

HISTORY AND PHYSICAL EXAMINATION

The initial approach to uncovering the cause of hypertension requires a careful clinical evaluation that, in many cases, can provide clues not only to a specific diagnosis, but also to the most successful diagnostic procedure.

When recording family histories, it is not sufficient simply to ask which relatives have high BP, one needs to know the age at detection of hypertension in these relatives. A strong familial history of hypertension or hemorrhagic stroke in young members points to the presence of specific hereditary conditions [polycystic kidney disease (39), familial pheochromocitoma in multiple endocrine adenomatosis (MEN type II), von Hippel Lindau disease or neurofibromatosis (40)] or to one of the familial syndromes (glucocorticoid-remediable aldosteronism, mineralocorticoid apparent excess, Liddle syndrome, Gordon syndrome, and mineralocorticoid receptor hypersensitivity syndrome), and that in some of the latter, there is a specific responsible mutation with a mendelian trait (41).

Table 35.3 Most common causes of hypertension by age group

<1 Month
Renal arterial thrombosis
Coarctation of the aorta
Congenital renal disease
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 to 18 Years
Essential hypertension
Renal parenchymal disease
Renovascular disease

Episodic hypertension indicates the presence of pulsatil secretion of hypertensive substances, mainly chatecolamines, and indicates the necessity to look for a secreting tumour of neural or adrenal origin. Exposure to pressor substances (recreational drugs, liquorice, vasoconstrictor drops, glucocorticoids) or neurologic processes (dysautonomia, increased intracranial pressure, Guillem-Barré syndrome), need to be excluded. Other situations like orthopedic traction, stress, cyclic vomiting, and burns also temporarily increase BP.

Among the additional information that needs to be recorded are birth weight, development data, recent changes in weight, headaches, visual problems, weakness, muscle cramps, sexual development, abdominal pain, dysuria, nicturia, and enuresis. Any of these may raise the suspicion of disease.

Things to seek out during physical examination include the presence of edema, cutaneous stigmata of facomatosis, Cushing morphological changes, virilization or thyroid enlargement, heart murmurs, bruits over the great vessels or in the epigastrium, absence or delayed femoral pulses, and unilateral or bilateral abdominal masses. All are indicative of specific diseases.

LABORATORY STUDIES

In the absence of any telltale data obtained from the family and personal histories or from the physical exploration, there are several analytical procedures that should then be performed. Assessments of glomerular filtration rate by serum creatinine, of potassium levels and of urinalysis are mandatory. High creatinine levels or abnormal urinalysis herald a renal cause of hypertension, although the renal impact of an otherwise secondary hypertension needs to be considered.

Hypokalemia, in the absence of diuretic intake, is a low sensitive but high specific marker for diseases which lead to urine potassium wasting. An algorithm diagnostic (Figure 2) is used if hypokalemia is present. Hyperkalemia, in conjunction with metabolic acidosis, may suggest chronic renal disease, which is confirmed by elevated serum creatinine. A more uncommon situation is hyperkalemia with a normal glomerular filtration rate, suggesting the presence of Gordon syndrome.

The next step includes an assessment of the renin-aldosterone axis. High peripheral plasma renin activity may suggest a renal, parenchymal or renovascular cause for hypertension, and other studies then need to be performed in order to delineate these lesions. Low plasma renin activity points to several of the monogenic syndromes which lead to volume expansion. The algorithm diagnostic is shown in Figures 35.2 and 35.3.

IMAGE-DIAGNOSTIC TECHNIQUES

If the previously mentioned procedures do not point to a specific cause of the hypertension, and considering that renal

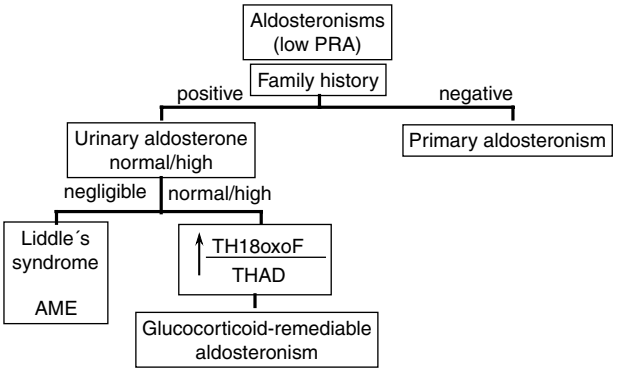

Fig. 35.3 Algorithm diagnostic of low rennin aldosteronisms. *Abbreviations*: AME, apparent mineralocorticoid excess; PRA, plasma renin activity; THAD, urinary tetrahydroaldosterone.

causes are the most frequent ones, a renal ultrasound is appropriate early in the evaluation. Masses, cortical scars or asymmetry of the kidneys prompt the performance of more specific procedures to better delineate the nature of the disease.

TARGET ORGAN DAMAGE

Although it is generally agreed that early essential hypertension poses little immediate risk to most children, it carries the potential for future end-organ damage In children, the accurate identification of hypertension at the earliest possible age would, therefore, give health-care providers the opportunity to initiate preventive measures, thereby reducing the chance of developing end-organ damage and its attendant morbidity and mortality. Consequently, repeated BP measurements over time should become a routine part of pediatric well-child care.

Because overt morbid cardiovascular events are rare in the majority of hypertensive children, attention has focused on other markers of hypertension 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 hypertension, such as left ventricular hypertrophy and dysfunction and atherosclerosis, may not become clinically relevant before adulthood.

HEART

The abnormal increase of left ventricular mass and/or geometry has been recognized as one of the most important markers of risk for hypertension-induced cardiovascular morbidity and mortality in adults. In children and adolescents, the relationship between hypertension and left ventricular mass is more difficult to recognize because children and adolescents grow rapidly and their BP increases with age.

Cross-sectional studies have shown that the major determinants of left ventricular growth are body size and sex, with a smaller contribution made by BP (42,43). The important contribution of the somatic growth and the recognition that lean body mass contributes somewhat more to cardiac growth than fat mass were nicely demonstrated in the Bogalusa Heart Study (44). In a longitudinal study, left ventricular mass tracks from early to late adolescence to about the same degree as other important risk factors, such as BP and cholesterol (45). Recently, 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. Moreover, the increase in left ventricular mass from the child to the young adult is related to the degree of increase in body mass index (46).

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 pathologically increased left ventricular mass index. Sensitivity and response to hemodynamic load seems to vary with age, sex, and ethnicity, which explains some of the differences among published results.

Although epidemiological studies do not help to establish the difference between appropriate and excessive increases in left ventricular mass, operational thresholds have been established. Both the allometric definition of excessive mass ($>51\,g/m^2$) as well as the percentile distribution of mass and geometry have been recommended. 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 (47–51).

The relationship between left ventricular mass index and systolic BP is more evident when BP is measured using 24-hour ambulatory BP monitoring. Consequently, hemodynamic load seems to play a more important role in the growth of left ventricular mass than previously recognized by using office BP. According with this, left ventricular mass tends to be greater in those groups with a higher ambulatory BP. In one cross-sectional study, both subjects with sustained hypertension as well as masked hypertensives had significantly higher left ventricular mass index than confirmed normotensive (50). Moreover, in a group with adolescents who had sustained masked hypertension, left ventricular mass index was significantly higher than that observed in normotensive adolescents (17).

Cardiac end-organ damage from hypertension exists in children and left ventricular mass assessment seems to be important in the management of childhood hypertension, since it is the most prominent evidence of target-organ damage in childhood hypertension. The recently released Task Force for BP in Children has recommended performing echocardiography in all hypertensive children and in those prehypertensives in the presence of diabetes or kidney disease (6).

The presence of left ventricular hypertrophy is an indication to initiate or intensify antihypertensive therapy. Studies assessing the effect of medical therapy of pediatric hypertension on left ventricular mass need to be performed in the future to further reinforce the necessity of monitoring left ventricular mass.

KIDNEY

Evidence of the importance of BP values in the progression of renal disease has come from several clinical studies in children with or without established renal insufficiency. In a randomized multicenter study (52) in children with chronic renal failure, a significant difference in the loss of the glomerular

filtration rate (GFR) was related to systolic BP. In those with systolic BP above 120 mmHg, a steeper decline of GFR was observed. In this study, the decrease in creatinine clearance strongly correlated with absolute BP rather than with height-corrected BP. The correlation between the decrease in creatinine clearance and BP was found even when BP was generally well controlled according to conventional criteria used to define BP control. These data suggest that BP in the low-normal range should probably be the target BP for patients with renal disease (53,54).

Besides the GFR reduction, an increase in urinary albumin excretion is a marker of hypertension-induced renal damage. Proteinuria is a marker of glomerular damage in primary and secondary glomerulopathies that can increase as a consequence of elevated BP values, so it should be targeted by lowering BP. More than twenty years ago, the Framingham Study demonstrated that an increase in urinary proteins was associated with a high risk of cardiovascular events, both coronary heart disease, as well as stroke (55). Even small amounts of urinary albumin excretion (UAE), microalbuminuria, are correlated with the progression of nephropathy and to a higher cardiovascular risk. Initially, information came from cross-sectional studies which demonstrated a clustering of cardiovascular risk factors and organ damage associated with a subtle increase in UAE. Later on, from follow-up studies, a given value of UAE measured at the beginning was associated with total and with cardiovascular mortality or morbidity over time. Furthermore, the level of albuminuria during antihypertensive treatment was closely related to cardiovascular risk during treatment, implying that changes in albuminuria translate to changes in risk (56).Then, assessment of increases in UAE is a powerful method to identify those adults at risk for multiple cardiovascular risk factor intervention. Changes in UAE seem to run in parallel to cardiovascular risk, and prompt intervention to avoid the progressive increment of UAE may result in better protection against hypertension-induced morbility and mortality (57). The role of microalbuminuria assessment in pediatrics, however, is limited to diabetic children and adolescents. Its significance in pediatric essential hypertension has yet to be established and a routine urinary albumin assessment is, therefore, not recommended yet (6).

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 non-invasive 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 age and sex influence the values of intima-media thickness (58), measured values should be related to percentiles or expressed as standard deviation scores.

In the few pediatric studies available, hypertensive children and adolescents tend to have an increase of intima-media thickness compared to those of normotensive controls (48,59,60), although one study did not observe differences among normotensives, white-coat, masked or sustained hypertensives (50). Moreover, a relationship between intima-media thickness and endothelial function has been established in the Cardiovascular Risk in Young Finns Study (61). The impact of other cardiovascular risk factors besides hypertension, 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 (62). 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 (6).

TREATMENT APPROACH

The goal of treatment for hypertension is to decrease the short- and long-term risks of cardiovascular and renal disease (1,63). Reducing BP alone is insufficient to obtain this objective; the issues of obesity, hyperlipidemia, smoking and glucose intolerance must also be addressed if present. There is agreement that therapy is warranted in children who have a persistent elevation of BP above the given thresholds.

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 (6). 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 to 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 (6).

In making treatment decisions for children, clinicians previously had to adapt the results of adult trials in selecting antihypertensive agents (64,65). 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 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 (8).

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 (66). The choice of the drug to be added needs to look for additive antihypertensive activity and to buffer potential secondary effects. Until more information is available for children and adolescents, the scheme proposed by the European Society of Hypertension/European Society of Cardiology guidelines should be used for drug combination (63) (see Chapter 30).

The target BP goal in children with uncomplicated primary hypertension and no hypertensive target-organ damage should be $<95^{th}$ percentile for gender, age and height. For children with chronic renal disease, diabetes or hypertensive target-organ damage, the goal BP should be <90th percentile. (67)

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. After starting treatment, the frequency of office BP readings depends on the severity of hypertension and on the given BP goal. Stage 2 hypertension 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 counselled 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 (68).

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 (69). 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 is still a matter of debate.

The appropriate duration of treatment for a child or adolescent is unknown. Some patients require lifelong therapy 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.

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HYPERTENSION IN PREGNANCY 36

Renata Cífková

INTRODUCTION

Hypertensive disorders in pregnancy remain a major cause of maternal, fetal, and neonatal morbidity and mortality not only in developing but, also, in developed countries. Pregnant women with hypertension are at higher risk for severe complications such as abruptio placentae, cerebrovascular accident, organ failure, and disseminated intravascular coagulation. The fetus is at risk for intrauterine growth retardation, prematurity, and intrauterine death. Hypertension is the most common medical problem in pregnancy; it may complicate up to 15% of pregnancies, and accounts for approximately a quarter of all antenatal admissions. As women in developed countries delay childbirth, the impact of pre-existing hypertension will increase, because the prevalence of hypertension increases with age. In 70% of cases, hypertension develops after 20 weeks' gestation, and only 30% of cases with hypertension are women with pre-existing hypertension.

PHYSIOLOGICAL CHANGES IN BLOOD PRESSURE DURING PREGNANCY

Early in the first trimester, there is a fall in blood pressure (BP), caused by active vasodilatation due to the action of local mediators, such as prostacyclin and nitric oxide. This reduction in BP primarily affects diastolic BP (DBP), and a drop of 10 mmHg is usual by 13–20 weeks' gestation. BP continues to fall until 20–24 weeks when a nadir is reached. After this, there is a gradual increase in BP until term when pre-pregnancy levels are achieved. This BP fluctuation occurs in both normotensive and hypertensive women.

Women with pre-existing hypertension tend to have even greater decreases in their BP in early pregnancy, and their "normal" rise in the third trimester may be misdiagnosed as pre-eclampsia. Women with DBP of 75 mmHg or systolic BP (SBP) of 120 mmHg in mid-pregnancy, or 85 mmHg DBP or 130 mmHg SBP in later pregnancy, should be monitored closely (1).

Immediately after delivery, BP usually falls, then increases over the first five postnatal days. Even women whose BP was normal throughout pregnancy may experience transient hypertension in the early postpartum period, perhaps reflecting a degree of vasomotor instability. A summary of changes in major hemodynamic parameters is given in Table 36.1.

BP MEASUREMENT

It is essential to confirm high BP readings on two occasions (2), using mercury sphygmomanometry as the gold standard in the sitting position. BP measurement in the left lateral recumbency, on the left arm, does not differ substantially from the BP value recorded in the sitting position. Therefore, the left lateral recumbent position is a reasonable alternative, particularly during labor.

Whether to measure DBP with Korotkoff phase IV or V has been an area of controversy. The 2003 European Society of Hypertension–European Society of Cardiology (ESH–ESC) guidelines for the management of arterial hypertension recommend that both phase IV and V Korotkoff sounds be recorded. Until recently, most classifications recommended use of phase IV whose proponents argued it more closely approximated intra-arterial BP while phase V was often very low or near zero. However, phase V seems to be closer to true intra-arterial BP and several large studies have reported phase V is rarely very low or zero (3). Also, phase IV is more difficult to detect than phase V. Lack of reproducibility of phase IV in pregnancy has been reported (4).

Concerns about the safety of a change from phase IV to phase V were addressed in a prospective randomized trial of 220 pregnant women with diastolic hypertension in the second half of pregnancy. Investigators reported that a change in practice would need that one case less of severe diastolic hypertension would be recorded for every six hypertensive pregnancies but all other episodes of severe hypertension would be recorded with a similar frequency. No clinically significant differences in outcome were noted when phase V was used instead of phase IV (5).

Therefore, Korotkoff phase V is now recommended for the measurement of DBP in pregnancy (6–8). If Korotkoff sounds persist as the level approaches 0 mmHg, then the point of muffling of the sound is used (phase IV) to indicate the DBP.

Automatic devices for BP measurement have been shown to be unreliable in severe pre-eclampsia and tend to under-record the true value. It is imperative that only devices validated

Table 36.1 Cardiovascular changes in pregnancy

Parameter	Change	Timing
Systolic blood pressure	↓4–6 mmHg	All bottom at 20–24 weeks, then rise gradually to pre-pregnancy values at term
Diastolic blood pressure	↓8–15 mmHg	
Mean arterial pressure	↓6–10 mmHg	
Heart rate	↑12–18 beats/min	Early 2nd trimester, then stable
Stroke volume	↑10–30%	Early 2nd trimester, then stable
Cardiac output	↑33–45%	Peaks in early 2nd trimester, then until term

according to recognized protocols to determine their accuracy are used in pregnancy (see: http://www.dableducational.org). Mean differences reported have been as great as 15 mmHg when compared with mercury sphygmomanometry and 25 mmHg when compared with intra-arterial measurements.

Several ambulatory BP monitoring (ABPM) devices have been successfully validated specifically for use in pregnancy and used to generate normal ranges for ABPM throughout gestation. Clinical application of ABPM has been assessed in three main areas: white-coat hypertension; early prediction of pre-eclampsia; and prognostic assessment of hypertension in later pregnancy. As white-coat hypertension is a common phenomenon in pregnant women who appear to be hypertensive according to routine BP measurement early in pregnancy, ABPM might be useful in the initial assessment to avoid unnecessary antihypertensive treatment (9). On the other hand, hypertension in pregnancy, as diagnosed by ABPM, has been shown to be associated with lower birth weights (10,11), and is superior to the office measurement of BP in predicting the outcome of pregnancy (12–14). Ambulatory BP monitoring is a better predictor of proteinuria, pre-term delivery, and low birth weight (13,14). It is therefore clinically useful in high-risk pregnant women with hypertension, or in those with diabetic or hypertensive nephropathy (15).

DEFINITION OF HYPERTENSION IN PREGNANCY

The definition of hypertension in pregnancy was not uniform for a long time (2,16,17). It used to include an elevation in BP during the second trimester from a baseline reading in the first trimester, or to pre-pregnancy levels, but a definition based on absolute BP values (SBP ≥140 mmHg or DBP ≥90 mmHg) is now preferred (17).

CLASSIFICATION OF HYPERTENSION IN PREGNANCY

Hypertension in pregnancy is not a single entity but comprises (18):

- Pre-existing hypertension
- Gestational hypertension
- Pre-existing hypertension plus superimposed gestational hypertension with proteinuria
- Antenatally unclassifiable hypertension

PRE-EXISTING HYPERTENSION

It complicates 1–5% of pregnancies and is defined as BP ≥140/90 mmHg that either predates pregnancy or develops before 20 weeks of gestation. Hypertension usually persists more than 42 days post partum. It may be associated with proteinuria.

However, there are several caveats to the diagnosis of pre-existing hypertension. Undiagnosed hypertensive women may appear normotensive in early pregnancy because of the normal fall of BP commencing in the first trimester. This may mask the pre-existing hypertension and, when hypertension is recorded later in pregnancy, it may be interpreted as gestational. Sometimes, the diagnosis is only made several months postpartum when the BP fails to normalize as would be expected with gestational hypertension.

GESTATIONAL HYPERTENSION

Gestational hypertension, which is pregnancy-induced hypertension with or without proteinuria, complicates 6–7% of pregnancies. Gestational hypertension associated with significant proteinuria (>300 mg/l or >500 mg/24 hr or dipstick 2+ or more) is known as pre-eclampsia. Hypertension develops after 20 weeks' gestation. In most cases, it resolves within 42 days postpartum. Gestational hypertension is characterized by poor organ perfusion.

Pre-eclampsia is a pregnancy-specific syndrome that occurs after mid-gestation, defined by de novo appearance of hypertension, accompanied by new-onset proteinuria >0.3 g/24 hr. It is a systemic disorder with both maternal and fetal manifestations. Pre-eclampsia was classically defined as a triad of hypertension, edema and proteinuria, but edema is no longer considered part of the diagnostic criteria, as it occurs in up to 60% of normal pregnancies, and is no longer included because of the lack of specificity. Overall, pre-eclampsia complicates 5–6% of pregnancies, but this figure increases to up to 25% in women with pre-existing hypertension. Risk factors for developing pre-eclampsia are given in Table 36.2.

Pre-eclampsia remains one of the three most frequently cited causes of maternal death and is responsible for an estimated 64,000 deaths a year worldwide (19). Developing countries have had persistently higher rates of maternal and child mortality due to pre-eclampsia compared with developed countries. While the immunological and genetic alterations are relevant in the development of pre-eclampsia in developed countries, nutritional, metabolic and infectious factors are largely responsible for the high incidence of pre-eclampsia in developing countries. In the United States, the rate of pre-eclampsia increased by 40% between 1990 and 1994, probably as a consequence of increasing maternal age and multiple births, factors predisposing to pre-eclampsia (20).

The risks to the fetus from pre-eclampsia include growth restriction secondary to placental insufficiency and premature delivery. Pre-eclampsia is one of the most common causes of prematurity accounting for 25% of all infants with very low birth weight, <1,500 g; it is also associated with an increased

Table 36.2 Risk factors for developing pre-eclampsia

Nulliparity
Multiple pregnancy
Family history of pre-eclampsia
Chronic hypertension
Diabetes
Increased insulin resistance
Increased body mass index
Hypercoagulability (inherited thrombophilia)
Renal disease even without significant impairment
Low socioeconomic status
Antiphospholipid syndrome (acquired thrombophilia)
Previous pre-eclampsia
Hydatidiform mole
Black ethnicity

incidence of cardiovascular disease in later life in mothers and babies (21,22). A paternal, but not maternal, history of essential hypertension is associated with increased risk of hypertension in children, the risk being greater in daughters than sons. Pregnancy may thus unveil or exacerbate this effect, possibly reflecting underlying endothelial vulnerability (23).

The main feature of pre-eclampsia is impaired perfusion to virtually every organ of the body. There is vasospasm and activation of platelets and the coagulation system resulting in the formation of microthrombi. The link between the placenta and the systemic disorder appears to involve endothelial dysfunction and oxidative stress. Symptoms and signs of severe pre-eclampsia include left upper quadrant/epigastric pain due to liver edema ± hepatic hemorrhage; headache ± visual disturbance (cerebral edema); occipital lobe blindness; hyperreflexia ± clonus; and convulsions (cerebral edema). Management of pre-eclampsia essentially focuses on recognition of the condition and, ultimately, delivery of the placenta, which is curative.

As proteinuria may be a late manifestation of pre-eclampsia, it is advised to be suspicious when de novo hypertension is accompanied by headache, abdominal pain, or abnormal laboratory tests, specifically low platelet count and abnormal liver enzymes; and it is recommended to treat such patients as pre-eclamptic ones.

The pathophysiology of pre-eclampsia can be divided into two stages: alterations in placental perfusion (stage 1) and maternal syndrome (stage 2). The placenta is the key component of pregnancy that leads to pre-eclampsia. The reduced placental perfusion is primarily due to abnormalities in implantation and vascular remodeling (24). In normal pregnancy, the spiral arteries that perfuse the placenta undergo remarkable remodeling from small muscular arteries in the pregnant state to significantly distended vessels that have lost both their smooth muscle and inner elastic lamina layers. This extensive remodeling does not occur in pre-eclampsia. There may be some superficial remodeling but it never extends beyond the decidual lining whereas, in normal pregnancy, the modified vessels extend into the inner third of the myometrium (25). Many vessels in pre-eclamptic women undergo no remodeling, and this results in reduced placental perfusion. It is now evident that these interactions include precisely regulated expression molecules involved in attachment and invasion in response to environmental and maternal signals, and that this process is impaired in pre-eclampsia (26). Several conditions associated with macrovascular disease such as hypertension, diabetes, and collagen vascular diseases also increase the risk of pre-eclampsia, leading to speculation that impaired placental perfusion may be the common denominator. Obstetric conditions associated with large placentas (hydatidiform mole, hydropic placentas, and placentas with multiple gestations) all increase the risk of pre-eclampsia (27). It is proposed that, in these large placentas, there is a relative reduction in placental perfusion. Another alteration of the spiral arteries in pre-eclampsia, atherosis, results in occlusion of the decidual vessels reminiscent of the vascular findings of allograft rejection supporting an immunological component of pre-eclampsia (28).

Stage 2, the maternal syndrome, begins when the plasma volume is reduced, with decreased blood flow to organs other than placenta, resulting in hemoconcentration, hemorrhage, and necrosis (29). In the liver, evidence can be found of reduced perfusion with secondary necrosis and hemorrhage. In the heart, subendocardial necrosis can occur similar to that seen in hypovolemic shock. The explanation for systematically reduced perfusion includes vasoconstriction, microthrombi, and reduced plasma volume secondary to loss of fluid from the vascular compartment. The vasoconstriction is not attributable to increased endogenous pressors but, rather, to an increased sensitivity to virtually all circulating pressor agents. Pre-eclampsia is also characterized by activation of the coagulation cascade. Renal biopsy specimens from women with pre-eclampsia reveal a change seen in no other form of hypertension. Termed glomeruloendotheliosis, the lesion consists primarily of enlargement of the glomerulus caused by hypertrophy of endothelial cells. Numerous markers of endothelial activation are present in the circulation of pre-eclamptic women weeks to months before clinically evident disease (30). Vessels from women with pre-eclampsia manifest reduced endothelium-mediated relaxation and plasma or serum from pre-eclamptic women can adversely alter endothelial function in vitro either with cells in culture or intact vessels.

PRE-EXISTING HYPERTENSION PLUS SUPERIMPOSED GESTATIONAL HYPERTENSION WITH PROTEINURIA

Pre-existing hypertension is associated with further worsening of BP and protein excretion ≥3 g/day in 24-hour urine collection after 20 weeks' gestation; it corresponds to the previous terminology "chronic hypertension with superimposed pre-eclampsia."

ANTENATALLY UNCLASSIFIABLE HYPERTENSION

This is hypertension with or without systemic manifestation, if BP was first recorded after 20 weeks' gestation. Re-assessment is necessary at or after 42 days post partum. If hypertension is resolved by then, the condition should be re-classified as gestational hypertension with or without proteinuria. If the hypertension is not resolved by then, the condition should be re-classified as pre-existing hypertension.

RECOMMENDED LABORATORY INVESTIGATIONS

Hypertensive disorders in pregnancy, particularly gestational hypertension with or without proteinuria, may produce changes in the hematologic, renal and hepatic profiles that may adversely affect prognosis and both neonatal and maternal outcomes.

Basic laboratory investigations recommended for monitoring patients with hypertension in pregnancy are presented in Table 36.3. Some authors (31) recommend ultrasound investigation of the adrenals and urine metanephrine and normetanephrine assays in all pregnant women with hypertension as pheochromocytoma may be completely asymptomatic and, if not diagnosed before labor, fatal.

MANAGEMENT OF HYPERTENSION IN PREGNANCY

The majority of women with pre-existing hypertension in pregnancy have mild to moderate hypertension (140–179/90–109 mmHg), and are at low risk for cardiovascular complications within the short timeframe of pregnancy. Women with essential hypertension and normal renal function have good maternal and neonatal outcomes; they are candidates for non-drug therapy because there is no evidence that pharmacological treatment results in improved neonatal outcome. Some women with treated pre-existing hypertension are able to stop their medication in the first half of pregnancy because of the physiological fall in BP during this period. However, close monitoring and, if necessary, resumption of treatment are essential.

There are not sufficient data regarding treatment of hypertension in pregnancy as pharmaceutical companies have been reluctant to test drugs in this small market with a high potential of litigation. Child-bearing potential without reliable contraception is an exclusion criterion in basically all clinical trials testing antihypertensive drugs. Pharmaceutical companies are not willing to take any, even a small risk and, as no data are available for most of the antihypertensive drugs marketed over the last 20 years, the vast majority of newer antihypertensive drugs is strictly contraindicated in pregnancy.

The only trial of treatment of hypertension in pregnancy with adequate infant follow-up (7.5 years) was performed more than 30 years ago with alpha-methyldopa, now rarely used in non-pregnant women (32,33). Past clinical trials also have not supported a beneficial effect on pregnancy outcome of treating mild hypertension. There has been no reduction in perinatal mortality, placental abruption, or superimposed pre-eclampsia (34,35). All these trials are subject to criticism including small numbers, starting the drug too late in pregnancy, or flawed study design; however, no other data are available. These studies have led to recommendations to treat only on the basis of BP sufficiently elevated to pose a potential acute risk to the mother (36). Small and frequently poorly designed studies have recently suggested that therapy of mildly elevated BP may prevent progression to pre-eclampsia (37,38). Even for women with BP elevation sufficient to justify therapy for their own benefit, it is not clear whether it is beneficial for or detrimental to the fetus. In several studies, treatment of hypertensive women resulted in an increased risk of growth restriction in their infants (39). It is not known whether this is the inevitable consequence of lower BP during pregnancy or whether it is due to excessive pressure decreases or too specific drugs.

NON-PHARMACOLOGICAL MANAGEMENT AND PREVENTION OF HYPERTENSION IN PREGNANCY

Non-pharmacological management (40) should be considered for pregnant women with SBP of 140–150 mmHg or DBP of 90–99 mmHg or both, measured in a clinical setting. A short-term hospital stay may be required for confirming the diagnosis of and ruling out severe gestational hypertension (pre-eclampsia), in which the only effective treatment is delivery. Management, depending on BP, gestational age and presence of associated maternal and fetal risk factors, includes close supervision, limitation of activities, and some bed rest in the left lateral position. A normal diet without salt restriction is advised. Preventive interventions, aimed at reducing

Table 36.3 Basic laboratory investigations recommended for monitoring patients with hypertension in pregnancy

Hemoglobulin and hematocrit	Hemoconcentration supports diagnosis of gestational hypertension with or without proteinuria. It indicates severity. Levels may be low in very severe cases because of hemolysis.
Platelet count	Low levels $<100{,}000 \times 10^9$/L may suggest consumption in the microvasculature. Levels correspond to severity and are predictive of recovery rate in post-partum period, especially for women with HELLP syndrome.
Serum AST, ALT	Elevated levels suggest hepatic involvement. Increasing levels suggest worsening severity.
Serum LDH	Elevated levels are associated with hemolysis and hepatic involvement. May reflect severity and may predict potential for recovery post partum, especially for women with HELLP syndrome.
Proteinuria (24-hour urine collection)	Standard to quantify proteinuria. If in excess of 2 g/day, very close monitoring is warranted. If an excess of 3 g/day, delivery should be considered.
Urinalysis	Dipstick test for proteinuria has significant false-positive and false-negative rates. If dipstick results are positive (≥1), 24-hour urine collection is needed to confirm proteinuria. Negative dipstick results do not rule out proteinuria, especially if DBP ≥ 90 mmHg.
Serum uric acid	Elevated levels aid in differential diagnosis of gestational hypertension and may reflect severity.
Serum creatinine	Levels drop in pregnancy. Elevated levels suggest increasing severity of hypertension; assessment of 24-hour creatinine clearance may be necessary.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HELLP, Hemolysis, Elevated Liver enzyme levels, and Low Platelet count; LDH, lactate dehydrogenase.

the incidence of gestational hypertension, especially pre-eclampsia, including calcium supplementation (2 g/d) (41), fish oil supplementation (42) and low-dose acetylsalicylic acid therapy (43), have failed to consistently produce the benefits initially expected, especially on the fetus. A recent Cochrane database systematic review showed that calcium supplementation of at least 1 g daily during pregnancy almost halved the risk of pre-eclampsia without causing any harm. The effect was greatest for high-risk women (44). In a multicenter randomized clinical trial of effect of fish oil in a high-risk population of pregnant women with pregnancy complications, fish oil supplementation delayed the onset of delivery in low and middle, but not in high, fish consumers (45). Low-dose aspirin is, however, used prophylactically in women with a history of early-onset (<28 weeks) pre-eclampsia. Increased energy and protein intake are not beneficial in the prevention of gestational hypertension. Although weight reduction may be helpful in reducing BP in non-pregnant women, it is not recommended during pregnancy in obese women. Weight reduction can be associated with reduced neonatal weight and slower subsequent growth in infants of dieting obese mothers.

The value of continued administration of antihypertensive drugs to pregnant women with chronic hypertension continues to be an area of debate. While there is a consensus that drug treatment of severe hypertension in pregnancy is required and beneficial (46), treatment of less severe hypertension is controversial. Although it might be beneficial for the mother with hypertension to reduce her BP, lower BP may impair uteroplacental perfusion and thereby jeopardize fetal development. Much uncertainty about the benefits of BP lowering in pregnant women with mild pre-existing hypertension stems from published trials too small to detect a modest reduction in obstetric complications.

PHARMACOLOGICAL MANAGEMENT OF HYPERTENSION IN PREGNANCY

All antihypertensive drugs have either been shown or are assumed to cross the placenta and reach the fetal circulation. However, none of the antihypertensive agents in routine use have been documented to be teratogenic, although angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists are fetotoxic.

While the goal of treating hypertension is to reduce maternal risk, the agents selected must be efficacious and safe for the fetus (6,47). SBP ≥170 or DBP (DBP) ≥110 mmHg in a pregnant woman should be considered an emergency, and hospitalization is absolutely essential. Pharmacological treatment with intravenous labetalol, oral methyldopa, or nifedipine is to be initiated. Intravenous hydralazine should no longer be thought of as the drug of choice as its use is associated with more perinatal adverse effects than other drugs. The drug of choice in hypertensive crises is sodium nitroprusside given as intravenous infusion at 0.25–5.0 μg/kg/min. Prolonged treatment with sodium nitroprusside is associated with an increased risk of fetal cyanide poisoning as nitroprusside is metabolized into thiocyanate excreted into urine (48). The drug of choice in pre-eclampsia associated with pulmonary edema is nitroglycerine (given as intravenous infusion of 5 μg/min, gradually increased every 3–5 min to a maximum dose of 100 μg/min).

Otherwise, the thresholds at which to start antihypertensive treatment are SBP of 140 mmHg or DBP of 90 mmHg in women with gestational hypertension without proteinuria or pre-existing hypertension before 28 weeks' gestation, those with gestational hypertension and proteinuria or symptoms at any time during the pregnancy, those with pre-existing hypertension and underlying conditions of target organ damage, and those with pre-existing hypertension and superimposed gestational hypertension. The thresholds in other circumstances are SBP of 150 mmHg and DBP of 95 mmHg. For non-severe hypertension (Table 36.4), methyldopa, labetalol, and calcium antagonists are the drugs of choice. Beta-blockers appear to be less effective than calcium antagonists. Atenolol should be avoided in the early stages of pregnancy and given with caution in the later stages, as it is associated with fetal growth retardation related to duration of treatment (Table 36.5) (49). Calcium-channel blockers are considered to be safe if not given concomitantly with magnesium sulfate (risk of hypotension due to potential synergism). ACE inhibitors and angiotensin II antagonists should not be used in pregnancy. The plasma volume is reduced in pre-eclampsia; diuretic therapy is therefore inappropriate unless there is oliguria. Magnesium sulfate i.v. is recommended for the prevention of eclampsia and treatment of seizures (50).

DELIVERY INDUCTION

Induction of delivery is appropriate in gestational hypertension with proteinuria with adverse conditions, such as visual disturbances, coagulation abnormalities, or fetal distress.

BP POST PARTUM

Postpartum hypertension is common. BP usually rises after delivery over the first five days. Women experiencing hypertension during pregnancy may be normotensive after birth but then become hypertensive again in the first postnatal week. The need to obtain hypertensive control may delay

Table 36.4 Antihypertensive drugs used in pregnancy

Women with pre-existing hypertension are advised to continue their current medication except for ACE inhibitors and angiotensin II antagonists. In women with pre-existing hypertension with DBP ≥100mmHg (lower when end-organ damage or underlying renal disease is present) and in women with acute hypertension (DBP ≥105 mmHg), the following agents are suggested:	
Central alfa agonists	Methyldopa is the drug of choice.
Alfa-/beta-blockers	Labetalol has comparable efficacy with methyldopa; in the case of severe hypertension, it could be given intravenously.
Calcium-channel blockers	Oral nifedipine or IV isradipine could be given in hypertensive emergencies. Potential synergism with magnesium sulfate may induce hypotension.

Abbreviations: ACE, angiotensin-converting enzyme; DBP, diastolic blood pressure; IV, intravenous.

Table 36.5 Antihypertensive drugs contraindicated in pregnancy or to be used with caution

ACE inhibitors, angiotensin II antagonists	Fetal abnormalities including death can be caused and these drugs should not be used in pregnancy.
Diuretics	Diuretics are recommended for chronic hypertension if prescribed before gestation or if patients appear to be salt-sensitive. They are not recommended in pre-eclampsia.
Direct vasodilators	Hydralazine is no longer the parenteral drug of choice because of its perinatal adverse effects.
Beta-blockers	Atenolol and metoprolol appear to be safe and effective in late pregnancy; they should be avoided in early pregnancy.

Abbreviation: ACE, angiotensin-converting enzyme.

discharge. Methyldopa should be avoided post partum because of the risk of postnatal depression.

HYPERTENSION AND LACTATION

Breast-feeding does not increase BP in the nursing mother. Bromocryptin, which is used to suppress lactation, may induce hypertension. All antihypertensive agents taken by the nursing mother are excreted into breast milk. Most of the antihypertensive drugs are present at very low concentrations, except for propranolol and nifedipine, whose concentrations in breast milk are similar to those in maternal plasma.

RISK OF RECURRENCE OF HYPERTENSIVE DISORDERS IN A SUBSEQUENT PREGNANCY

Women experiencing hypertension in their first pregnancy are at increased risk in a subsequent pregnancy. The earlier the onset of hypertension in the first pregnancy, the greater the risk of recurrence.

LONG-TERM CARDIOVASCULAR CONSEQUENCES IN PREGNANCY-INDUCED HYPERTENSION

Women who develop gestational hypertension or pre-eclampsia are at increased risk of hypertension and stroke in later adult life (51). Furthermore, there is evidence of an increased risk of ischemic heart disease in women who experience pre-eclampsia or isolated intrauterine growth retardation together with increased death from ischemic heart disease (52). Therefore, it is of utmost importance that all women with pregnancy-induced hypertension have their BP measured annually.

Endothelial dysfunction and early alteration of carbohydrate and lipid metabolism are present in otherwise healthy women with previous gestational hypertension. These abnormalities, along with a relative hyperandrogenism, could explain, at least in part, the increased risk for cardiovascular disease in later life in these women (53).

On the other hand, women who go through pregnancy without developing hypertension are at reduced risk of becoming hypertensive in later life when compared to nulliparous women. Thus, pregnancy may offer a window into the future cardiovascular health of women that is unavailable in men.

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POSTTRANSPLANT HYPERTENSION 37

Martin Hausberg, Karl Heinz Rahn

SUMMARY

Solid organ transplantation is increasingly available worldwide. Due to modern immunosuppressive drugs, graft survival improved significantly. However, a major side effect of many of these immunosuppressants is the development of hypertension, affecting the majority of patients. The use of calcineurin inhibitors is a major cause of hypertension after transplantation; other significant causes are progressive native kidney damage and the development of a metabolic syndrome in solid organ recipients. In the case of kidney transplantation, the situation is even more complex. Major causes of hypertension besides the use of calcineurin inhibitors are: impaired graft function due to chronic allograft nephropathy or other types of graft disease, including recurrence of primary disease; humoral or neurogenic pressor signals arising from the graft or the diseased kidneys; and stenotic lesions of arteries supplying the graft, possibly also a genetic predisposition to hypertension of the graft donor. Hypertension in kidney transplant recipients is of major prognostic relevance for graft survival but also for cardiovascular disease in the recipients. Even modest elevations of blood pressure (BP) are associated with premature graft loss. Recipient systolic BP is one of the best predictors. Hypertension amplifies vascular injury in the graft and accelerates the deleterious effects of other nonimmunologic factors, e.g., hyperlipidemia, and immunologic factors, e.g., chronic rejection, promoting graft loss. Aggressive treatment of hypertension in solid organ transplant patients is mandatory. A target BP $<130/80$ mmHg seems to be advisable. Antihypertensive treatment is required in most cases. Calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and diuretics are drugs of first choice. Studies are required to assess the effects of calcineurin inhibitor withdrawal on posttransplant hypertension and long-term patient and graft survival in solid transplantation.

INTRODUCTION

Hypertension is a common problem after solid organ transplantation and affects primarily the recipients of kidney, heart, and liver transplants. Significant causes are the use of calcineurin inhibitors as immunosuppressive drugs and progressive deterioration of kidney function. The situation in kidney transplant recipients is more complex and is discussed in detail below.

The prognostic relevance of hypertension in heart and liver transplant recipients is not yet clearly established. Myers and co-workers could not establish systemic arterial BP as predictor of survival after heart transplantation (1). Also, in liver transplant recipients, Guckelberger and co-workers did not observe BP as an independent predictor of cardiovascular outcome (2). However, from the available evidence, the management of hypertension in solid organ transplant recipients does not differ significantly with regards to the transplanted organ. Effective BP control is mandatory not only in kidney transplant recipients but also in other solid organ transplant recipients. Ojo et al. recently reported a cumulative 5-year incidence of end-stage renal disease in nonrenal solid organ transplant recipients between 7% and 21% depending on the organ transplanted (3). A significant risk factor for renal failure was hypertension, and the occurrence of renal failure was associated with excess mortality (relative risk 4.55).

Since kidney transplant patients represent the majority of solid organ transplant recipients, causes of hypertension in nonrenal solid organ transplant recipients apply also to kidney transplant patients, and the relevance of hypertension is best established after kidney transplantation, this chapter focuses on hypertension after kidney transplantation.

PREVALENCE OF ARTERIAL HYPERTENSION AFTER KIDNEY TRANSPLANTATION

Three decades ago, with modern immunosuppressants not available, only 30% to 40% of kidney transplant recipients developed hypertension. However, 1-year graft survival was in general not much above 50% (4). The introduction of calcineurin inhibitors, first cyclosporine two decades ago, followed later by tacrolimus, greatly improved short-term graft survival in kidney transplant patients. One-year graft

survival reached 80% to 90% after the introduction of cyclosporine (4). Unfortunately, the use of calcineurin inhibitors is associated with a large prevalence of hypertension in kidney transplant patients. More than 80% of patients develop hypertension during the first year after transplantation according to International Society of Hypertension (ISH) and World Health Organization (WHO) criteria, i.e., BP values >140/90 mmHg (5). Schwenger and co-workers reported a single center survey, showing only 42.9% of renal allograft recipients with BPs <140/90 mmHg, 22.4% of patients with BPs <130/85 mmHg, and mere 4.1% of patients with BPs <125/75 mmHg—despite antihypertensive treatment (6).

Moreover, ambulatory BP profiles are disturbed in most patients after kidney transplantation. Interestingly, a correlation between serum creatinine and nighttime BP change was reported (6). Patients with high serum creatinine concentrations, i.e., impaired graft function, showed a paradoxical nighttime increase in BP.

CAUSES OF HYPERTENSION IN KIDNEY TRANSPLANT PATIENTS

First, immunosuppressive treatment is to be noted. The calcineurin inhibitors cyclosporine and tacrolimus cause hypertension in kidney transplant patients, in recipients of heart (7) and liver transplants (8), but also unrelated to transplantation in patients with or without renal disease requiring immunosuppressive treatment (9). The mechanisms of calcineurin-inhibitor-induced hypertension have been best studied for cyclosporine. This drug causes acute decreases in renal plasma flow and glomerular filtration rate, mediated by vasoconstriction predominantly affecting the afferent glomerular arteriole (10). This contributes to enhanced tubular sodium absorption and resulting hypervolemia (11). The vasoconstrictor effects of cyclosporine are attributable to both enhanced pressor and decreased vasodilator mechanisms. Cyclosporine activates the renin–angiotensin system (12), induces the expression of endothelin 1, and increases the production of thromboxane (13), all resulting in vasoconstriction. Moreover, cyclosporine may cause activation of the sympathetic nervous system. This could be well demonstrated in animal models (14), however, the results of human studies are equivocal (7,15). We could show only small acute increases in sympathetic nerve activity with cyclosporine in kidney transplant patients, tacrolimus had no effect. In contrast, we could not demonstrate any chronic sympathoexcitatory effect of cyclosporine. Cyclosporine withdrawal in renal transplant patients with chronic allograft nephropathy was associated with a decrease in BP but sympathetic nerve activity remained elevated (16). Sympathetic activation by cyclosporine has been linked to excitation of renal afferent nerves, which depend on synapsin in afferent nerve endings (17). It is conceivable that the synapsin-mediated activation of renal sensory nerves is disturbed in kidney transplant patients who have severely diseased native kidneys and denervated grafts. Therefore, cyclosporine may not induce any additional activation of renal afferent nervers in patients with renal disease (Table 37.1).

Beyond these pressor effects, cyclosporine impairs nitric oxide-mediated vasodilation and decreases the production of vasodilator prostacyclin (18).

Many of the above-stated mechanisms apply also to the other commonly used calcineurin-inhibitor tacrolimus. However, many clinical studies show that hypertension induced by tacrolimus is less pronounced (19). A switch from cyclosporine to tacrolimus resulted in a decrease in BP in most kidney transplant recipients (20).

In the long run, calcineurin inhibitors, notably cyclosporine, cause interstitial fibrosis and vascular as well as tubular damage in the graft, possibly mediated by a common endothelin–TGFβ1 pathway (21).

Also, steroid therapy contributes to hypertension in kidney transplant patients. BP could be linked to both current and cumulative steroid dose (22).

Second, vascular alterations in kidney transplant patients contribute to hypertension. We have shown impaired functional—i.e., disturbed endothelial function and large artery elasticity—and structural wall properties of large arteries (23,24). These atherosclerotic lesions are not induced by kidney transplantation, i.e., exist already before transplantation in patients with end-stage renal disease. Disturbed endothelial function—i.e., nitric oxide-dependent vasodilation—and large artery stiffness are major determinants of increased pulse pressure, predominantly systolic hypertension and increased cardiac afterload (25).

Third, disease of the graft is a major determinant of hypertension after kidney transplantation. Animal studies document well that hypertension can by acquired by transplantation of a kidney from a hypertensive donor into a normotensive recipient (26). The kidney appears to have an important role in long-term BP regulation overriding other control mechanisms. The same has been observed in humans. For example, Curtis and co-workers reported remission of hypertension after kidney transplantation from normotensive donors in six hypertensive patients who developed end-stage renal disease due to nephrosclerosis (27). These patients did not receive calcineurin inhibitors.

In patients with primary renal disease, hypertension is common. Even patients with glomerular filtration rates still in the normal range often have elevated BP. Hypertension in patients with renal disease has been to be shown sodium sensitive (28). The severity of hypertension rises with increasing serum creatinine as marker of progressive renal injury (29). This is also true for kidney transplant recipients. Curtis and co-workers demonstrated sodium dependency in renal transplant patients (11). Several authors observed an inverse

Table 37.1 Causes of hypertension after kidney transplantation

Immunosuppressive drugs, e.g., calcineurin inhibitors and steroids
Alterations of large artery structure and function
Progressive decline in graft function, due to:
Chronic allograft nephropathy, including chronic rejection
Recurrence of primary renal disease in the graft
De novo glomerulonephritis in the graft
Diseased native kidneys via:
Secretion of humoral factors such as rennin
Sympathetic activation by excitation of renal afferent nerves
Stenosis of the graft artery
Rare causes, e.g., posttransplant erythrocytosis, genetic factors linked to the graft

relationship between BP and graft function in kidney transplant patients (30).

The renal allograft is subject to a number of immunologic, e.g., chronic rejection, and nonimmunologic processes, e.g., hyperlipidemia and impaired glucose metabolism, which cause progressive graft failure and eventually graft loss (31). Besides these factors, recurrence of the primary renal disease in the graft may also contribute to progressive graft failure (32). Examples for renal disease likely to recur in the graft are focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, but also Ig-A nephropathy. As stated above, progressive decline of graft function is associated with increasing BP levels.

Importantly, hypertension and impaired graft function constitute a vicious circle, impaired graft function promoting hypertension and hypertension accelerating chronic graft failure due to both immunologic and nonimmunologic causes (33). In this context, transplantation of marginal grafts has to be reconsidered (30). It has been shown that measures to increase the number of functioning nephrons, i.e., double kidney grafting in the case of elderly donors with marginal renal function, may result in well-controlled BP in the recipients (34).

Fourth, the diseased native kidneys, though nonfunctional, may significantly contribute to hypertension in renal transplant patients. With effective antihypertensive treatment available, bilateral native kidney nephrectomy is rarely performed in kidney transplant recipients. However, several studies clearly document lower BP in patients after bilateral native kidney nephrectomy (35). Signals arising in the diseased native kidney seem to be responsible for the BP elevation. Excitation of renal afferent nerves mediates an increase in central sympathetic outflow (36). Even moderate damage of the kidney is sufficient to elicit a sustained increase in sympathetic nerve activity and BP that can be prevented by renal denervation (37). We recently showed that, not uremia-related toxins, but other factors, such as local renin release or the activation of mechano- and chemoreceptors by fibroproliferative scarring in the diseased kidneys, are responsible for sustained sympathetic activation in patients with end-stage renal disease and renal allograft recipients (Figure 37.1) (38).

Fifth, stenosis of the kidney graft artery causes hypertension in 2–7% of renal transplant patients despite technical progress in surgical procedures, such as the use of aortic patches and improved perfusion techniques before transplantation (Figure 37.2). Major causes of graft artery stenosis are immunologic factors related to rejection and infection, e.g., cytomegelovirus infection, and nonimmunologic factors such as hyperlipidemia (39). Preexistent atherosclerosis of the graft artery, particularly in elderly donors, favors the development of hemodynamically relevant stenosis. The risk of developing graft artery stenosis increases with cold ischemia time. In a recently published survey, the prevalence of kidney graft artery stenosis was 4.1% in recipients from cadaveric donors, contrasting with 0.8% in recipients from living donors (39). Noninvasive techniques, such as color-coded Duplex ultrasound or magnetic resonance angiography, reliably establish the diagnosis of kidney graft artery stenosis.

Finally, rare causes of hypertension in kidney transplant patients, such as posttransplant erythrocytosis (40) due to unregulated secretion of erythropoeitin from the graft or genetic factors, possibly linked to the graft (41), have to be considered.

IMPACT OF HYPERTENSION IN KIDNEY TRANSPLANT RECIPIENTS

Hypertension is of prognostic relevance for both patient and graft survival. Patients with end-stage renal disease are characterized by a large burden of cardiovascular disease (42). Hypertension in these patients is particularly related to atherosclerotic disease with alterations of large artery elastic wall properties and endothelial function. As summarized by London and co-workers, increased large artery stiffness results in increased cardiac afterload, thus left ventricular hypertrophy, and at the same time reduced diastolic perfusion—both leading to an increased risk of coronary events (43). Structural alterations of large arteries are paralleled by cardiac

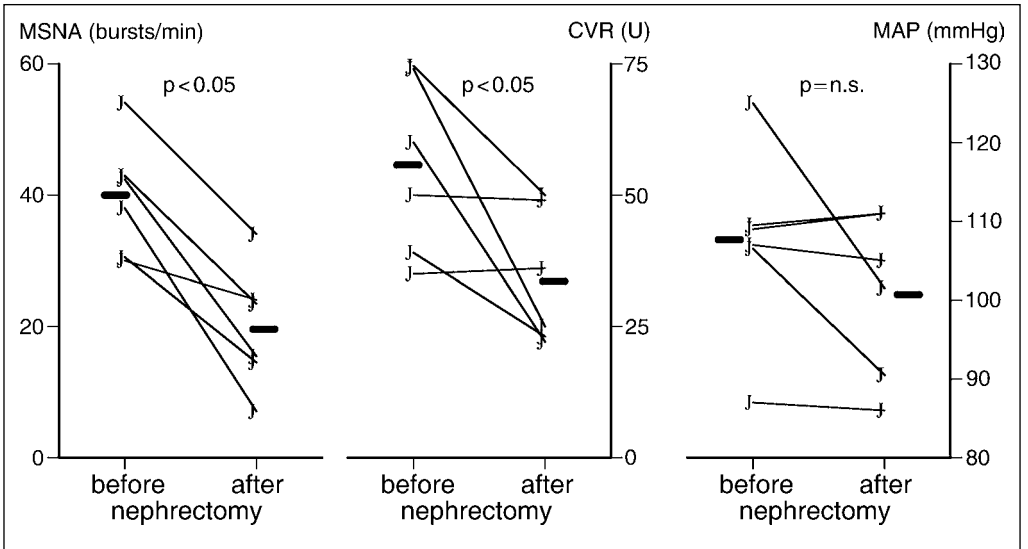

Fig. 37.1 Muscle sympathetic nerve activity (MSNA), calf vascular resistance (CVR), and mean arterial pressure (MAP) in six renal transplant recipients before and after native kidney nephrectomy. Horizontal bars indicate mean values. *Source*: From Ref. 48.

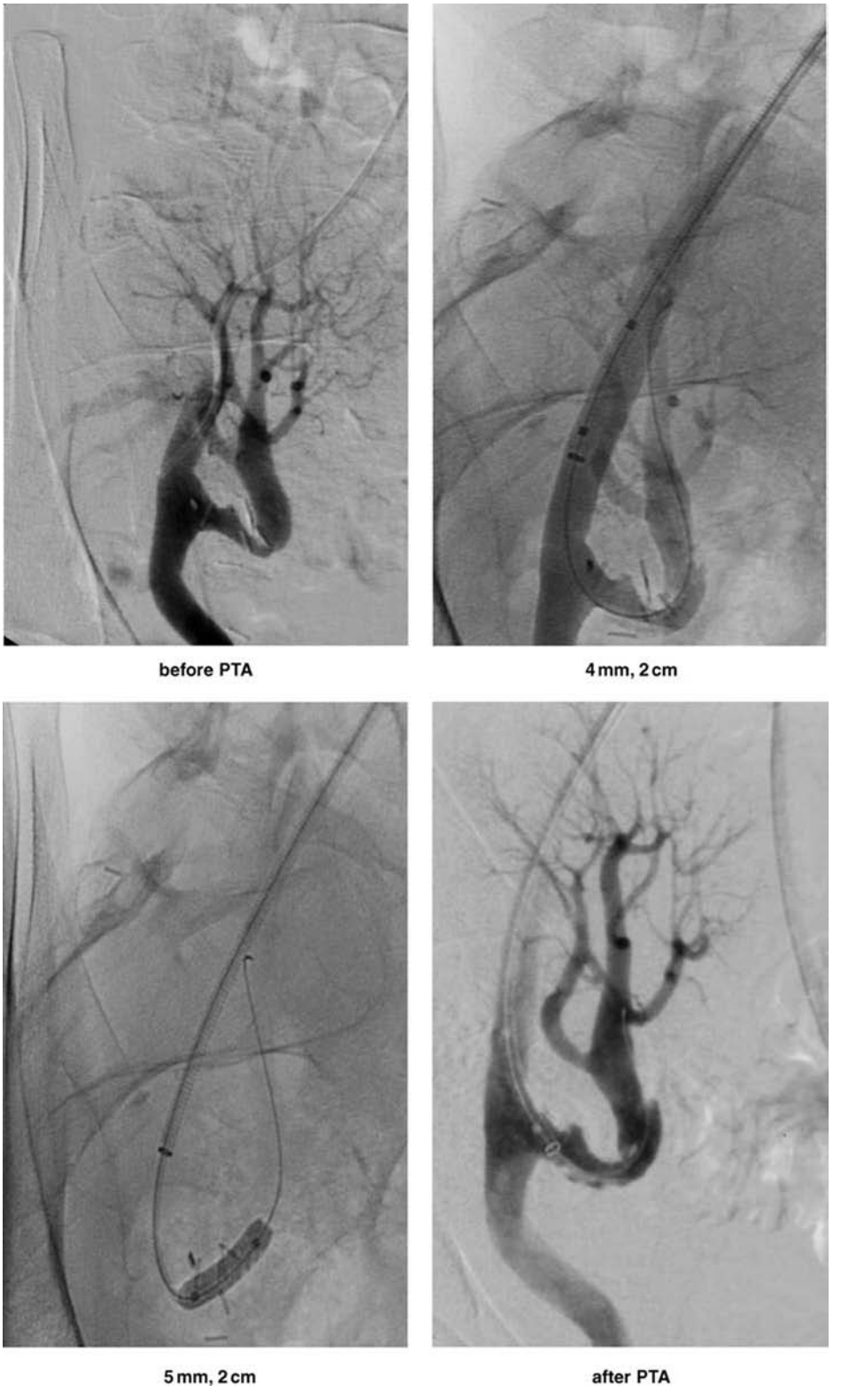

Fig. 37.2 Transplant renal artery stenosis in one patient leading to graft failure and severe hypertension. Graft failure resolved and hypertension improved after successful percutaneous transluminal angioplasty (PTA) with stenting.

hypertrophy (25). Indeed, London et al. could demonstrate that increased large artery stiffness is an independent predictor of cardiovascular and overall mortality in patients with end-stage renal disease (44). These issues are not resolved by successful kidney transplantation. McGregor and co-workers could show that echocardiographic abnormalities, i.e., left ventricular hypertrophy, at the time of kidney transplantation predict survival of allograft recipients (45). Our group

could show that left ventricular hypertrophy and structural alterations of large arteries persist after kidney transplantation despite effectively treated hypertension (24). Moreover, large artery stiffness measured during the first year after transplantation is an independent factor predicting subsequent cardiovascular morbidity in kidney transplant patients (46). Cardiovascular mortality in kidney transplant patients is approximately four times higher than observed in an age- and sex-matched general population and hypertension could be identified as major determinant of the excess mortality (42).

Hypertension is related to endothelial cell injury although endothelial damage in kidney transplant patients is multifactorial (23). Endothelial injury may be a link between hypertension and progressive graft dysfunction after kidney transplantation. In patients with chronic renal disease of diabetic and nondiabetic origin, hypertension is a major if not the most important factor determining the progression of renal failure. The same could be demonstrated in kidney transplantation—in animal models and in humans. Kidney transplant recipients, particularly those with already impaired graft function, often have an inadequate number of functionally intact nephrons (30). The consequences are hyperfiltration with excessive glomerular protein excretion and subsequent interstitial and glomerular inflammation and finally scarring which results in a further reduction of the number of functional nephrons. This vicious circle is accelerated by hypertension which increases glomerular filtration pressure and causes endothelial damage and therefore substantially contributes to enhanced filtration of macromolecules across the capillary barrier (47).

Opelz and co-workers (48) have published an impressive analysis where systolic BP 1-year after transplantation was strongly related to long-term graft survival (Figure 37.3), even when corrected for patients dying with a functioning graft. Importantly, the relation was stronger for systolic than for diastolic or mean arterial pressure. Since systolic BP is better related to functional and structural arterial damage than diastolic or mean BP (49), this suggests that arterial injury predicts kidney graft survival. From the correlation analysis no definite conclusions can be made whether hypertension is a marker or a cause of arterial injury and graft loss in kidney transplant patients. However, several observations suggest that hypertension is a cause of graft loss. First, the above cited relation between BP and graft survival was also observed in recipients of living related donors who had excellent human leukocyte antigen (HLA) matching and no rejection episodes, thus who were unlikely to have lost their grafts due to immunologic causes. Second, the outcome of vascular rejection episodes appears to be aggravated by hypertension (50). Third, animal models allow to separate the effects of immunologic factors and hypertension on graft damage and clearly identify hypertension as cause of kidney graft loss (51).

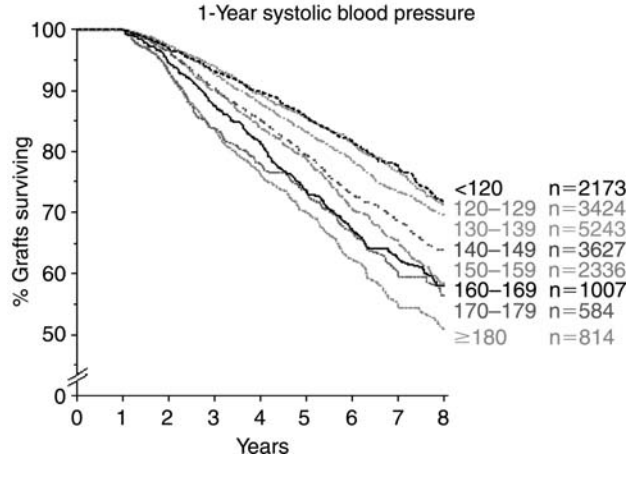

Fig. 37.3 Depicted is kidney graft survival as function of systolic blood pressure 1-year after transplantation. The analysis included only those patients with graft survival of at least 1-year and no rejection episode during the first year after transplantation. *Source*: From Ref. 38.

ANTIHYPERTENSIVE THERAPY IN KIDNEY TRANSPLANT RECIPIENTS

Early studies demonstrated the sodium-dependency of hypertension in kidney transplant recipients (11). This concept has proven true up to date. Diuretics are effective antihypertensive drugs after kidney transplantation and they are particularly useful in patients with impaired graft function (52). Also beta-blockers have been proven effective.

More than a decade ago, calcium channel blockers were recognized as very effective drugs for the treatment of hypertension in renal transplant patients. They combine vasodilating with natriuretic properties, lower BP substantially and counteract cyclosporine-induced hypoperfusion (53). Therefore, they could be expected to exert some nephroprotective action after renal transplantation. Rahn et al. (54) evaluated the effects of the calcium antagonist nitrendipine on graft function in renal transplant patients receiving cyclosporine during an observation period of 2 years. Indeed, they observed a protective effect of nitrendipine on graft function, which was independent of the BP lowering effect.

Initially, ACE inhibitors (ACEI) were only administered to a relatively small proportion of renal transplant patients and used with great caution. Indeed, several reports exist on acute renal failure in renal transplant recipients after administration of ACEI. In some cases, this was attributable to renal artery stenosis of the graft (55). Ahmad et al. observed serious impairment of graft function induced by captopril in renal transplant patients receiving cyclosporine, even in the absence of renal artery stenosis (56). Also Murray et al. observed enalapril-associated acute graft failure in cyclosporine-treated kidney transplant recipients (57). This phenomenon could be explained by additive adverse effects of cyclosporine and ACEI on glomerular hemodynamics with a subsequent substantial decrease in glomerular filtration pressure.

However, several recent trials could prove the effectiveness and safety of ACEI after kidney transplantation.

Several studies compared the effects of calcium channel blockers with those of ACEI in renal transplant patients. Mourad et al. (58), van der Schaaf et al. (59), Sennesael et al. (60), Curtis et al. (61), and Abu-Romeh et al. (62) compared the effects of an ACEI with those of a calcium antagonist in cyclosporine treated renal transplant patients. None of these studies showed adverse effects for the ACEI. Mourad et al., after a treatment period of 30 months, showed a similar degree of renal protection and reduction of arterial pressure

with lisinopril and nifedipine (58). Van der Schaaf et al. found amlodipine to have a more pronounced antihypertensive effects than lisinopril in renal allograft recipients (59). Glomerular filtration rate increased with amlodipine, whereas it remained unchanged during lisinopril treatment. In this cross-over study, patients were treated for 2 months with each drug. In a similar cross-over design, Sennesael et al. compared perindopril and amlodipine in 10 renal allograft recipients and found no significant differences in BP reduction or renal function (60). Curtis et al. (61) and Abu-Romeh et al. (62) both showed a slight decrease in glomerular filtration rate with the ACEI but not with the calcium antagonist. However, these two studies comprised only treatment periods of less than 1 month. Grekas et al. showed that combination therapy of a calcium antagonist with an ACEI in renal allograft recipients for 2 months results in superior BP control, reduction in proteinuria, and no significant change in glomerular filtration rate when compared to antihypertensive therapy with a calcium antagonist alone (63). Taken together, ACEI appear as effective as calcium antagonists with regards to BP reduction and preservation of graft function. The effects of the ACEI quinapril and those of the β-blocker atenolol on BP and graft function were compared in cyclosporine-treated hypertensive kidney transplant recipients (64). Quinapril and atenolol were equally effective in the treatment of posttransplant hypertension in renal allograft recipients. Renal transplant function did not differ between patients treated with quinapril and with atenolol. In neither group could a significant deterioration of renal allograft function be observed at the end of the 24 months treatment period. However, when compared to the changes in the atenolol group, quinapril treated renal allograft recipients showed a significant reduction of proteinuria and urinary albumin excretion at the end of the 24 months observation period (Figure 37.4).

From these studies it appears that ACEI are equally effective but apparently not better than other classes of antihypertensive drugs such as calcium channel blockers or β-blockers with regards to the preservation of allograft function in hypertensive kidney transplant patients. However, a major limitation of all these studies is a relatively short observation period. ACEI but not the other antihypertensive drugs unequivocally showed a reduction in proteinuria. Therefore, it is conceivable that, after a longer observation period, beneficial effects of ACEI—and possibly angiotensin receptor blockers (ARB)—as compared to other classes of antihypertensive drugs may appear with respect to graft function. In favor of this argues the following: first, a progressive decline in graft function was found to correlate with the amount of protein excreted in the urine (31,33). Hohage et al. observed a negative influence of even mild proteinuria (less than 1 g/day; Figure 37.5). on long-term graft survival in renal transplant patients (65). Second, Barnas et al. observed a beneficial effect of the ACEI lisinopril on graft function in those renal transplant patients with chronic allograft dysfunction in whom proteinuria decreased after initiation of ACEI treatment (66). Third, in many large studies on the effects of ACEI on the progression of chronic renal disease, reduction of proteinuria precedes

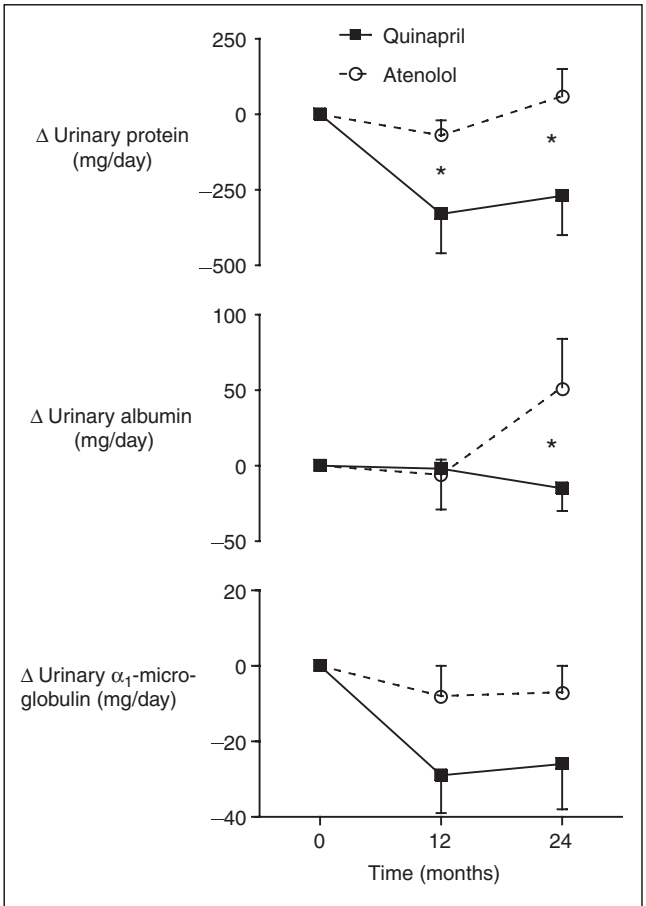

Fig. 37.4 Changes in urinary total protein, albumin, and α_1-microglobulin excretion in hypertensive renal transplant patients treated with quinapril or atenolol. $*p < .05$ for trend, group *x* time interaction. *Source*: From Ref. 64.

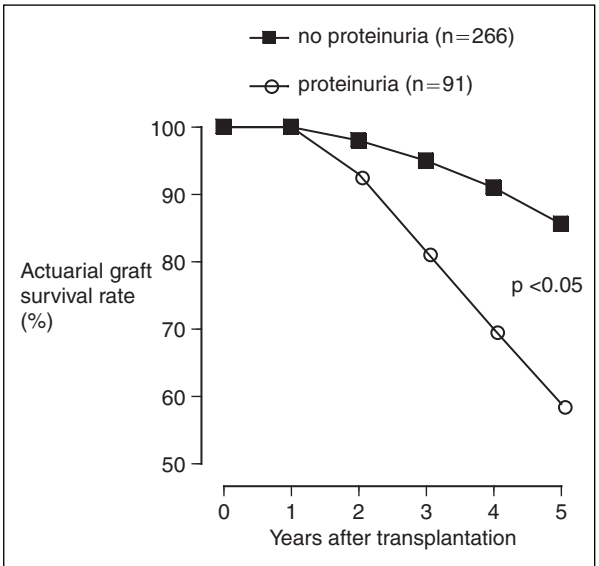

Fig. 37.5 The graph shows actuarial graft survival in renal transplant patients with a functional graft for at least 12 months after transplantation and normal urinary protein excretion, and in renal transplant patients who had a functional graft for at least 12 months after transplantation and developed proteinuria (0.25–1 g/d) within the first year, persisting over a period of 6 months or more. *Source*: Modified from Ref. 65.

and consistently correlates with the nephroprotective effect (67,68). Reduction of proteinuria was observed early, a significant benefit of ACEI on the course of renal function often appeared only after 2 years of treatment. This is consistent with the idea that excessive glomerular protein filtration leads to increased reabsorbtion in the proximal tubulus with subsequent perinuclear organelle overload and upregulation of vasoactive and inflammatory genes. These processes contribute to tubulo-interstitial injury and scarring (69). Genetic variants of the renin–angiotensin system in renal transplant recipients may contribute to the rate of progression of chronic graft nephropathy (70).

Fourth, two recent retrospective studies suggest a beneficial effect of ACEI and ARB on graft survival in renal transplant recipients. Heinze and co-workers observed a 10-year graft survival rate of 59% in ACEI/ARB users versus 41% in nonusers ($p < .001$) (71). However, functional graft survival (adjusted for death with functioning graft) did not differ between groups in that study. We observed significantly increased functional graft survival in renal transplant patients receiving long-term treatment (>2 years) with ACEI or ARB, particularly when combined with calcium antagonists (72).

When considering specific advantages of individual classes of antihypertensive drugs it has to be considered that hypertension in kidney transplant recipients is generally severe, especially when calcineurin inhibitors are used. Combination of multiple antihypertensive drugs is required for adequate BP control, e.g., combination of a diuretic, a calcium antagonist, and an ACEI or beta blocker.

Studies investigating calcineurin inhibitor withdrawal after kidney transplantation are on the way. Recent reports clearly demonstrate a pronounced decrease in BP after discontinuation of calcineurin inhibitors (73,74). However, the long-term effects of calcineurin inhibitor withdrawal on graft survival still need to be clarified.

CONCLUSIONS

Hypertension is common in solid organ transplant recipients, especially with the use of modern immunosuppressive drugs such as cyclosporine. In kidney transplant recipients, hypertension is of major prognostic relevance for graft survival but also for the incidence of cardiovascular events. Also, in non-renal solid organ transplant recipients, hypertension emerges as significant prognostic factor. Effective antihypertensive therapy is mandatory and possible by combination of different classes of antihypertensive drugs.

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HYPERTENSION IN PATIENTS WITH RENAL PARENCHYMAL DISEASE, CHRONIC RENAL FAILURE, AND CHRONIC DIALYSIS

38

José L Rodicio

HYPERTENSION IN PATIENTS WITH RENAL PARENCHYMAL DISEASE AND CHRONIC RENAL FAILURE

Renal parenchymal disease is the most frequent form of secondary hypertension. It is calculated that it occurs in 5% of all the cases of arterial hypertension. In the United States, 3% of the adult populations have elevated creatinine and 70% of these patients have hypertension (1). Prevalence of hypertension in chronic kidney disease depends on the patient's age, severity of renal failure, proteinuria, and underlying renal disease (2). Table 38.1 shows the most frequent renal parenchymal diseases associated with hypertension and Table 38.2 the prevalence of hypertension in different renal diseases.

MECHANISMS OF HYPERTENSION IN RENAL PARENCHYMAL DISEASE AND CHRONIC RENAL FAILURE

The mechanisms by which hypertension is produced in renal parenchymal disease, especially when the grade of renal failure increases, are expressed in Figure 38.1.

SODIUM AND WATER RETENTION

Sodium and water retention play a fundamental role in the development of hypertension as it is difficult for the kidney to eliminate them, giving rise to an increase of exchangeable sodium (3), to increased sodium in the vascular wall (4), and to an expansion of extracellular volume, mainly intravascular, with an increase in cardiac output volume. The consequence is volume-dependent arterial hypertension. It has been demonstrated that salt restriction in the diet of elderly patients with systolic hypertension increases large artery compliance and reduces blood pressure (BP) (5).

RENIN–ANGIOTENSIN SYSTEM

There are other factors that regulate BP in renal failure, such as the renin–angiotensin–aldosterone system, which is stimulated especially in patients with mild or moderate chronic renal failure. These produce hemodynamic actions, such as vasoconstriction, activation of the sympathetic nervous system, as well as nonhemodynamic actions, such as the activation of endothelial cells, mesangial cells, and the production of inflammation and fibrosis. The outcome of this effect of angiotensin II is progressive renal damage and hypertension (6).

SYMPATHETIC NERVOUS SYSTEM

The sympathetic nervous system significantly contributes to hypertension in renal failure, producing an increase in cardiac output volume and peripheral resistances. An increase of norepinephrine in plasma with a decrease in the pressor response to its infusion has been demonstrated in these patients (7). Baroreceptor desensitization is another cause that contributes to hypertension in patients with end-stage renal disease (ESRD) (8).

ENDOTHELIUM

The endothelium also plays an important role in the development of hypertension through the release of vasodilator and vasoconstrictor substances. The principal vasodilator substance is nitric oxide (NO). This, as is known, acts by regulating vascular tone, leukocyte adhesion, platelet aggregation, and proliferation of the vascular smooth muscle. NO has its origin in arginine and produces cyclic guanosine monophosphate (cGMP) through guanylate cyclase, which activates the potassium channels (9). Asymmetrical dimethylarginine (ADMA), which is increased in patients with renal failure (10), is an inhibitor of NO. This, therefore, reduces the vasodilator capacity of this substance.

Secretion of prostaglandins and kinins has been found to be normal, high, or low in renal failure according to the data of different authors, although the administration of nonsteroid

Table 38.1 Causes of hypertension in renal parenchymal disease

Idiopathic diseases
Glomerulonephritis
Interstitial nephropathy
Diseases with unilateral injuries
Reflux nephropathy
Unilateral pyelonephritis
Hydronephrosis
Renin-secreting tumor
Adenocarcinoma
Systemic diseases
Diabetes
Lupus erythematosus
Polyarteritis nodosa
Wegener disease
Scleroderma
Hemolytic uremic syndrome
Multiple myeloma
Cryoglobulinemia
Hereditary diseases
Polycystic kidney disease
Metabolic disease
Metabolic syndrome

anti-inflammatory drugs produces an increase in BP, a decrease of the glomerular filtration rate (GFR) and a reduction of urinary prostaglandins (11).

Endothelin and thromboxane are found among the vasoconstrictor agents. They also produce an increase in platelet aggregation and vascular contraction, these having been found to be elevated in chronic renal failure (12).

ATRIAL NATRIURETIC PEPTIDE

Atrial natriuretic peptide (ANP) is elevated in renal failure (13). It increases its production with extracellular volume expansion and reduces it with its contraction.

OTHER HYPERTENSIVE MECHANISMS

Administration of erythropoietin (EPO) in patients with renal failure and anemia is a common practice before and after entering into a dialysis program. EPO may cause hypertension in 20% of the patients. This was first attributed to an increase of hematocrit and blood viscosity (14), but it was later shown that it was due to an increase in platelet cytosolic calcium (15).

DIABETIC NEPHROPATHY

Special mention should be made to hypertension in type 1 or type 2 diabetic nephropathy, since it is the most common cause of entry into the dialysis and transplant programs both in the United States and in Europe. Type 1 diabetes has familial involvement, it having been demonstrated that insertion/deletion polymorphism in the ACE/ID gene of the converting enzyme seems to protect against nephropathy and cardiovascular morbidity (16), while polymorphism M235T of the angiotensinogen gene is more common in type 1 diabetic patients who develop nephropathy. The renal injury mechanism in diabetes appears to be related with cytokines, especially with the transforming growth factor β1 (TGFβ1) (17).

Table 38.2 Prevalence of hypertension in renal parenchymal disease

Focal glomerulosclerosis	75–85%
Diabetic nephropathy	65–75%
Membranoproliferative glomerulonephritis	60–70%
Membranous nephropathy	35–45%
Mesangioproliferative glomerulonephritis	30–40%
IgA nephropathy	20–30%
Minimal changes disease	10–15%
Polycystic kidney disease	55–65%
Chronic interstitial nephritis	15–25%

Control of hyperglycemia and BP is necessary to reduce nephropathy progression rate. This subject is treated more extensively in Chapter 34.

STUDIES TO DIAGNOSE RENAL PARENCHYMAL DISEASE AND CHRONIC RENAL FAILURE

The symptoms of hypertension in renal failure vary greatly according to the cause of the insufficiency itself. In glomerular processes, a change is observed in the color of the urine and in the presence of edema and high BP. There are also skin disorders, lymphatic vessels, and other organ damage in the

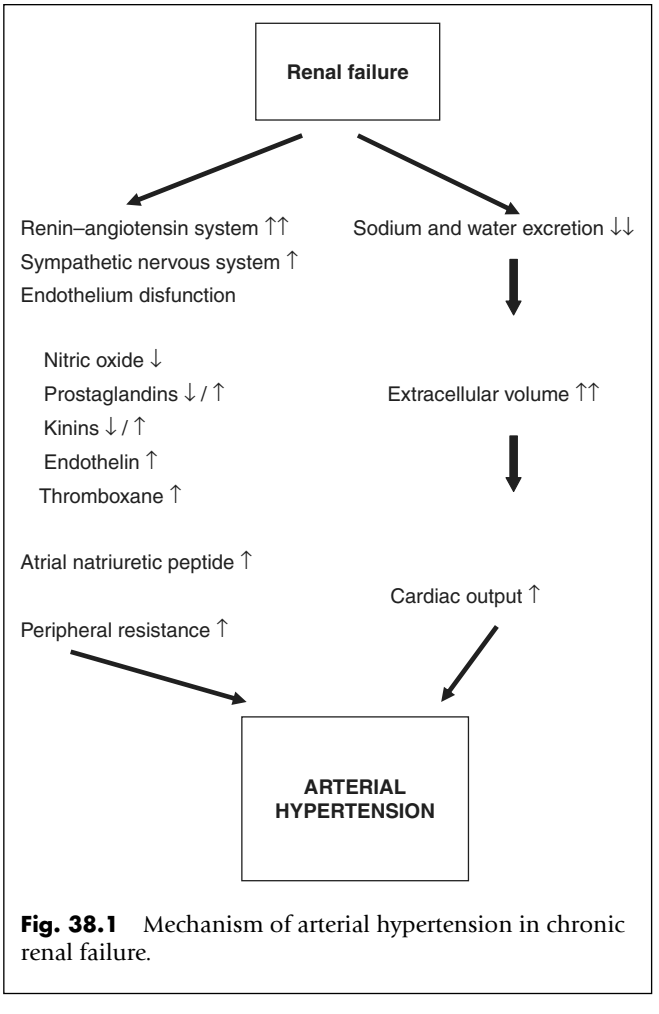

Fig. 38.1 Mechanism of arterial hypertension in chronic renal failure.

systemic conditions. The existence of burning, frequency, suprapubic pain, and nocturia in interstitial nephropathies is very frequent, especially if accompanied by urinary infection. The presence of an abdomen increased in size, with a sensation of fullness, may indicate the existence of polycystic kidneys.

Those studies needed to diagnose arterial hypertension in chronic renal failure are listed in Table 38.3 where three sections are clearly differentiated: clinical history of renal disease, physical examination, and the complementary studies of renal function, sediment, blood sample determinations, and renal morphology.

Besides measuring BP in the office and at home, 24-h ambulatory BP monitoring should be done. It has been demonstrated that patients whose nighttime BP does not decrease (nondippers) have a worse prognosis in regards to morbidity and mortality and to the progression of chronic renal failure (18,19).

TREATMENT OF HYPERTENSION IN CHRONIC RENAL FAILURE

Arterial hypertension in chronic renal failure is a serious complication that may lead to ESRD in a short period of time. For this reason, both the Joint National Committee number seven (20) and the Guidelines of the European Society of Hypertension and Cardiology (21) recommend reducing BP below 130/80 mmHg in all patients with renal failure and 125/75 mmHg if there is also proteinuria superior to 1 g/24 h.

NONPHARMACOLOGICAL

The nonpharmacological treatment of arterial hypertension in patients with chronic renal failure (22) is similar to that of other types of hypertension although this must be stricter, reducing sodium intake in the diet to less than 60 mmol/day and water to an amount similar to that of daily diuresis. Calories intake should be adapted to the needs of each patient and should never be less than 35 calories/kg/day, with carbohydrates around 50–60% and saturated fats between 30% and 40% of the total calories, as long as the triglycerides are not elevated.

Protein intake should be reduced in accordance with renal function. When the GFR is above 50 ml/min, 1 g of proteins/kg of weight/day is recommended. When GFR is between 20 and 50 ml/min, 0.8 g/kg/day and if the GFR is below 15 ml/min, 0.50 g/kg/day are recommended.

Phosphorous intake should not exceed 750 mg/day, reducing milk, cheese, and protein intakes. Hyperkalemia is an

Table 38.3 The following studies are required to appropriate diagnosis of arterial hypertension in renal parenchymal disease and chronic renal failure

Clinical history
Family background of renal disease (polycystic kidney, Alport and Fabry disease)
Date of diagnosis of hypertension
Background of diabetes mellitus
Symptoms of hematuria, edema, lithiasis
Symptoms of peripheral arteriopathy, ischemic heart disease, cerebrovascular accident
Chronic administration of analgesics, NSAIDs
Physical examination
Blood pressure, weight, and height
Neck palpation and auscultation of both carotids
Pulmonary, cardiac auscultation
Abdomen: abdominal masses, bruits
Limbs: pulse palpation, edema
Eye fundus: retinopathy degree
Complementary examinations
Renal function
Determination of serum creatinine, cystatine C, creatinine clearance, MDRD, or Cocroft–Gault formulas
Urine: quantification of proteins; micro- or macroalbuminuria; protein/creatinine ratio
Urine sediment, microhematuria, casts
Renal morphology: renal ultrasonography
Renal morphology and function: urography scintigraphy and isotopic renal flow
Blood sample determinations: hemoglobin, leukocytes, platelet, sugar, lipids, uric acid, calcium, phosphorus, transaminases, ionogram, acid–base
Systemic and viral disease with renal involvement markers
Complement
Cryoglobulinemias
ANA anti-DNA
Immunoglobulins
ANCAs
Viral B and C and HIV serology
Renal vascularization: scintigraphy, renal arteriography
Renal histological study: renal biopsy

Abbreviations: ANA, antinuclear antibody; ANCAs, antineutrophil cytoplasmic antibodies; MDRD, modification of diet in renal disease; NSAIDs, non-steroidal anti-inflammatory drugs.

important complication in chronic renal failure so that intake of fruits, juices, nuts, and vegetables should be restricted.

Weight loss, exercise, and elimination of alcohol and tobacco consumption are other measures to take into account.

PHARMACOLOGICAL

The drugs used most in renal failure are included in this chapter. However, their effect and progression are dealt with in Chapter 27.

In principle, any medication that controls BP protects the kidney, but there are some drugs that are used more. The principal drugs used in the treatment of arterial hypertension of patients with chronic renal failure and in the dialysis program are shown in Table 38.4. Excretion pathway, dosage according to renal function and supplement in dialysis program of the different drugs are provided. When there is glomerular injury, angiotensin-converting enzyme inhibitors (ACEI) (23) and angiotensin II receptor blockers (ARB) (24) are those used most in both diabetic and nondiabetic patients due to their action on the efferent arteriole vasodilatation which reduce intraglomerular pressure and for their effect on mesangial receptors reducing the fibrotic process. Special care should be taken when associating them with distal diuretics or eplerenone (25) especially when there is significant renal failure due to danger of hyperkalemia. These drugs are indicated in diabetic patients because they do not modify glycemia, they improve sensitivity to insulin and they reduce the risk of developing micro- or macrovascular complications. ACEI doses should be reduced in significant renal failure (GFR $<$15 ml/min) but this is not necessary in the ARBs.

The side effects of ACEI are well-known: hyperkalemia, cough, bronchospasm, angioedema, anaphylasis, loss of taste, deterioration of renal function, and leukopenia. ARBs are better-tolerated drugs without the side effects attributed to an excess of bradykinin from the ACEI. However, they may cause also hyperkalemia and deterioration of renal function. Both drugs have fetal toxicity and are contraindicated during pregnancy.

The effects of the calcium antagonists on the glomerulus cause vasodilation of the afferent arteriole with the danger of increasing intraglomerular pressure and proteinuria if the systemic BP is not well controlled. Diltiazem and verapamil seem to have a greater kidney protector role than dihydropyridines (26), although manidipine has been the drug that has demonstrated the greatest reduction of proteinuria due to its dilator effect on both the afferent and efferent arterioles (27). In addition to the good control of systemic BP, calcium antagonists have natriuretic properties. Therefore, they are good drugs to be associated to renin–angiotensin system inhibitors in these types of patients who retain water and sodium, especially in diabetic patients.

The most important side effects of calcium antagonists are: local ankle edema, headaches, tachycardia, palpitations, flushing, and gingival hyperplasia. Constipation and bradycardia have been described with verapamil. In the past, more serious complications were attributed, such as bleeding, cancer, and myocardial infarction, which has not been confirmed in recent studies.

Diuretics are widely used medications in these types of patients, since they are characterized by water and sodium retention. When the GFR is greater than 50 ml/min, thiazide diuretics alone or associated to distal diuretics such as amiloride, triamterene, and spironolactone can be administered. However, when filtration is less than 30 ml/min, loop diuretics such as furosemide, bumetadine, or torasemide should be administered. Furthermore, distal diuretics are contraindicated due to the danger of hyperkalemia (28).

The side effects of thiazide and loop diuretics are: hypokalemia, hyperuricemia, dyslipidemia, glucose intolerance, insulin resistance, hyponatremia, hypomagnesemia, and impotence. Distal diuretics may cause hyperkalemia, skin rash, and spironolactone-induced gynecomastia.

Beta-blockers can be administered for their effect on the reduction of nervous system stimulus but may become accumulated in advanced phases of renal failure, so that the dose must be reduced. They should not be administered in combination with other drugs that cause bradycardia (verapamil, diltiazem, digoxin) or used in diabetic patients as they inhibit hypoglycemia signs (tremor, tachycardia) and increase blood glucose levels (29). They should be used with caution in patients with peripheral vascular disease.

Side effects of beta-blockers are: bradycardia, asthenia, dyslipidemia, glucose intolerance, impotence, and hyperkalemia.

Alpha-blockers (30) are also used in renal failure not only due to their vasodilator properties but also due to their antiproliferative, platelet antiaggregant, and antiatherogenic effect. They are indicated in benign prostatic hypertrophy due to their capacity to relax the smooth muscle of the bladder neck and proximal urethra.

Side effects of the alpha-blockers are hypotension with the first dose and orthostatic hypotension, headache, mouth dryness, fatigue, and weakness. These effects have been reduced with the new galenic formulations.

Central action drugs as clonidine or guanfacine have also been used, although they are not used nowadays.

Drug associations of two, three, or even more drugs are the rule in kidney patients, especially in diabetics. The most frequent combination used is ACEI or ARB with thiazides or loop diuretics. If this is not sufficient, a calcium antagonist or beta-blocker would be added.

The association of an ACEI or ARB with a calcium antagonist in diabetic patients has provided good results (31) and that of an ACEI with an ARB has produced the maximum decrease of proteinuria with improvement of the kidney function (32).

HYPERTENSION IN CHRONIC DIALYSIS PATIENTS

When the patients reach ESRD, the treatment possibilities are dialysis and kidney transplant. These two options are not self-exclusive, but rather complementary. Dialysis may be hemodialysis or peritoneal dialysis, the first being more frequent in most of the countries except for the United Kingdom, Canada, and Australia.

Prevalence of hypertension in patients on hemodialysis, according to a recent study (33), is 86%, 70% of whom were not controlled. In peritoneal dialysis, where the extracellular volume is better regulated, there should be better control of BP. However, in the long term there is no difference with hemodialysis, especially when the function of the native kidneys is lost (34).

Most of the patients have systolic arterial hypertension and increased pulse pressure as a consequence of the arterial wall stiffness due to atherosclerosis (35). Presence of both these parameters is a cardiovascular mortality risk factor.

Table 38.4 Antihypertensive drugs, excretion pathway, dosage, and supplement in chronic renal disease and chronic dialysis

	Excretion pathway	Dosage mg/day	Reduce dosage when GFR <15 ml/min	Supplement for dialysis
Angiotensin-converting enzyme inhibitors				
Benazepril	K (L)	10–40	50%	25–30%
Captopril	K	25–150	25–50%	25–30%
Enalapril	K (L)	5–40	50%	20–25%
Fosinopril	K–L	10–40	75%	None
Lisinopril	K	5–40	25%	20%
Perindopril	K (L)	2–8	25–50%	None
Quinapril	K (L)	5–80	25–50%	25%
Ramipril	K (L)	1.25–10	25–50%	20%
Trandolapril	K (L)	0.5–4	25–50%	20%
Angiotensin II receptor blockers				
Losartan	K (L)	25–100	100%	None
Ibersartan	L	75–300	100%	None
Candesartan	K (L)	8–32	100%	None
Eprosartan	L	600–1200	100%	None
Olmesartan	K (L)	10–40	100%	None
Telmisartan	L	40–80	100%	None
Valsartan	L (K)	80–320	75%	None
Calcium antagonists				
Amlodipine	L	2.5–10	100%	None
Nifedipine	L	30–90	100%	None
Felodipine	L	2.5–20	100%	None
Lacidipine	L (K)	2–6	100%	None
Nicardinipine	L	60–120	100%	None
Nisoldipìne	K (L)	10–40	100%	None
Nitrendipine	L (K)	10–40	100%	None
Manidipine	L	10–20	100%	None
Diltiazem	L (K)	120–360	100%	None
Verapamil	L	120–480	100%	None
Beta–blockers				
Atenolol	K (L)	25–100	30–50%	25–50 mg
Propranolol	K	40–320	100%	None
Metoprolol	K (L)	50–200	100%	50 mg
Carvedilol	K (L)	12.5–25	100%	None
Alpha blockers				
Doxazosin	L	1–16	100%	None
Prazosin	L	1–15	100%	None
Direct vasodilators				
Minoxidil	L	2.5–40	100%	None
Hidralazine	L	50–300	Prolonged effect	None
Diuretics				
Thiazides	K	12.5–50	Avoid	Not applicable
Indapamide	K	1.25–2.5	Avoid	None
Furosemide	K (L)	40–240	100%	None
Torsemide	L (K)	2.5–20	100%	None
Amiloride	K	2.5–5	Avoid	Not applicable
Triamterene	K	25–100	Avoid	Not applicable
Spironolactone	K (L)	25–100	Avoid	Not applicable

Abbreviations: GFR, glomerular filtration rate; K, kidney; L, liver.

BP measurement should be done pre- and postdialysis with the usual clinical apparatuses and 24-h ambulatory monitoring should be used in the cases where it is suspected that pressure control is not good and the patient is nondipper, as occurs in half of the patients.

MECHANISM OF HYPERTENSION IN CHRONIC DIALYSIS

Hypertension mechanisms in patients on dialysis are very similar to those described in chronic renal failure. Without

any doubt, water and sodium retention, with the consequent increase of extracellular and vascular volume, is the most frequent cause. Thus, the first step to be taken is to eliminate fluid retention and to get the patient down to his/her dry weight; the weight below which the patient has hypotension or muscle cramps. This can be done by increasing the number of hours of dialysis or number of days, especially if daily nighttime dialysis is done (36), reducing sodium concentration in dialysis liquid below 140 mEq/l.

The renin–angiotensin system and sympathetic nervous system are stimulated in these patients. The norepinephrine levels are high when they are measured and there is a correlation with dialysis mortality (37). One recent discovery that may explain the mechanism of sympathetic activation in renal failure is the identification of the protein renalase (38), a novel soluble monoamine oxidase that is produced in the kidney, skeletal muscle, and heart. This protein is able to degrade dopamine, norepinephrine, and epinephrine. In hemodialysis patients, renalase is clearly reduced. EPO administration, very frequent in these patients, is another cause of arterial hypertension. Other pathophysiological mechanisms are similar to those explained in renal parenchymal disease and chronic renal failure.

TREATMENT OF HYPERTENSION IN CHRONIC DIALYSIS

NONPHARMACOLOGICAL

Nonpharmacological treatment of patients in a chronic dialysis program is very similar to that of chronic renal failure. Water and sodium restriction should be maintained, adapting this to changes of dry weight between dialysis. Protein intake should be approximately 1 g/kg/day, controlling the uremia grade.

PHARMACOLOGICAL

The number and efficacy of antihypertensive drugs presently available have ruled out the use of bilateral nephrectomy for the control of BP in patients on hemodialysis as occurred years ago.

According to most of the works published in the literature, the group of drugs used most are calcium antagonists (71.8%), followed by ACEI/ARB (31.6%), and beta-blockers (25.4%) (39). It is best to administer them at night due to the frequency of nondipper patients and with long-term formulations. Table 38.4 shows the supplement on the different medications needed to be administered to patients in the dialysis program.

Calcium antagonists, both dihydropyridines and nondihydrophines, reduce cardiovascular mortality and decrease intracellular calcium levels, including those produced by secondary hyperparathyroidism in ESRD (40). These drugs are not removed from the blood through the dialysis membrane, and the pharmacokinetics does not change so that it is not necessary to adjust the doses.

ACEI and ARB are also used in the treatment of hypertension in hemodialysis, reducing left ventricle hypertrophy, and the control of BP is similar to that of other antihypertensive drugs. They also reduce cardiovascular mortality and may produce hyperkalemia as well as increase anemia on decreasing the production of endogenous EPO, although not all the authors agree with this effect (41). Anaphylactic reactions have been described due to release of bradykinins in those patients treated with ACEI and using AN69 dialytic membrane. ACEI dose should be supplemented between 20% and 30% while it is not necessary in the ARB. Lisinopril and quinapril can be administered 3 times weekly after dialysis.

Beta-blockers seem to be medications indicated in dialysis patients due to the significant increase of the sympathetic nervous system activity in these types of patients, however they are scarcely used. Nonselective beta-blockers cause an increase of hyperkalemia (42), something that does not occur with the B1 selective beta-blockers. Treatment with beta-blockers reduces cardiovascular mortality and produces secondary prevention of coronary disease. Administration of a dosage of some drugs, such as atenolol with a prolonged half-life has been recommended 3 times a week postdialysis.

Alpha-blockers and direct vasodilators, such as hydralazine and minoxidyl (43), are used in hemodialysis patients resistant to the other medications, and it is not necessary to adjust the doses, except for hydralazine, which has a prolonged effect.

Loop diuretics, furosemide, bumetadine, and torasemide, are only indicated in patients in hemodialysis programs when the residual diuresis is greater than 300 ml in 24 h, because, if not, the response is very poor. Loop diuretics not only increase water and electrolyte excretion by the kidney but also dilate the capacitance vessels (44). In any case, usage time of diuretics in dialysis is short because residual kidney function decreases rapidly.

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HYPERTENSION AND THE METABOLIC SYNDROME 39

Josep Redon

INTRODUCTION

Arterial hypertension is often part of a larger constellation of anthropometric and metabolic abnormalities that includes abdominal (or visceral) obesity, characteristic dyslipidemia [low high-density lipoprotein (HDL) cholesterol and high triglycerides], glucose intolerance, insulin resistance (IR), and hyperuricemia. These features occur simultaneously to a higher degree than would be expected by chance alone, supporting the existence of a discrete disorder, the so-called metabolic syndrome (MS). The MS is currently considered to be a cluster of metabolic and cardiovascular risk factors that confer an increased risk of cardiovascular events attributed to, in part, the individual risk factors that concur in defining it, and in part to a cluster of other factors, such as the proinflammatory state, impaired fibrinolysis, and oxidative stress that usually goes along with it.

The existence of such a clustering of blood pressure (BP) elevation, diabetes, obesity, and other metabolic abnormalities was already recognized in the 1920s (1,2), and the concept was highlighted by Reaven in his Banting lecture at the American Diabetes Association Annual Meeting in 1988 (3). Reaven pointed out that IR was the central component of a cluster of metabolic abnormalities that did not necessarily include classical risk factors such as raised LDL-cholesterol, but rather was comprised of elevated triglyceride concentrations, low HDL-cholesterol, fasting hyperinsulinemia, and elevated BP.

Although the clinical significance and utility of diagnosing MS in an individual have been recently challenged (4,5) since it seems to confer a higher cardiovascular risk on top of the risk induced by BP elevation. Nevertheless, the assessment of MS components may have clinical utility in an individual, risk-based strategy to manage hypertension. Considering that MS is highly prevalent among hypertensive populations, the impact of a diagnosis of MS is of interest, therefore, in terms of risk stratification and management.

DEFINITION

There is no internationally accepted definition for the MS. Since the description by Reaven, many names and definitions have been given to various clusters of cardiovascular risk factors. The most commonly used names are MS and the insulin-resistance syndrome or Reaven's syndrome; however, other names include metabolic dyslipidemia, MS X, the deadly quartet (upper body obesity, glucose intolerance, hypertriglyceridemia, and hypertension), and civilization syndrome.

The MS has been defined by several scientific organizations: World Health Organization (WHO) (6), European Group of Insulin Resistance (EGIR) (7), Adult Treatment Panel (ATP III) (8), International Diabetes Federation (IDF) (9), and American Heart Association (AHA) (10). The different definitions are summarized in Table 39.1. Two of them, those of WHO and of EGIR, were based on carbohydrate metabolism abnormalities, while the remaining were based on abdominal obesity. The diagnosis of MS is based on the presence of a principal criterion plus at least two other criteria or in those without a principal one but at least three criteria.

In children and adolescents, the criteria used to assess the MS are slightly modified compared to those used in adults. Instead of waist, body mass index (BMI) is the anthropometric parameter recommended (11). As impaired fasting glucose (levels above 100 mg/dL (5.6 mmol/L)) is rare in childhood, the impaired glucose tolerance test is used as a criterion in diagnosing MS. BP and fasting lipid levels are compared for population limits adjusted for age and sex.

PREVALENCE

Comparisons of published prevalence data for different populations are difficult to make, despite attempts to reach agreement on the definition of MS. The studies often differ with respect to study design, sample selection, the year the study was conducted, the precise definition of MS used, and the age and sex structure of the population itself. Among essential hypertensives, prevalence is higher than in the general population (12–15), and MS can be found in as many as one third of the patients (16–18). Prevalence of MS among hypertensives varies with age and whether subjects were selected from primary care or from referral clinics. The older the subjects, the higher the prevalence; likewise, prevalence is higher in subjects from referral clinics as compared to those coming from primary care. A higher prevalence of MS among uncontrolled hypertensives as compared to subjects with their BP under control has also been described (12). It may reflect a greater

Table 39.1 Criteria for diagnosing the metabolic syndrome according the different scientific organisms: WHO, EGIR, ATP III, IDF, AHA

	Principal criteria	Abdominal obesity	Glucose mg/dL	HDL mg/dL	Triglic mg/dL	BP mmHg
WHO (6)	DM, GI, or IR	BMI ≥ 30 kg/m^2 M ≥ 90 cm W ≥ 85 cm		M ≤ 35 W ≤ 39	≥150	≥140/90[a]
EGIR (7)	IR or FI >P75	BMI ≥ 30 kg/m^2 M ≥ 102 cm W ≥ 88 cm	≥110[a]	40	≥180	≥140/90[a]
ATPIII (8)		M ≥ 102 cm W ≥ 88 cm	≥110[a]	M ≤ 40 W ≤ 50	≥150	≥135/85[a]
IDF (9)	Central obesity	M ≥ 94 cm W ≥ 80 cm	≥100[a]	M ≤ 40 W ≤ 50[a]	≥150[a]	≥135/85[a]
AHA (10)		M ≥ 94 cm W ≥ 80 cm	≥100[a]	M ≤ 40 W ≤ 50[a]	≥150[a]	≥135/85[a]

[a]Or currently in treatment for.
Diagnosis of metabolic syndrome is based on: (*i*) principal criteria plus at least two other; (*ii*) in those without principal criteria, at least three. WHO and EGIR denote the definitions based on carbohydrate metabolism abnormalities. ATPIII, IDF, and AHA are based on abdominal obesity.
Abbreviations: AHA, American Heart Association; ATP III, Adult Treatment Panel; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; EGIR, European Group of Insulin Resistance; FI, fasting insulin; GI, glucosa intolerance; HDL, high-density lipoprotein; IDF, International Diabetes Federation; IR, insulin resistance; M, men; W, women; WHO, World Health Organization.

degree of difficulty in the control of BP in subjects with a cluster of cardiovascular risk factors and/or higher degrees of end-organ damage.

MECHANISMS OF THE METABOLIC SYNDROME

The MS is the result of interactions among a large number of interconnected mechanisms, which eventually lead to both an increase in cardiovascular and renal risk, and the development of diabetes. The close relationships among the different components of the syndrome and their associated disturbances make it difficult to understand what the underlying causes and consequences are. Each organ or cell type is typically both a target and an effector. In general, this situation has been defined by Unger as "a failure of the system of intracellular lipid homeostasis which prevents lipotoxicity in organs of overnourished individuals" (19).

Mechanisms involved in MS are obesity, IR, and a constellation of independent factors, which include molecules of hepatic, vascular, and immunologic origin with proinflammatory properties. Although IR is associated with obesity and central adipose tissue, not all obese subjects have IR. Skeletal muscle and the liver, not adipose tissue, are the two key insulin-response tissues involved in maintaining glucose balance, although abnormal insulin action in the adipocytes also plays a role in development of the syndrome.

At each of these key points, IR and obesity/proinflammatory molecules, are interactions of demographics, lifestyle, genetic factors, and environmental fetal programming. Superimposing upon these are infections and/or the chronic exposure to certain drugs, which can also make their contribution. All interact to create the final individual phenotype (Figure 39.1) (20–23).

OBESITY AND ADIPOSE TISSUE CYTOKINES

Abnormalities in the structure and function of adipose tissue, mainly in visceral fat, have been identified as early events which preclude the development of the other features of MS, including impaired glucose homeostasis (24). The first structural event, which follows from fat tissue increase, is the infiltration of adipose tissue by bone marrow-derived macrophages in response to as-yet-unknown signals (25,26). This is both a paracrine regulator of adipocyte function influencing free fatty acid (FFA) liberation and hormone secretion of leptin and adiponectin, as well as a source of the inflammatory mediators interleukin (IL)-6 and tumor necrosis factor (TNF)-α released by adipose tissue.

Besides the structural changes, various functional abnormalities of adipose tissue-derived products have been described. These include an increase in FFA, leptin and cytokine release, and a reduction in adiponectin secretion. All of these contribute to a reduction in glucose disposal in peripheral tissues (26–32), to an increase in the quantity of an inflammatory phenotype (33) and to the induction of apoptosis of pancreatic β cells (34).

Adipose tissue is also a source of renin–angiotensin–aldosterone system (RAAS) components, and that the RAAS contributes to the homeostasis of adipose tissue has been recognized over the last decade (35–38). Angiotensinogen is

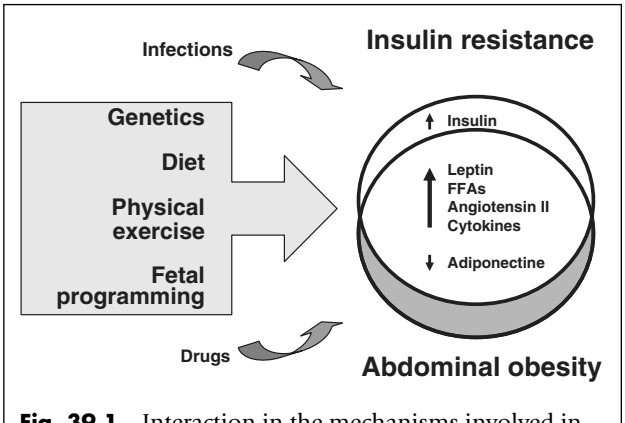

Fig. 39.1 Interaction in the mechanisms involved in the development of metabolic syndrome. *Abbreviation*: FFAs, free fatty acids.

primarily synthesized in the liver, but mRNA is also present in human fat. A rise or fall of angiotensinogen levels leads to a parallel change in the formation of angiotensin II. Therefore, increased synthesis from abundant adipose tissue may participate in the systemic impact of angiotensin II (39).

INSULIN RESISTANCE

From the beginning, IR and its consequent hyperinsulinemia have been considered key issues in the development of MS, although the mechanistic links between IR and some of the MS components have not been well established (40). While IR is strongly associated with atherogenic dyslipidemia and inflammation, it is less so with hypertension and a prothrombotic state (41).

IR in skeletal muscle and in the liver is the result of the inhibition of insulin-stimulated glucose transport activity produced mainly by the accumulation of acyl CoAs and diacylglycerol in the cytoplasm (42). This accumulation increases serine kinase activity, which leads to the suppression of insulin signaling by reducing insulin receptor substrate 2 (IRS-2) and Glut-4 transporter (43).

Several mechanisms contribute to the promotion of intracellular lipid accumulation in the muscle and liver and, consequently, to IR. FFA and cytokine overload from adipose tissue (44) and/or a decrease in mitochondrial oxidation capacity are the key mechanisms (45).

The consequences of IR are disturbances in glucose tolerance, which creates a predisposition to diabetes and dyslipidemia. Dyslipidemia associated with IR is characterized by elevated triglyceride and total cholesterol levels, seemingly normal or low plasma levels of LDL-C, and low HDL-C plasma levels. The LDL and HDL particles tend to be smaller in patients with IR because of increased hepatic lipase activity and decreased intravascular catabolism of the triglyceride-rich particles. The role of IR in endothelial dysfunction, hypertension, and atherogenesis will be discussed later.

HYPERTENSION IN THE METABOLIC SYNDROME

Hypertension is one of the components of MS, and the presence of MS increases the risk of hypertension-induced organ damage. An understanding of the individual contribution of some of the MS components to the increment in BP levels is complex since each of them interacts with the other MS components and with the mechanisms inducing hypertension.

The impact of the two main components of MS, obesity and IR, on the increment of BP and on the development of hypertension has been recognized for many years, although the role of the operating mechanisms remains partially unresolved. Crucial points associated commonly with both obesity and IR are overactivity of the sympathetic (46) and RAAS (36,39), abnormal renal sodium handling (47), and endothelial dysfunction (Figure 39.2) (48,49). The importance of adipose tissue hormones and cytokines has been outlined above.

SYMPATHETIC NERVOUS SYSTEM OVERACTIVITY

Overactivity of the sympathetic nervous system is a common feature of obesity in humans, playing a key role in the

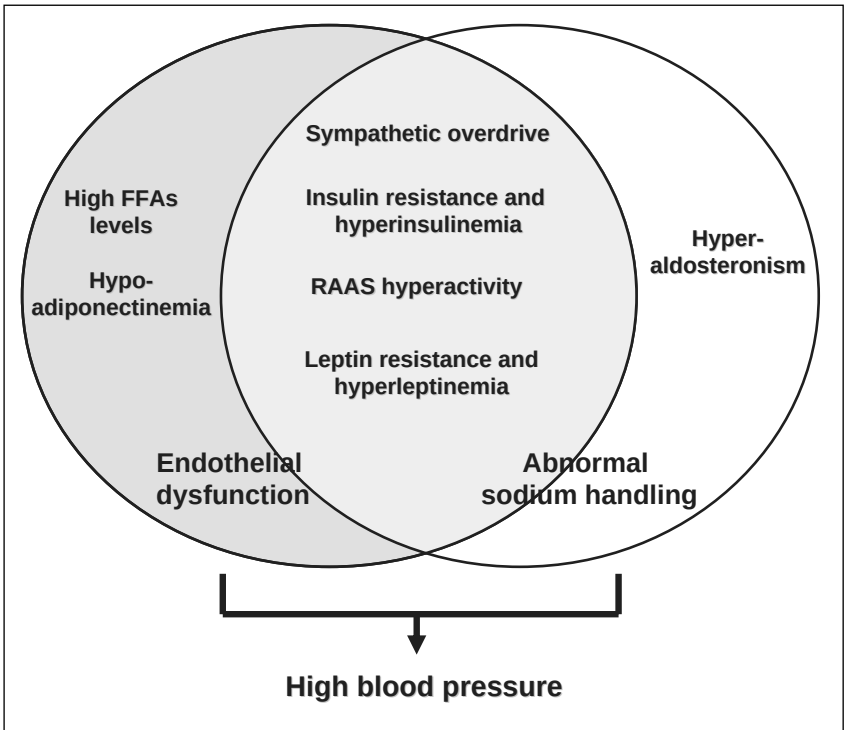

Fig. 39.2 Main mechanisms contributing to blood pressure elevation in the metabolic syndrome. Many of them produce both endothelial dysfunction and abnormal sodium handling. *Abbreviations*: FFAs, free fatty acids; RAAS, renin–angiotensin–aldosterone system.

development of hypertension. Compared to lean people, obese ones have an increased norepinephrine turnover in peripheral tissues and an increased muscle sympathetic activity, as measured directly by microaneurographic methods (50). Long-term activation may raise arterial pressure by causing peripheral vasoconstriction and by increasing renal tubular sodium reabsorption (51). Regional sympathetic nerve overactivity in the kidney (52) is the consequence of partial leptin resistance, hyperinsulinemia, high levels of circulating FFAs and low levels of ghrelin and adiponectin (46). Besides these metabolic components, an increase in angiotensin II or oxidative stress stimulates sympathetic activity in the kidney (53).

RAAS ACTIVATION

Activity of the RAAS is significantly increased in most obese individuals despite marked sodium retention and increased extracellular fluid volume. The cause of the relatively high RAAS activity may be either enhanced renin production by diminished sodium delivery to the macula densa due to higher reabsorption in the loop of Henle, or direct activation of the sympathetic nervous system in the kidneys (47). The increase in angiotensinogen formation in adipose tissue may also contribute to the RAAS activation and the final product, angiotensin II, enhances tubular sodium reabsorption, increases peripheral arterial resistance and boosts sympathetic overactivity (48,49).

ALDOSTERONE

Recently, the role of aldosterone in obesity-associated hypertension has been emphasized. Plasma aldosterone levels are elevated in hypertensives with visceral obesity (54). Although the mechanisms implicated in the overproduction of aldosterone are not well delineated, production of potent mineralocorticoid-releasing factors in fatty tissue (55), or the ability of oxidized derivatives of linoleic acid to induce aldosterone synthesis (54), has been suggested. Aldosterone may raise BP in obesity through an action on mineralocorticoid receptors located in different tissues, including not only the kidney, but also the vasculature and the brain.

ABNORMAL RENAL SODIUM HANDLING

Hypertension associated with weight gain is accompanied by increased sodium reabsorption and impaired renal-pressure natriuresis. These are the consequences of mechanisms previously analyzed: increased sympathetic activity, RAAS activation, hyperaldosteronism, and altered intrarenal physical forces (46). Glomerulosclerosis develops as the result of long-term hyperfiltration, and contributes to the BP sodium-dependency of advanced stages (56).

ENDOTHELIAL DYSFUNCTION

Various components of MS have an impact on the endothelium, leading initially to a dysfunctional state and, later, to vascular damage. Endothelial dysfunction is characterized by both impaired endothelium-dependent vasodilatation and the endothelial activation manifest in the proinflammatory, proliferative, and procoagulant milieu that favors all stages of atherosclerosis. A reduction in nitric oxide bioavailability as a consequence of increased oxidative stress is the cornerstone of endothelial dysfunction and its sequels (57). Among the mediators of MS, insulin and leptin resistance, FFAs, and adiponectin contribute to induce the endothelial dysfunction and its consequences.

Hemodynamic effects of insulin and its implications on the structural changes in arterial wall thickness and/or in arterial compliance have been widely reviewed. Insulin's vasodilator capacity is well established in healthy normotensive subjects. The mechanisms leading to vasodilatation seem to be mediated by nitric oxide synthesis and/or its release by the endothelium through the phosphoinositol pathway, which results in Akt activation. Akt directly phosphorylate endothelial nitric oxide synthase (eNOS) at Ser^{1177}, resulting in increased eNOS activity and nitric oxide production (58). However, in insulin-resistant states, insulin-mediated vasodilatation may be blunted in part by the reduction of the phosphoinositol pathway (PI-3) and the consequently lower nitric oxide production and abnormal glucose uptake, which reduces the calcium influx to muscle cells. Moreover, while the PI-3 pathway is partially blunted, the MAP-kinase pathway is unaffected leading to the synthesis of endothelin 1 (ET-1), which, in turn, favors vasoconstriction (59), and cellular activation throughout the MAP-kinase system promotes vascular smooth muscle cell growth and migration in the vessel wall affecting wall thickening and stiffness Taken together, these phenomena may explain the increased BP and cardiovascular risk associated with hyperinsulinemia (57,60).

In addition to insulin, there is a growing list of hormones involved in the regulation of vascular physiology that acutely activate eNOS in the vascular endothelium by PI-3-dependent signaling mechanisms leading to phosphorylation of eNOS. These include leptin (61), adiponectin (62), estrogen (63), glucocorticoids (64), and dehydroepiandrosterone (65). All of these mimic insulin signaling in the endothelium.

A close association between hypoadiponectinemia and endothelial dysfunction has been demonstrated, and low plasma adiponectin levels are associated with impaired endothelium-dependent vasodilation (66). Hypoadiponectinemia contributes to the development of obesity-related hypertension via a direct effect on vasculature, in addition to its effect on IR. In vitro experiments show that endothelial cells express adiponectin receptors, that adiponectin increases nitric oxide production in human aortic endothelial cells and modulates inflammation by inhibiting monocyte adhesion to endothelial cells (67). The mechanisms through which adiponectin protects the endothelium are its insulin-sensitizing, antioxidant, and anti-inflammatory properties (68).

Free fatty acids may also influence endothelium-dependent vasodilatation. Plasma FFA elevation lowers the circulating levels of most amino acids, including L-arginine, the substrate for NO production (69), and direct inhibition of NO production has been described. Reduction of FFA levels using thiazolidinediones lessens endothelial dysfunction, as assessed by induced vasodilatation (70).

In summary, many of the mechanisms present in MS may contribute to raising BP values and to producing vascular damage, thus explaining the additional cardiovascular and renal risk observed in hypertensives who share other components of MS.

METABOLIC SYNDROME AND HYPERTENSION-INDUCED ORGAN DAMAGE

Some recent studies reported an increased prevalence of left ventricular hypertrophy (LVH), diastolic dysfunction, early carotid atherosclerosis, impaired aortic distensibility, hypertensive retinopathy, and microalbuminuria in hypertensive patients with MS when compared to those without it (Table 39.2), although the grade of association with MS and its individual components differs with each of the markers. The increased occurrence of these early signs of subclinical target organ damage, most of which are recognized as significant independent predictors of adverse cardiovascular and renal outcomes, may partially explain the association of MS with higher cardiovascular and renal risk.

CARDIAC

Several studies have demonstrated that a diagnosis of MS is associated with a high prevalence of LVH in hypertensives, an association maintained throughout age. Moreover, the number of MS components has been directly related to the risk of having EKG-LVH (18) and echocardiographic LVH in some studies (16,17,71), although not in others (72,73). The effect of MS seems to be more pronounced in women than in men, and it was partly independent of the effect of hemodynamic and nonhemodynamic determinants of LV mass (74). Analysis of the components of LV mass revealed that posterior wall and interventricular septal thickness, but not LV chamber size, were significantly and independently associated with the number of MS disorders. Likewise, atrial enlargement, a prognostic factor for the development of atrial fibrillation, has also been associated with overweight, high-fasting glucose, and MS, independent of LV mass and geometry (72,75).

RENAL

An increase in the prevalence of abnormal urinary albumin excretion has been observed among hypertensives with MS, as compared to those in the absence of MS (16,17,75,76). In fact, microalbuminuria is considered a component of MS according to the WHO definition. The prevalence of microalbuminuria increases across the number of MS components even in nondiabetic subjects (16), and hyperinsulinemia, as an expression of insulin-resistance, has been associated with microalbuminuria in hypertensive subjects (77,78).

The relationship between MS and glomerular filtration rate (GFR) has been analyzed in several study populations, although the number of studies is scarce in hypertensives. In a cross-sectional survey of hypertensives visited in primary care, the presence of MS was associated with lower GFR, as estimated by the MDRD formula. Likewise, the number of MS components was linearly related to the prevalence of GFR $<60\,ml/min/1.73m^2$ (18).

GREAT VESSELS

Aortic pulse wave velocity, a surrogate marker of aortic compliance and an independent prognostic factor for cardiovascular morbidity and mortality, is higher in hypertensives with MS, and it is associated with MS irrespective of age and systolic BP (79,80).

A weaker association between MS and carotid intima-media thickness has been observed in several studies. The degree of association is weaker than that observed for the other target organ damage markers, LVH, and microalbuminuria, and is strongly influenced by the presence or absence of hypertension and by other confounding factors such as LDL-cholesterol, GFR, and smoking. In a large survey carried out on Japanese subjects (81), upon comparing subjects with an equal number of components of MS, it was found that the prevalence of carotid atherosclerosis has been significantly higher in subjects with elevated BP than in those without, and the prevalence increased significantly with the number of components in hypertensives but not so in normotensives.

Finally, MS has also been associated with faster progression of aortic stiffness with age, supporting premature senescence independent of the major individual CV risk factors (82).

PROGNOSTIC VALUE OF THE METABOLIC SYNDROME IN HYPERTENSION

The importance of MS diagnosis and of its individual components in the prognostic value of hypertensives has been analyzed in a limited number of studies (Table 39.3).

In the Copenhagen Male Study (83), 2,906 participants were divided into three groups according to their fasting plasma triglyceride and HDL levels, two lipid parameters highly related to IR and hyperinsulinemia. Men whose plasma triglyceride and HDL-cholesterol concentrations were in the upper or lower tertile, respectively, of the whole population were assigned to a group that was compared with the other extreme, triglyceride and HDL-cholesterol in the lower and upper thirds, respectively, of the total population. An intermediate group was also defined. Cardiovascular risk was not increased in patients with hypertension in the absence of dyslipidemia as defined above, and the group with the highest risk was made up of those with high BP and dyslipidemia.

The prognostic significance of MS in hypertension was also analyzed in the PIUMA cohort. Among 1,742 hypertensives, patients without cardiovascular disease were followed prospectively for up to 10.5 years; MS patients, as defined by the ATP III criteria, had an almost doubled cardiovascular event rate than did those without risk. The MS patients' cardiovascular remained higher after adjusting for age, gender, total cholesterol, creatinine, smoking, LV hypertrophy, and 24-h systolic BP. The MS was an independent predictor of both cardiac and cerebrovascular events and still higher after removal of diabetic subjects (84).

In a Turkish study, 2,225 men and women, high-normal or hypertensive and free of cardiovascular disease at baseline were followed up for a mean of 4.1 years. Subjects defined as dyslipidemic hypertensives, defined in terms of BP, plasma triglycerides, and HDL-cholesterol consistent with the MS criteria of the National Cholesterol Education Program guidelines, had a higher cardiovascular risk as compared to hypertensives in the absence of dyslipidemia after adjustment for sex, age, LDL-cholesterol, and smoking status. The dyslipidemic phenotype, which has a higher risk than the MS definition, was associated to half of the attributable cardiovascular risk attributed to MS (85).

In the Hoorn study (86), 615 men and 749 women aged 50 to 75 years and without diabetes or a history of CVD at

Table 39.2 Cross-sectional studies analyzing the association of metabolic syndrome with hypertension induced organ damage

Author, year (ref)	Number of subjects (ethnicity)	Organ damage assessment	Diagnostic criteria for MS	Main result
Left ventricular hypertrophy				
de Simone, 2005 (71)	1,627	Echocardiography	ATPIII	Increases risk Related to the number of components
Cuspidi et al., 2005 (72)	447 (Caucasian)	Echocardiography	ATPIII	Increases risk
Leoncini et al., 2005 (16)	354 (Caucasian)	Echocardiography	ATPIII	Increases risk (twice risk) Related to the number of components
Mulè et al., 2005 (17)	353 (Caucasian)	Echocardiography	ATPIII	Increases risk
Burchfiel et al., 2005 (73)	1,572 (black)	Echocardiography	ATPIII	Increases risk (twice) Related to the number of components
Mancia et al., 2007 (14)	2,051 (Caucasian)[a]	Echocardiography	ATPIII	Prevalence twice
Schillaci et al., 2006 (74)	618 (Caucasian)	Echocardiography	ATPIII	Increases risk More in women (OR 4.3) Related to the number of components
Navarro et al., 2007 (18)	8,425 (Caucasian)	Echocardiography	ATPIII	Increases risk (OR 1.43) Related to the number of components
Atrial size				
Cuspidi et al., 2005 (75)	2,500 (Caucasian)	Echocardiography	ATPIII	Increases risk
Microalbuminuria				
Cuspidi et al., 2005 (75)	447 (Caucasian)	24-h UAE	ATPIII	Increases risk
Leoncini et al., 2005 (16)	354 (Caucasian)	Albumin/creatinine ratio	ATPIII	Increases risk (OR 2.0) Related to the number of components
Mulé et al., 2005 (17)	353 (Caucasian)	24-h UAE	ATPIII	Increases risk
Palaniappan et al., 2003 (76)	5,659 (NHANES III)	Albumin/creatinine ratio	ATPIII	Increases risk
Glomerular filtration rate				
Navarro et al., 2007 (18)	8,425 (Caucasian)	GFR <60 mL/min/ 1.73 m^2 MDRD formula	ATPIII	Increases risk (OR 1.43)
Carotid IMT				
Scuteri et al., 2004 (79)	471 (Caucasians)	Echography		Increases risk (16%)
Kawamoto, 2005 (81)	1,297 (Japanese)	Echography		Increases risk (OR 1.56) Related to the number of components
Leoncini et al., 2005 (16)	354 (Caucasian)	Echography		Increases risk (OR 2.0)
Vascular stiffness				
Scuteri et al., 2004 (79)	471 (BLSA)	Eco-derived calculation		Increases risk (32%)
Schillaci et al., 2004 (80)	162 (Caucasian)	Applanation tonometry		Increases risk

[a]Population-based study.
Abbreviations: BLSA, Baltimore Longitudinal Study on Aging; MDRD, modification of diet in renal disease; GFR, glomerular filtration rate; MS, metabolic syndrome; UAE, urinary albumin excretion; OR, odds rate; NHANES, National Health and Nutritional Examination Survey.

baseline in 1989 to 1990 were followed during a 10-year follow-up period. With a prevalence of the MS at baseline ranging from 17% to 32%, MS was associated with a higher cardiovascular disease risk. Risk increased with the number of risk factors. When compared, the definitions proposed by the ATPIII, WHO, EGIR, and American College of Endocrinology (ACE) with respect to the association with 10-year risk of fatal and nonfatal cardiovascular disease, the ATPIII definition was associated with about a twofold increase (compared to baseline?) in age-adjusted risk of fatal cardiovascular disease in men and nonfatal disease in women. For the WHO, EGIR, and ACE definitions, these hazard ratios were slightly lower.

The PAMELA study has recently provided further data on the association of MS with cardiac organ damage and increased cardiovascular risk (14). The MS, as diagnosed using the 2003 ATP III criteria, was identified in 16.2% of the 2,051 subjects representative of an urban population from northern Italy, with the prevalence increasing to about 25% in middle-aged and elderly subjects. The most and least frequent MS components were high normal BP and impaired fasting glucose, respectively. Echocardiographically documented LV hypertrophy was seen significantly more often in subjects with than in those without MS (10.6% versus 20.6%), the difference occurring in males and females, at all ages, after exclusion from either group of individuals with hypertension (BP ≥140 mmHg systolic or 90 mmHg diastolic or use of antihypertensive drugs), as well as after adjustment of data for 24 h mean systolic BP values.

Over 148 months of follow-up, the risk of cardiovascular and all-cause death was significantly greater in MS individuals, the difference versus those without this condition remaining significant (about 70% and 40%, respectively) after

Table 39.3 Follow-up studies on the impact of metabolic syndrome in prognosis of hypertension

Author, year (ref)	Number of subjects (ethnicity)	Outcome assessment (follow-up)	Diagnostic criteria for MS	Main result
Jeppesen et al., 2001 (83)	2,906 (Caucasian) population-based	Events-rate (8 years)	Fasting plasma triacylglycerol and HDL	Higher risk in subjects which combine hypertension and dyslipidemia
Schillaci et al., 2004 (84)	1,742 (Caucasian) Hypertensives	Cardiac and cerebrovascular events-rate (10.9 years)	ATPIII	Twice risk for both cardiac and cerebral
Onat et al., 2005 (85)	2,225 (Caucasian) Hypertensives	Cardiovascular morbidity and mortality (4.1 years)	Plasma triglycerides, and HDL	Higher the risk in subjects with dyslipidemia
Dekker et al., 2005 (86)	1,564 (Caucasian) Population-based	Cardiovascular morbidity and mortality (10 years)	ATPIII, WHO, EGIR, ACE	Twice the risk
Mancia et al., 2007 (14)	2,051 (Caucasian) population-based	All cause death (148 months)	ATPIII	Higher risk

Abbreviations: ACE, American College of Endocrinology; ATPIII, third adult treatment panel; EGIR, European Group of Insulin Resistance; HDL, high-density lipoprotein; MS, metabolic syndrome; WHO, World Health Organization.

adjustment for differences in age, gender, and other cardiovascular risk factors (14).

MANAGEMENT OF HYPERTENSION IN THE PRESENCE OF THE METABOLIC SYNDROME

The objective of treatment for MS is both to reduce the high cardiovascular and renal risk associated with the individual components of the MS, as well as to reduce the risk of developing type-2 diabetes. There is a need for treatment that can modulate the underlying mechanisms of MS as a whole, and thereby reduce the impact of all the risk factors and the long-term metabolic and cardiovascular consequences. These mechanisms are not well understood, however, and specific pharmacological agents are, therefore, not yet available. Partial approaches have been developed and insulin-sensitizer drugs and endocannabinoid receptor C1 blockers exert some beneficial effects on the main components of the syndrome. As a consequence, it is currently necessary to treat the individual components of the syndrome in order to achieve a reduction in the individual risk level associated with each component, thereby reducing their overall impact on cardiovascular, renal, and diabetes risk.

Treatment of individual components of MS implies establishing the threshold for intervention and the desired goal to be achieved. Besides establishing these two key elements, it is also relevant to know the best treatment to be used for each of the components, and what the potential impact of treatment on the other components of the syndrome in terms of improving or worsening is in MS. A brief summary is shown in Table 39.4.

TARGETING METABOLIC SYNDROME MECHANISMS

LIFESTYLE MEASURES

All current guidelines on the management of the individual components of the MS emphasize that lifestyle modification, with weight loss and physical activity in particular, is first-line therapy. Nevertheless, lifestyle intervention is unfortunately often neglected in routine practice despite its having the potential to reduce the severity of all metabolic risk factors and to slow their progression (87).

PHARMACOLOGICAL TREATMENTS

Besides the positive impact of physical exercise and weight loss on the mechanisms leading to MS, there have been, to date, two types of drugs which interfere with the central mechanisms of MS: insulin-sensitizers and endocannabinoid C1-receptor blockers. While the former increase peripheral glucose disposal by acting on the peroxisome proliferator-activated receptor-gamma (PPRγ), the latter reduce abdominal obesity and the consequent modification in the status of adipose-tissue substances.

Thiazolidinediones (88), drugs acting as PPRγ ligands, may increase lipogenesis in adipose tissue, which decreases serum FFA concentrations and increases subcutaneous adipose tissue mass and body weight. Adipose tissue expression and serum levels of adiponectin also increase. Thiazolidinediones have received approval for use as part of a type-2 diabetes treatment, but there has been no indication that IR treatment is accepted in absence of diabetes to date. The role of these drugs in the early stages of IR has been analyzed in the DREAM study (89). The impact on BP values is not well established yet, although some evidence points to a beneficial effect in terms of BP reduction, at least in type-2 diabetes individuals and in those with refractory hypertension. Systematic reviews of the literature, however, have found no notable benefits of thiazolidinediones with regard to BP (90).

Cannabinoids and endocannabinoids act via G protein-coupled receptors, and the majority of the metabolic-related actions are linked to the endocannabinoid type-1 (CB1) receptor (91), represented mostly, though not exclusively, in the central nervous system. The presence of CB1 receptors in adipose tissue, muscle, liver, and pancreas has been demonstrated. The overall effect of the inhibition of CB1 receptors is both to decrease appetite and lipogenesis, as well as to increase peripheral energy expenditure (92). A beneficial impact on some of the MS components has been observed with rimonabant, an endocannabinoid type-1 receptor, in the RIO trials (93–95) carried out on overweight and obese subjects with or without dyslipidemia. Even though no specific studies have been conducted to monitor BP levels carefully, it seems no BP reduction was observed in the above trials.

TARGETING HYPERTENSION

The threshold for intervention in BP values is based on the recognition that underlying risk factors raise BP to ranges

Table 39.4 Management recommendations for hypertension and metabolic syndrome

MS component	Threshold	Goal	Recommended	Observations
High BP	130/85 mmHg	<130/80 mmHg (in absence of CHD)	Nonpharmacologic treatment Antihypertensive treatment First choice: ACEI or ARB Second choice: CCB or β-blockers with vasodilatory activity	Thiazide-like diuretics should be avoided in monotherapy or in high-dose β-blockers should be avoided if not compelling indication exists
Dyslipidemia	Triglyceride >150 mg/dl (1.7 mmol/L) HDL <40 mg/dl (1.03 mmol/L) in men or <50 mg/dl (1.29 mmol/L) in women	LDL<75 mg/dL	Nonpharmacologic treatment Statins alone or with ezethamibe Fibrates other than gemfibrozil are recommended to combine with statins	
Impaired fasting glucose	>110 mg/dL	<100 mg/dL	Nonpharmacologic treatment First choice: Thiazolidinediones Second choice: Metformin	OGTT should be performed in subjects with fasting glucose >110mg/dL
Hypercoagulability	In subjects with high risk or creatinine >1.4 mg/dL	Reduce platelet aggregability	Aspirin	Avoid until BP is under control

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II-AT1 receptor blockers; BP, blood pressure; CCB, calcium channel blockers; CHD, coronary heart disease; LDL, low-density lipoprotein; MS, metabolic syndrome; OGTT, oral glucose tolerance test.

that increase the risk of cardiovascular disease. Furthermore, subjects with MS seem to be at risk of developing BP. Consequently, 130/85 mmHg should be the threshold for intervention in absence of diabetes, although when BP is <140/90 mmHg and no organ damage is present, nonpharmacological treatment needs to be introduced first (96,97). Hypertension should be managed according to the individual risk assessment of the European Society of Hypertension–European Society of Cardiology (ESH–ESC) guidelines (96). If diabetes is present, antihypertensive drugs should be introduced at even lower levels, 130/80 mmHg (98). The goal is to maintain BP lower than 130/80 mmHg.

Ideally, treatment of high BP in MS should be based on lifestyle changes, diet, and physical exercise, which allows for weight reduction and improves muscular blood flow.

Concerning antihypertensive drugs, whether or not a particular antihypertensive agent is superior to others has not been tested in trials including subjects specifically with MS. However, a large body of information is available from both long-term antihypertensive trials with major outcomes, as well as from myriad shorter studies.

After changes in life style are introduced, the drugs to be used should be those which may induce reduction of IR and consequent changes in lipid profile and in glucose levels. Therefore, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II-AT1 receptor blockers (ARAII) or even calcium channel blockers (CCBs) are preferable over diuretics and β-blockers in monotherapy, if no compelling indications are present for use of the last two. If a combination of drugs is required, low-range doses of diuretics can be used.

The impact of particular antihypertensive drugs on other components of the MS is an important clinical issue with consequences for the success of the treatment. Changes in metabolic components, mainly in the lipid profile and IR, during antihypertensive treatment with diuretics and β-blockers have been claimed as the culprit for lower reductions than expected in coronary heart disease morbidity and mortality (99). To the contrary, evidence shows reductions in the rates of new-onset diabetes have been observed during treatment with ACEI, angiotensin II-AT1 receptor blockers (ARB) or even CCBs as compared with diuretics and beta-blockers (100,101).

For many years, metabolic changes associated with the use of antihypertensive drugs have received attention, looking at both worsenings as well as at improvements in the metabolic profile. Not all the studies report the same conclusions, however, in part because of the different doses of the drugs used, the particularities of drug mechanisms even within the same therapeutic group, the duration of treatment and, mainly, because of the different characteristics of the subjects included. Age and hormonal status have been recognized as important modulators of drug impact but, besides these, personal or family histories of metabolic disorders are among the most important factors.

The most recognized metabolic change associated with the antihypertensive drug classes is IR. This condition is induced by a combination of different mechanisms including a reduction of the microcirculatory flow in the muscle and a reduction in the rate of intracellular glucose disposal. The former is a consequence of the use of β˜-blockers, since β˜-blockade activity goes unopposed by the α-receptors. The latter is not as well understood. Beta-blocker agents with additional properties can reduce the impact of the pure beta-blockade and even exert partially beneficial effects. The simultaneous beta-blockade of carvedilol (102) or the increment in the nitric oxide bioavailability of nebivolol (103) or even carvedilol (104) have shown a neutral effect on glucose metabolism indexes and a trend toward a favorable lipid profile (105,106).

The reduction of glucose disposal is less when insulin secretion decreases. This can occur as a direct consequence of the β-blockade, reducing the response of the pancreatic beta-cell, and by hypokaliemia induced by thiazide-like diuretics. Reductions in glucose disposal and in the compensatory insulin secretion lead to metabolic abnormalities of the glucose homeostasis and dyslipidemia, as previously described.

The potential effect of β-blockers in the favoring of gaining weight needs to be mentioned. A large review concerning weight changes in studies using beta-blockers has shown subjects tend to increase body weight, as a consequence of reducing fuel expenditure (107). The clinical consequences of weight gain during β-blocker treatment, however, seem to be negligible.

A beneficial impact of decreasing the risk for the development of diabetes with ACEI or ARB-based treatments has been described. Detailed systematic reviews of the potential beneficial effects have been published recently. In general, treatment with these classes of drugs reduces the rate of new-onset

diabetes as compared with the use of diuretics and/or β-blockers (100,101). Inhibiting the RAAS may improve blood flow to muscles, decrease the activity of the sympathetic nervous system, enhance insulin signaling, lower FFA levels, increase plasma adiponectin levels, and improve glucose disposal. Another putative mechanism by which the inhibition of the RAAS may improve insulin sensitivity is through effects on PPARγ, which is inhibited by angiotensin II.

The controversy concerning whether this effect is a consequence of the risk induced by diuretics or β-blockers and not a real beneficial effect was in part resolved by the observation that the reduction in new-onset diabetes has been observed in a trial against placebo (108) and by data furnished by the VALUE study (109,110). In the latter study, valsartan-based treatment significantly reduced the rate of new-onset diabetes as compared with amlodipine, a CCB. Mechanisms that led to improved glucose metabolism were increased in the microcirculatory flow and in the bioavailability of the Glut4 transporter. The results of the DREAM study (111) challenge the concept of protection against development of new-onset diabetes by using drugs blocking the RAAS. The study reports the effects of ramipril on the risk of diabetes in a randomized trial designed with diabetes as a primary outcome in subjects who had impaired plasma glucose levels after an overnight fast or impaired glucose tolerance. Rates of the primary end point, mainly diabetes, were not significantly lower in the ramipril group. Regression to normoglycemia, a secondary outcome, however, was significantly more frequent in the ramipril group than in the placebo group, although the absolute difference between the groups was small.

An additional mechanism for some ARBs that has been tested in experimental models is the partial PPRγ agonism of telmisartan (112) and even irbesartan (113), with further improvement in IR. The significance and the clinical impact of this additional mechanism, however, need to be tested in appropriately designed studies.

The impact of other antihypertensive drug classes has demonstrated the neutral effect of both long-acting CCBs, as well as other sympaticolytic drugs with central action such as reserpine, α-methyl-dopa or moxonidine. The pure peripheral α-blocker, doxasozin, improves the lipid profile, reducing IR and consequently increasing HDL-cholesterol and reducing triglycerides (99). A trend to reduce total cholesterol has also been described. The main mechanism implicated in the positive changes of β-blockers seems to be mediated by increasing microcirculation flow. Additional effects of a blockade of β-receptors on the activity of key enzymes of lipid metabolism are less known.

A final question is the net effect of the interaction when two different kinds of drugs, with opposite effects, are combined. This is the case of combination treatments with diuretics. Simultaneous administration of thiazide diuretic with ACEI or ARBs reduces the hypokaliemia and does not significantly modify the lipid and glucose profile. Whether or not this combination reduces at large the beneficial effects in cardiovascular risk needs to be assessed. Two recent publication introduce some warnings. The recently published STAR study (The Study of Trandolapril/Verapamil SR and Insulin Resistance) reduced the risk of new-onset diabetes in patients with impaired glucose tolerance, normal kidney function, and hypertension treated with the fixed-dose combination of trandolapril/verapamil compared to losartan/hydrochlorothiazide-based therapy (114). In another study, valsartan alone reduced the levels of high sensitivity C-reactive protein (115). In contrast, a combination of valsartan plus hydrochlorotiazide, despite a significantly larger BP reduction, was unable to reduce the high sensibility of CR values. No interaction with statins was demonstrated.

CONCLUSIONS

The MS is a highly prevalent condition currently considered to be a cluster of metabolic and cardiovascular risk factors including BP elevation. A higher risk to progress in MS subjects with high-normal BP has been observed and, when hypertension is established, seems to be what confers an additional, higher cardiovascular risk than that induced by BP elevation. Therefore, assessment of MS components can be a clinically useful strategy to manage hypertension based on individual risk. Development of hypertension is commonly associated with both obesity and IR. The main mechanisms include overactivity of the sympathetic and the RAAS, abnormal renal sodium handling, and endothelial dysfunction. The objectives of MS treatment in the hypertensive patient are both to reduce the high cardiovascular and renal risk associated with the individual components of MS, and to reduce the risk of developing type-2 diabetes. Diet and regular physical exercise should be strongly recommended. The first choice among the antihypertensive drugs should be those that may induce reduction of IR and the consequent changes in lipid profile and glucose levels. Besides close BP control, LDL-cholesterol and glucose levels should be targeted to be reduced as much as possible. Drugs improving IR may contribute to the control of components of MS, although further knowledge of cardiovascular and renal morbidity and mortality needs to be obtained from current studies.

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Economic and organizational issues

SECTION 8

PHARMACOECONOMIC AND COST–BENEFIT ASPECTS 40

Ettore Ambrosioni, Claudio Borghi

INTRODUCTION

The previsions of health care expenditure both in Europe and United States indicate a continuous increase at least up to 2030. Cardiovascular diseases (CVD) are the first cause of death worldwide and are mainly responsible for high health care costs in more developed countries. The cost of stroke and ischemic heart disease in the United States in the year 2000 was 298 billion dollars and in 2005 was estimated to reach 393 billion dollars. CVD was estimated to cost the EU 169 billion euro annually (1). This situation is a cause of concern for health authorities and insurance companies who are taking all efforts to identify the principal factors contributing to this unlimited increase of the costs.

Since the major risk factor for CVD is high blood pressure (BP) (2), a clinical condition with high prevalence together with evidence from trials of benefit from treatment (3,4), it has been considered the object for approaching the cost–benefit evaluation of CVD. Many studies have investigated the cost–benefit ratio of reducing BP by considering patients characteristics and therapeutic options (5). The awareness of both physicians and patients of the importance of treating hypertension resulted in a tremendous rise in annual prescriptions and costs for antihypertensive drugs in United States and Europe. The evidence of an incomplete benefit by the reduction of BP with drug treatment obtained in earlier clinical trials, led to a progressive introduction of new but more expensive antihypertensive drugs in the market. The annual cost of new drugs, calcium channel blockers (CCB) and angiotensin-converting enzyme inhibitors (ACEI) were, in fact, five to six times greater than diuretics. The rapid growth of the costs for the treatment of hypertension has been attributed to these new classes of drugs. A further support to this interpretation has been offered by the meta-analysis of clinical trial results demonstrating a nonsignificant difference in the ability of old and new antihypertensive drugs in reducing BP, cardiovascular (CV) events, and mortality (6). On this basis the optimization of cost–benefit ratio of BP reduction appeared largely, if not entirely, dependent on the price of the agent used in clinical trials. Surprisingly, conclusions reached in clinical trials have been considered entirely applicable to the general practice, and as a consequence, the price of drugs became the key factor for containing costs of treating hypertension in the population. But general practice differs in many relevant aspects from clinical trials where the patients are more motivated, more controlled and followed by experts in the field for a relatively short period of time. In general practice, there is important differences among drugs in causing side effects and in the degree of compliance and persistence (7,8). In this situation the ability of antihypertensive drugs in controlling BP and/or preventing CV events, may no longer be equivalent and the weight of drug price substantially reduced. Any proposed cost–benefit analysis of treatment of hypertension requires a validation in general practice: a positive cost–benefit ratio of a drug in clinical trials may turn into a negative ratio or even be a cause of uncontrolled hypertension in the population (9).

In clinical trials, the percentage of hypertensive patients with a satisfactory control of their BP is around 70%; a value that, on the contrary, represents the percentage of uncontrolled BP in the general population. The cost of uncontrolled hypertension is responsible for the largest part of the amount of money spent for the health care of patients with high BP and it should be considered the first target of any project of cost containment. A complete evaluation of all factors contributing to the cost both of the disease and of the treatment is essential in order to perform a cost–benefit analysis. Referring to the drug price without relating it to the benefit obtained in general practice is nonsense.

Thus, in evaluating the cost effectiveness of an antihypertensive drug treatment, it is necessary to assess the total cost of hypertension and the outcomes in general practice. The cost differences among drugs are much less relevant as total cost determinants than a better BP control in the population.

METHODS FOR ECONOMICAL EVALUATION

The economical evaluation of medical care is intended to measure the cost of an intervention for improving outcome of the patients. Four types of economical analysis are currently used: cost minimization, cost effectiveness, cost utility, cost benefit. The choice of the method depends on the question being asked in relation to the clinical situation to be evaluated.

Cost-minimization analysis or cost identification compare treatments on the basis of costs and evaluate which treatment

is less expensive assuming an equivalence of outcomes. Therefore it should be used when a new antihypertensive drug, considered as effective as previously available drugs, should be evaluated. It provides the cost of a therapeutic intervention irrespective of the entirety of obtained benefit and it answers the question on which treatment is less expensive. The cost minimization analysis is frequently misunderstood. Since the large majority of antihypertensive drugs cause similar BP decreases, the outcome of patients is assumed to be the same. This interpretation is not true: the same BP decrease does not correspond to the same reduction in CV risk.

Cost-effectiveness analysis relates cost of treatment to outcomes and it determines if added medical benefits are worth the high cost of a treatment. This type of economical analysis requires a complete evaluation of costs and benefits for prolonged periods of follow up: not less than 3–6 years. The outcomes are expressed in terms of years of life saved. The calculation of cost–effectiveness ratio indicates the increased cost of a new treatment as compared to an older one and comparisons among antihypertensive therapies can be assessed as cost–effectiveness ratio. The incremental cost–effectiveness ratio results from the additional cost divided by additional benefit. If the quality of life is added, the duration of time that a subject spends in this condition is expressed in terms of quality-adjusted life-years (10).

The quality-adjusted life-years are also termed as cost utility analysis.

Cost benefit analysis is used when the compared treatments cause different quantitative and qualitative effects: the benefit is measured in units of currency and it enables health authorities to compare the net cost between two treatments largely different (i.e., anti-smoking campaign versus vaccination program).

The incremental cost–effectiveness ratio represents the most appropriate way for establishing the best use of money for health care and it should be considered as the reference guide to decision making.

COSTS OF HYPERTENSION

A comprehensive evaluation of economical resources consumed for detection, treatment, and prevention of hypertension should be referred to an evidence-based cost-effectiveness ratio. For the calculation of the global cost it is necessary to consider all the contributors: health care costs, informal care costs, and productivity losses (Table 40.1). The exclusion from global cost of informal care costs, as it frequently happens, reduces the total cost to a partial cost; it is absolutely misleading because the informal care costs paid by patients or by their families are calculated as savings. A detailed list of the most important factors contributing to health care costs, which represents the major part of total costs, should consider at least: CV complications, hospitalization, and treatment. The inclusion of these factors is essential in order to calculate the cost effectiveness that results by dividing the net cost for quality-adjusted life-years. The net cost can be obtained by subtracting the costs of CV complications and hospitalization from the costs of drug treatment.

The cost-effectiveness analysis has been performed mainly on the results of clinical trials providing reliable evaluations. But these calculations can not be restricted to the effectiveness of interventions as measured in clinical trials, they should be extended to the evaluation of the use of health care resources and related costs. It is well documented than no more than 50% of treated hypertensive patients have their hypertension controlled in Europe. The failure in achieving targets for BP control causes an excess of CV morbidity. The annual costs only for acute hospitalization for three CV events have been estimated to reach 10.3 billions euros considering five European countries (11). The annual health care cost of three CV events (myocardial infarction, stroke, and heart failure) due to uncontrolled hypertension in Italy (year 2003), has been estimated to be: 16.3 billion euros, an amount to which 2.84 billion euros should be added as the cost of antihypertensive drug therapy, with a total cost of 19.14 billion euros. The expected figure, if 100% of Italian hypertensive patients have their BP controlled, would be: 10.2 billion euros for CV events; 10.24 billion euros for drug therapy; total cost 16.32 billion euros, with a positive balance of 2.82 billion euros (Table 40.2).

A definite improvement in BP control of hypertensive subjects doubles the cost of drug therapy but decreases the total costs of the disease. For National Health Service the cost of nontreating hypertension results higher than the cost of treating hypertension. The difference becomes much larger when informal care and productivity losses are included in the calculations. These observations confirm that treating hypertension is cost effective and that the five major classes of antihypertensive drugs are all cost effective.

Thus, the definition of the most cost effective treatment remains a priority for reducing costs of hypertension. Since the price of drugs represents the largest part of the total cost of treatment and there are large differences in the price among antihypertensive drugs, many National Health Services decided to promote the use of so-called inexpensive antihypertensive drugs (diuretics, beta-blockers), as drugs of first choice for patients with uncomplicated hypertension. They based their decisions on the results of clinical trials and meta-analysis that have documented no significant difference among antihypertensive drugs on reducing BP.

Table 40.1 Costs of hypertension

Healthcare costs	Non-healthcare costs	Contributors to the cost of drug therapy
Hypertension-related visits	Informal care	Price of drug
Clinical and laboratory evaluation	Productivity loss	Clinical and laboratory costs
Consultations		Compliance
Hospitalization		Persistence
Cardiovascular complications		
Drug therapy		

Table 40.2 Annual expenditures for acute myocarial infarction, congestive heart failure, and stroke in Italy, with a hypertension prevalence in 38% of the population (billions €, 2003)

Current situation		If 100% pts treated
Drugs	2.84	6.08
Costs for NHS of CV events	16.30	10.24
Total costs	19.14	16.32
Savings 2.82 billions €/yr!		

Abbreviations: CV, cardiovascular; NHS, National Health System.

When even the nonsignificant differences have been excluded by reaching the same BP level with the comparative treatments, the efficacy of drugs appeared significantly different. Recent clinical trials have documented that, for an equivalent BP decrease, some antihypertensive drugs are more efficacious in preventing CV events than others in high risk hypertensive patients (12,13): angiotensin receptor blocker (ARBs), CCB, and ACEI-based therapy reduced the incidence of CV events, mainly stroke, by 20–25%, as compared to beta-blockers and diuretics. In secondary prevention of stroke, ARBs were significantly more efficacious than CCBs in reducing CV events at the same level of BP control (14). It has been calculated that an ARB reduced the direct stroke related cost per patient by 1,141 euro as compared to a diuretic/beta-blocker. The net cost per quality-adjusted life-years for ARB was 4,188 euro, which leads to a definite cost-effective intervention (15).

But these consistent differences in comparative efficacies among antihypertensive drugs have been considered of value only for high risk hypertensive patients. The remaining dominant opinion has been that it is the reduction of BP itself that leads to lower CV morbidity and mortality in low-moderate risk hypertensive patients that are the large majority of patients managed by general practitioners. The consequence was that the effectiveness of all antihypertensive drugs was considered equivalent and the price of drugs used as basis for comparative efficacy in clinical practice. On the contrary, there is a large body of evidence from the literature that, in clinical practice, not all antihypertensive drugs are equal in terms of compliance, persistence, and percentage of hypertensive patients with BP values at target. In a pharmacoepidemiological survey conducted in Italy to evaluate the limited achievement of BP control in clinical practice, the rate of discontinuation of treatment or switching to another drug was 66%. In the patients' opinion, occurrence of drug side effects was by far the most frequent cause of treatment discontinuation or switching (53%), followed by inadequate BP control in 34% (16). Switching from one drug to another increases the annual cost of therapy by 20%: switching and compliance together are responsible for 39% of direct costs of hypertension (17).

Poor compliance and persistence are the principal barriers to controlling hypertension, leading to an increased morbidity and mortality, and they explain the discrepancy between the efficacy of antihypertensive drugs in clinical trials and population-based findings.

In clinical practice, both compliance and persistence appear higher in hypertensive patients receiving ACEIs or ARBs than in those receiving diuretics, and drug choice and health service utilization both strongly related to good versus poor compliance in newly treated hypertensive patients (18). In a population-based study, the risk of discontinuation of antihypertensive therapy over a 39-month period was significantly lower in patients receiving ARBs as compared to all other antihypertensive drugs. Furthermore, patients initiated on an ARB had a significantly higher likelihood of starting a new course of therapy after the first discontinuation as compared to those initiated on all other antihypertensive drugs (19).

A recent study (20) evaluated the patterns of persistence with antihypertensive drugs in newly diagnosed hypertension in primary care: after the first year the rate of discontinuation has been 42.6% and that of switching 15.4%. The percentage of discontinuers was significantly higher (54%) in those receiving diuretics than in those receiving ARBs (38%). Discontinuers represented the least costly group but they accounted for 22.4% of total expenditure without foreseeable clinical benefit. Since an early drug discontinuation reproduces the condition of risk of untreated hypertension, the long-term costs are expected to be very high. The primary care cost per person per year of treatment was 238.6 euro. First-line treatment with ARBs was associated with an increase in cost of 145.2 euro as compared to diuretic treatment. The important question is whether the use of an ARB causing an incremental cost of 145.2 euros per person per year in comparison with diuretic, still provides an economic value to the National Health Service by reducing the need for the more expensive medical services in a relatively short period of time.

It has been documented that a net economic return can be provided by a good compliance to antihypertensive treatment. Hypertensive patients with a good compliance to medical treatment show a significantly lower hospitalization rate than those with nonoptimal compliance. High levels of adherence were associated with lower medical costs, despite the increased drug costs (21).

On this basis, it has been possible to compare the costs of antihypertensive treatments with ARBs and diuretics, taking into account the percentage of discontinuers in the first year of treatment in primary care. The health care costs paid by the National Health Service for patients receiving diuretic treatment are higher than those for patients receiving ARB treatment. This difference in favor of ARBs increases by adding to the health care costs the informal care costs (Table 40.3). Another possible economical disadvantage of diuretics is their ability to cause long-term metabolic effects. The use of diuretics and beta-blockers as antihypertensive drugs is associated with a higher incidence of new-onset diabetes mellitus as compared to ARBs, ACEIs, and CCBs (22).

The new-onset diabetes mellitus in treated hypertensive patients carries an adverse prognostic significance: the risk of subsequent CVD corresponds to that of previously diagnosed diabetes mellitus (23). The increase of costs caused by the development of diabetes mellitus in hypertensive patients treated with low-dose diuretic balance completes the higher cost of acquisition of ARBs and CCBs. The total cost per patient treated with diuretic and/or beta-blocker was US $1,105; in those treated with ARBs and/or CCBs US $549 (24).

All these studies have documented that in clinical practice there are major differences in efficacy and safety of antihypertensive drugs: the comparative cost of drugs can not be used as a final discriminator and diuretics, and beta-blockers do not represent the most cost-effective treatment of hypertension. A low-dose thiazide diuretic can no longer be considered the first choice drug for most hypertensive patients, both for medical and economical reasons.

Table 40.3 Costs of drug treatment and total medical costs according to different classes of hypertensiontherapy (Italy, thousands €, 1,000 pts/yr)

	Drug treatment	National health care	Informal care	Total costs
ARBs	286.8	644.7	621.4	1552.9
Diuretics	141.6	1101.9	829.4	2072.9
Incremental costs A versus D	+145.2	−457.2	−208	−520

Abbreviation: ARB, angiotensin receptor blocker.

A cost-effectiveness evaluation of drug combinations is at present more important than that regarding single drugs: the large majority of hypertensive patients require two or more drugs to control their BP. No data on the cost-effectiveness of the use of combinations of antihypertensive drugs are available for clinical practice. Cost effectiveness of one association may show results substantially different from another, depending on the type and dose of drugs used and whether they are combined in a single pill or not. Compliance and persistence may be more unpredictable for associations than for single drugs.

There is no doubt that the cost analysis is an useful tool to reduce the cost of drug treatment of hypertension. But the continuous increase in costs of hypertension is largely related to the cost of not treating this disease and, for the near future, to the increase in life expectancy due to the antihypertensive treatment.

In clinical practice, there are many costs of hypertension that do not produce any benefit. The different components of under treatment of hypertension (patients unaware of their BP values, untreated or refusing any treatment, not reaching BP control) are largely responsible for the continuous increase of costs of the disease. The elimination of costs without benefits represents the most effective method for reducing the waste of money in the treatment of hypertension. The implementation of population strategies should be reinforced in addition to clinical prevention. An extended involvement of nurses in the management of hypertension is both necessary and urgent for a definite improvement of compliance and persistence in antihypertensive treatment.

Life expectancy of hypertensive patients is increased by antihypertensive treatment for any level of CV risk and age. The improvement of life expectancy causes an increase of cost of treatment that could become very heavy for the ones who survive a CV event. Then, it is important to improve the quality-adjusted years of life gained by delaying the progress of CV disease and displacing CV events as close as possible to death (Figure 40.1). Epidemiological surveys have shown that people with low CV risk in middle age have a lower average annual health care cost in older age (25). High risk hypertensive patients have greater proportionate gains than those at low CV risk. The gains decrease with age in high risk patients without significant changes in low CV risk individuals (26). Since BP levels usually considered normal, high normal, and prehypertension are associated with an elevated risk of CVD (27) it would be useful to reconsider cost effectiveness of treating all hypertensive patients independently of their total CV risk.

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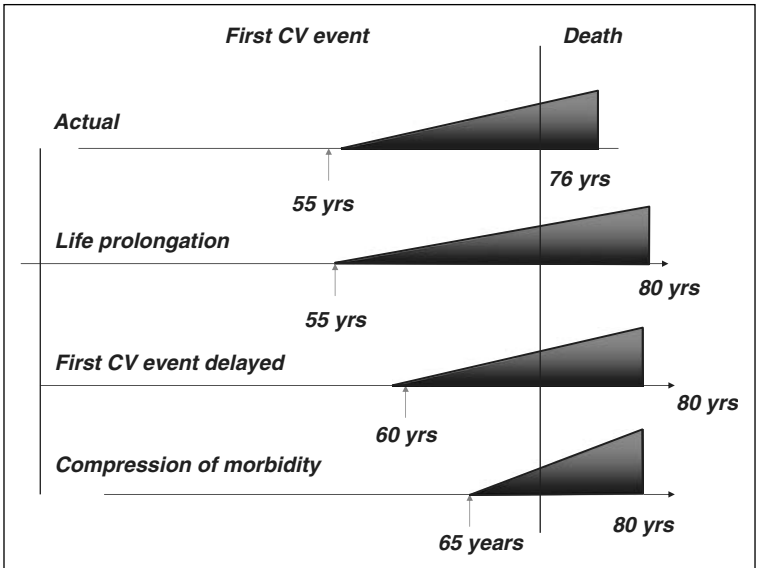

Fig. 40.1 Possible scenarios on future morbidity and mortality. *Abbreviation*: CV, cardiovascular.

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HOW TO ORGANIZE AND RUN A HYPERTENSION CENTER 41

Csaba Farsang

BACKGROUND

The average prevalence of hypertension of the adult population in the world is estimated to be 26.4% (1), increasing in older age (2–4). From the Framingham study, it became evident that the incidence of target organ damages attributed to hypertension (e.g., heart failure, stroke, coronary artery disease, hypertensive renal disease, and peripheral artery disease) increases with higher blood pressure (BP), and antihypertensive treatment has significant organ protective effects (5,6). However, the rates of well-controlled BP (<140/90 mmHg) in hypertensive patients are still between only 2.4% and 32% (2), but, using different limits in The Minnesota Heart Survey (<140 and/or 90 mmHg), it goes up to 44% of the men and 55% of the women (7). From about 1 billion hypertensives (1) only 24 to 320 million are estimated to be controlled. Large differences have been shown in physicians with different specialization. In general practices involved in the ForLife Study, the well-controlled rate (WCR) was 18.4% (8), while it was 21.7% in the recently published SMOOTH Study (9). But, in the study (10) involving cardiovascular specialists, the WCR was only 11.9%. The SILVIA Study (11) underlines the importance of hospital outclinic centers, as the WCR in this study was 37.5%, and that in the United States at hypertension specialists was 52% (20).

The European Society of Hypertension (ESH) initiated the Specialist in Clinical Hypertension program (see Web site: www.eshonline.org) for improving hypertension care. Eligibility criteria for being a Specialist in Clinical Hypertension are as follows:

1. Clinical experience in hypertension (not less than 10 years), with particular reference to referral of patients with difficult hypertension.
2. Training in a medical speciality germane to hypertension (internal medicine, nephrology, cardiology, endocrinology, primary care, etc.).
3. A certain degree of scientific activity (e.g., publications on clinical hypertension, participation in clinical trials, etc.).
4. Continuing interest and updating in hypertension as shown by participation in scientific meetings and membership in hypertension-related scientific societies.
5. Recognition by their peers at national levels.

Nominations will also be based on credits obtained through participation in scientific meetings and teaching courses organized/endorsed by the ESH. The following teaching courses are of importance:

- ESH Summer/Winter (advanced) School/courses (7 days): 3 credits.
- Teaching Courses organized by National Hypertension Societies; minimal duration two full days with program (theoretical and practical) endorsed by ESH: 2 credits.
- Online programs of theoretical and practical self-assessment; programs endorsed by ESH (distance learning program, starting in 2007).
- Teaching courses within yearly ESH meetings.

It will be desirable for applicants to have at least 10 credits from scientific meetings and 10 credits from teaching courses.

Scientific Meetings accredited by ESH for hypertension specialist program:

- Yearly meetings of ESH: 3 credits.
- International meetings endorsed by ESH: 2 credits.
- Meetings of National Hypertension Societies: 1 credit.

ORGANIZATION OF HYPERTENSION CENTERS

The Hungarian Society of Hypertension (HSH) started its hypertension specialist program and accredited Hypertension Regional Centers, Hypertension Subcenters, and Hypertension Outpatient Departments in the year 2002.

The Regional Center is a university clinic, a national institute, or a hospital with hypertension outpatient department having access to proper diagnostics of hypertension (primary or secondary), access to Internet, scientific grants for hypertension research, and teaching activity in continuing medical education (CME). The head of the department must have the clinical hypertension subspeciality license, a PhD, or doctor of sciences (DSc) academic degree, and university practice in teaching. In the institution, there have to be physicians specialized in internal medicine, cardiology, nephrology, endocrinology, angiology, neurology, gynecology & obstetrics, ophthalmology, radiology, and clinical chemistry.

The Hypertension Subcenter is a hospital department with outpatient hypertension care. It has to have an access to diagnostics and important hypertension-related specialities (cardiology, nephrology, angiology, gynecology & obstetrics, neurology), and an access to Internet. The head of the subcenter must have the specialist in clinical hypertension license and practice in CME courses.

The Hypertension Outpatient Department must have a direct connection to a general hospital, a connection to clinical chemistry and radiology, and access for referral to Hypertension Centers or Subcenters. Ambulatory BP measurement (ABPM) and electrocardiogram (ECG) devices and access to the Internet are also required. Personal conditions are: specialist in clinical hypertension license or practice in hypertension care, recognized by the head of the Regional Center, and specialization in internal medicine, cardiology, nephrology, endocrinology, or family practice.

RUNNING A HYPERTENSION CENTER: THE HUNGARIAN EXPERIENCE

HSH-accredited centers are in university clinics and major hospitals in Hungary. These centers have been involved in organizing the network of connecting subcenters and outpatient departments, the Hungarian Hypertension Register (HHR), CME teaching courses, and hypertension-related scientific research. Up to now there have been several research projects scientifically supported by the HSH and organized by Hypertension Centers.

The Effective Control of Hypertension Program (13), a prospective, randomized, group-controlled study involving 50 family practices in Budapest in 1996–1998, showed that the prevalence of registered hypertension among 71,040 subjects was 21.33%, but popular screening showed that, among those people who considered themselves normotensive, the rate of previously undetected hypertension was 36.5%. The rate of well-controlled hypertensive patients (WCR) was 12.5% and it did not change significantly (13.8% and 14.9% after 6 months and at the end of the Program, respectively) in patients of those physicians whose practice was three times investigated during the study period, but it increased to 25.5% (after 6 month) and to 34.5% (by the end of the Project) in those physicians who participated in a thorough teaching course ending with examination at baseline.

The Manage It Well Program (14) involved 6,500 hypertensive patients outside of Budapest. We used an integrated approach, involving patients' detailed education, regular teaching of the healthcare professionals, frequent office visits with questionnaires and discussion, regular home BP monitoring, induction of changes in lifestyle, and once daily pharmacotherapy for all patients. At baseline, the WCR was only 2.9% (a striking difference from that found in Budapest), but, by the end of the 6 month long program, it went up to 40.9%.

The Live Below 140/90 ongoing complex program involves physicians' and patients' education, home BP monitoring, telecommunication counseling, and uses the Hypertension Register of HSH distributed in Regional Centers, Subcenters, and Outpatient Departments, and 857 family physicians (15–19) showed detailed characteristics of 38,372 hypertensive patients and antihypertensive practice of physicians. These present data are representative for the Hungarian hypertensive population. The average age of patients was 61.1 years, and systolic office BP (OBP) was 141/83.9 mmHg. The mean body mass index was 28.6 kg/m^2. Abnormal values were found for total cholesterol (61% of patients), HDL cholesterol (12.1% of patients), triglycerides (54.7% of patients), and glucose (49.4% of patients). One fifths (20.5%) of patients were smokers, and regular alcohol consumption was declared by 19.3%. Early cardiovascular events in the family history appeared in 64.1%, type 2 diabetes in 30.2%, verified ischemic heart disease in 35.6%, and 6.6% suffered from stroke, 8% from renal disease, 16.3% from peripheral vascular disease, and 9.2% have had myocardial infarctions.

Of hypertensive patients, 83.8% were treated, and the most frequently used antihypertensive drug was an angiotensin-converting enzyme (ACE) inhibitor (56.5%), followed by a beta-blocker (42.6%), then a calcium antagonist (34.8%), and a diuretic (33.8%). ABPM values were significantly lower than OBPs. Both, office BP and ABPM values of diabetics' were higher than those of nondiabetics. WCRs were lower by ABPM (in 15.5% of patients) than by OBP (in 39.3% of patients), and lower in diabetics (7.5% of patients) than in nondiabetics.

THE EUROPEAN INITIATIVE

The ESH decided to organize a network of Hypertension Excellence Centers in Europe (HECE). It formed its Educational Committee, which elaborated the requirements for HECE (12), as follows. A Center of Excellence is an institution providing the highest level of both inpatient and outpatient hypertension care, including surgery, vascular interventions, and assessment of global cardiovascular risk. The institution should have in-house access to services rendered by cardiology, nephrology, endocrinology, angiology, gynecology, ophthalmology, neurology, urology, intensive care, surgery, vascular surgery, radiology (access to CT, MRI, ultrasound, isotope), angiography (+PTA with stenting), clinical chemistry (including special tests for diagnosis of secondary forms of hypertension), a library with important international journals, and access to Internet.

TASKS FOR HYPERTENSION EXCELLENCE CENTERS

In addition to clinical management of patients with high BP, the activity in CME and research (experimental/clinical/epidemiology) activity reflected by papers in peer-reviewed international, as well as in local scientific journals, and also by scientific degrees of personnel are required.

PERSONAL REQUIREMENTS FOR HYPERTENSION EXCELLENCE CENTERS

The head of the center should have international recognition in hypertension care/research (decided by the ESH Scientific Council). Doctors/scientists working in the center of excellence should have hypertension-related specializations (internal medicine, cardiology, nephrology, endocrinology, angiology, pediatrics), or that of molecular medicine, and employment of specialists with clinical experience in

hypertension management who either are ESH specialists in clinical hypertension or would qualify.

Applications for being an HECE will be evaluated by the Scientific Council of ESH and the results published in major hypertension journals (e.g., *J. Hypertension*, *Blood Pressure*).

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Current problems

SECTION 9

BLOOD PRESSURE CONTROL IN EUROPE 42

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INTRODUCTION

Tight blood pressure (BP) control in hypertensive patients is pivotal to ensure optimal protection against cardiovascular complications (1,2). It is widely accepted that antihypertensive treatment should be guided to reach predefined BP targets, for both systolic BP (SBP) and diastolic BP (DBP) measurements. In 1999, experts from the World Health Organization (WHO) and the International Society of Hypertension (ISH) thought it desirable to lower BP below 130/85 mmHg in young, middle-aged, and diabetic patients, and below 140/90 mmHg in elderly patients (3). Several international guidelines on the management of hypertension were issued a few years later, in 2003 (4–6): with regard to the treatment goals, they recommended lowering BP below 140/90 mmHg in every hypertensive patient with uncomplicated hypertension, and even below <130/80 mmHg in patients with diabetes, chronic renal disease, and established cardiovascular disease. This view has been adopted in most European countries, and is also shared by experts in the United States (7).

Despite major efforts over the last decades directed at diagnosing and treating hypertension, the world situation in terms of BP control rate is still unsatisfactory, even in industrialized countries, where patients are presumed to have easy access to healthcare (8). Actually, the BP normalization rate appears particularly poor when evaluated with the low targets proposed nowadays.

The present chapter reviews the status of hypertension awareness, treatment, and control in various European populations. Furthermore, it identifies, from the available experience, the main factors contributing to the underachievement of BP control in this part of the world. The recognition of such factors should allow a better translation of guidelines into clinical practice and, thereby, an improvement of cardiovascular outcome in the general population.

BP CONTROL RATE IN EUROPEAN POPULATION-BASED SURVEYS

A number of population studies have been conducted to assess levels of treatment and control of hypertension in Europe, with large differences observed across countries. The BP control was rather poor everywhere, even when the older cutoff limits (<160/95 mmHg) were used to define normotension. This was the case in the 1990s, before the large dissemination and acceptance of the hypertension guidelines promoting BP treatment goals <140/90 mmHg (9).

The pattern of hypertension control observed in a few representative European countries, ranked by alphabetical order, are presented here.

ENGLAND

A cross-sectional, household-based, nationwide survey involving 12,116 adults aged ≥16 years (5,604 men and 6,512 women) had been performed in 1994 (10). Subjects were considered hypertensives if they had BP levels ≥160/95 mmHg or were receiving antihypertensive treatment. The data were also analyzed by taking the ≥140/90 mmHg threshold to define hypertension. The prevalence of hypertension according to the conservative criteria (≥160/95 mmHg) was 18.6% in men and 20.2% in women. Among hypertensives, 50.1% were treated and 29.6% had BP <160/90 mmHg. The control rate was much lower, at 5.9%, using the <140/90 mmHg definition of BP normalcy. The most commonly used medications were diuretics (36%), followed by ß-blockers (29%), and calcium antagonists (22%), and the majority of patients were on monotherapy (60%).

A similar survey was carried out in 1998, providing the opportunity to evaluate whether the finding of the unexpectedly low BP control rate in 1994 was an effective incitation to improve the management of hypertension (11). Table 42.1 shows that this was indeed the case. An increase in awareness, treatment, and control of hypertension was seen over the 4-year period, although there was no manifest difference in terms of type and number of drugs prescribed. Notably, 30% of patients reported having received advice for lifestyle measures in 1994, compared with 59% in 1998. Relevantly, the British Hypertension Society guidelines recommending lowering BP to <140/85 mmHg were updated only in 1999 (12), whereas in previous years the target BP was <160/90 mmHg (13).

Table 42.1 Awareness, treatment, and control of hypertension among English adults in 1994 and 1998 surveys

	Old definition[a] of hypertension		New definition[b] of hypertension	
	1994	1998	1994	1998
Awareness				
Men	60%	68.3%	33.4%	40.3%
Women	65.8%	73.3%	46.0%	52.5%
Treatment				
Men	44.8%	53.9%	20.2%	25.7%
Women	54.4%	63.5%	31.6%	38.0%
Control[c]				
Men	26.7%	36.5%	4.7%	8%
Women	31.8%	40.1%	7.1%	10.7%

[a]Subjects with blood pressure ≥160/95 mmHg or being on antihypertensive treatment.
[b]Subjects with blood pressure ≥140/90 mmHg or being on antihypertensive treatment.
[c]Blood pressure <160/95 mmHg (old definition) or <140/90 mmHg (new definition).
Source: From Ref. 11.

Another nationally representative survey had been performed in 2000 and 2001 in a sample of 3,513 noninstitutionalized elderly people (aged >65 years) (14). The fraction of subjects exhibiting BP levels ≥160/90 (old definition) or ≥140/90 mmHg (new definition) was 62% and 81%, respectively. Among men and women identified as hypertensive according to the old definition of hypertension, 72% and 75% were on antihypertensive therapy, respectively. BP was controlled (<160/90 mmHg) in 72% of treated men and 65% of treated women. Of the subjects receiving antihypertensive drugs, 36% of men and 30% of women had their BP <140/85 mmHg.

FINLAND

Cross-sectional population surveys were conducted in 1982, 1987, 1992, 1997, and 2002 (15). This was done in a total of 29,127 subjects, aged 25 to 64 years, as part of the WHO MONICA Project (16). The population samples were collected in different areas. The prevalence of hypertension (subjects with BP ≥140/90 mmHg or taking antihypertensive treatment) decreased with years while, during the same period, the proportion of patients being aware of having high BP increased, as did the proportion of treated hypertensive patients with adequately controlled BP (<140/90 mmHg). Figure 42.1 depicts, as an example, the observations made in the North Karelia province. These data are impressive: they demonstrate that the care of hypertension can be markedly improved by intensifying efforts to diagnose and treat hypertension. Notably, the lack of SBP control accounted most of the time for the inadequate BP control. For instance, in the 2002 survey involving the North Karelia province, SBP was <140 mmHg in 37% and 39% of treated men and women, respectively. The corresponding fractions of patients with DBP <90 mmHg were substantially greater, attaining 60% and 74%, respectively.

FRANCE

A population survey had been carried out in five French cities during public sales exhibitions from October 1990 to April 1991 (17). A total of 7,107 individuals had their BP measured when visiting the booth of the French National Committee for the Control of Arterial Hypertension. Among them 1,289 were treated for hypertension (791 patients aged 35 to 65 years and 498 patients older than 64 years). BP was <160/95 mmHg in 60% and <140/90 mmHg in 27% of the younger patients. Regarding the older patients, 44% of them had BP <160/90 mmHg.

GERMANY

Surveys performed before the reunification of Germany in 1990 have permitted a comparative view on the prevalence of hypertension in populations exposed to a typically

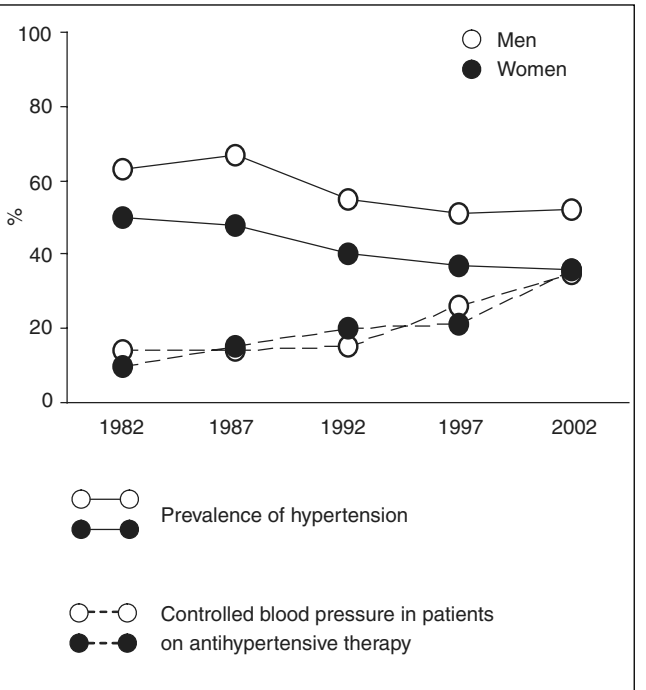

Fig. 42.1 Prevalence of hypertension [defined as a blood pressure ≥140/90 mmHg or the current intake of antihypertensive drug(s)] and blood pressure control rate in treated hypertensives (<140/90 mmHg) in the North Karelia province. *Source*: From Ref. 15.

centralized (German Democratic Republic, GDR) or decentralized health system (Federal Republic of Germany, FRG) (18). These early surveys were part of the WHO MONICA Project. The prevalence of hypertension was higher in the GDR (30% in men and 26% in women) than in the FRG (20% in men and 14% in women). Regarding the BP control rate in treated patients, it was however not really better in West Germany (13% in men and 27% in women) than in East Germany (13% in men and 22% in women).

Another national survey was completed between 1997 and 1999 (19). A total of 7,124 adults, aged 35–64 years, were evaluated. At a ≥160/95 mmHg threshold, hypertension awareness and treatment in the population was 52.7% and 41.0%, respectively. The corresponding values at a ≥140/90 mmHg threshold were 36.5% and 26.1%. Among treated hypertensives, 60.5% had BP <160/90 mmHg and 29.9% below 140/90 mmHg.

GREECE

A cross-sectional survey of all adults ($n = 694$) living in a village located in a rural area was carried out in 1997 (20). This study is of particular interest because all participants were evaluated on two visits to a general practitioner's office. As anticipated, BP was significantly lower ($p < 0.001$) on the second (122/74 ± 0.8/0.4 mmHg, mean ± SEM) than on the first visit (126.5/76.3 ± 0.8/0.4 mmHg). Only BP measured on the second visit was used as a criterion for the diagnosis and control of hypertension. The prevalence of hypertension, defined as a BP ≥160/95 mmHg or the use of antihypertensive drug(s), was 19.6%. The prevalence was significantly higher, at 28.4%, when the evaluation was made using the ≥140/90 mmHg threshold. The proportion of treated patients having their BP <160/90 mmHg or <140/90 mmHg was 83.5% and 49.5%, respectively.

ITALY

Large samples of adults (aged 30–79 years) living in the small town of Gubbio was included in a prospective epidemiological investigation (21). They had their BP measured twice, the first time between 1983 and 1985, and the second time approximately 6 years later. A cohort of 1,125 men and 1,445 women were examined at both screenings. The prevalence of hypertension (BP ≥160/95 mmHg, or use of antihypertensive drug(s)) increased only slightly during the follow-up, from 28% to 31% in men and 33% to 36% in women. The proportion of treated hypertensives was significantly greater ($p < 0.05$) at the last control (83% in men and 86% in women) than at the initial control (70% in men and 76% in women). The most striking feature was a marked improvement in the degree of BP control. The fraction of treated patients having achieved BP levels <160/95 mmHg rose significantly ($p < 0.05$) from 39% to 66% in men and from 42% to 61% in women. This improvement in BP control may reflect an enhanced motivation of patients and healthcare professionals, which might represent a positive impact of organizing epidemiological studies in the community.

The PAMELA study is large-scale survey ($n = 2,051$) of randomly selected adults (aged 25–74 years) from the city of Monza, near Milan (22). It is original since it was planned to measure not only clinic BP (average of 3 readings), but also home BP (average of a morning and an evening self-measurement), and 24-h ambulatory BP (average of all readings obtained at 20 min intervals during day- and nighttime). Based on clinic and home measurements, the participants were considered hypertensive if their BP was ≥140/90 mmHg or ≥132/83 mmHg, respectively. The corresponding threshold for 24-h ambulatory was set at ≥125/79 mmHg. The percentage of subjects with high clinic BP was 26.6%. The corresponding figures for home and 24-h BP values were 22.1% and 22.1%, respectively. A total of 398 hypertensives were on antihypertensive therapy. Figure 42.2 illustrates the percentage of these patients who had their BP controlled in the different settings of BP measurement. More patients exhibited normal BP values when the measurements were performed outside the medical environment, i.e., in conditions devoid of the white-coat effect. Notably, the control of DBP was significantly ($p < 0.05$) more frequent than the control of SBP. This was true for the three types of measurements.

THE NETHERLANDS

A cross-sectional analysis of 7,983 subjects (aged ≥55 years) included in the Rotterdam Study between 1990 and 1993 was performed (23). Hypertension was based on BP levels ≥160/95 mmHg or the use of antihypertensive medication(s). The prevalence of hypertension rose with age and was higher in women (39%) than in men (31%). A large fraction (70%) of treated hypertensives had their BP <160/95 mmHg. The probability to be successfully treated was greater in patients living in a home for the elderly.

A recent study investigated the influence of ethnicity on the diagnosis and the management of hypertension. A higher prevalence of hypertension, together with a poorer BP control, was found among Black and South Asian people compared with White people (24).

POLAND

Poland in the years 1987–1988 served as an example of a country undergoing major political and economic transitions.

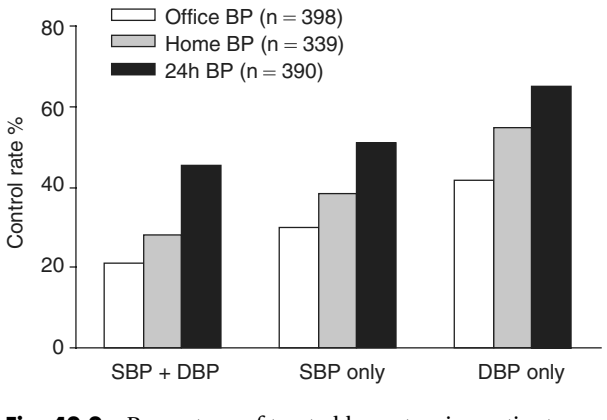

Fig. 42.2 Percentage of treated hypertensive patients having their BP controlled at the clinic (<140/90 mmHg), at home (<132/83 mmHg), and during 24-h ambulatory monitoring (<125/79 mmHg). *Abbreviations*: BP, blood pressure; DBP and SBP, diastolic and systolic blood pressure. *Source*: From Ref. 22.

In a survey conducted in this country at that time, a sample of 1,835 individuals aged 45 to 64 years was studied (25). They were residing in either an urban or a rural area and were considered hypertensive if their BP was ≥160/95 mmHg or the patients were on antihypertensive therapy. The prevalence of hypertension was similar in urban (37% in men and 40% in women) and rural populations (36% in men and 43% in women). Awareness of hypertension, however, was better in the urban (72% in men and 82% in women) than in the rural areas (57% in men and 70% in women). Among treated patients, BP control (<160/95 mmHg) was higher in men living in the urban (41%) than in the rural (31%) environment. No difference was observed in women (34% in urban and 31% in rural area).

SPAIN

A cross-sectional survey involving 2,021 individuals, aged 35 to 64 years, was conducted in 1990 (26). The data were analyzed by defining hypertension as BP levels ≥140/90 mmHg or the use of antihypertensive therapy. The prevalence of hypertension calculated using these criteria in the whole population was high, at 46.2%, increasing from 30.7% to 60.3% in men aged 35–44 and 55–64 years, respectively, and from 22.7% to 65.2% in women from the same age groups. The proportion of aware hypertensives was 39.8% among men and 47.7% among women. BP control (<140/90 mmHg) was achieved in 15.5% of the total population (13.6% in men and 16.5% in women).

The present review of data describing the prevalence of controlled BP across different European populations clearly shows that many hypertensive patients remain undertreated. The control of hypertension is still unsatisfactory even in countries where the healthcare system provides adequate resources to diagnose and manage patients with high BP. Today, it appears crucial to lower BP below 140/90 mmHg in all hypertensive patients, not just below 165/95 mmHg, as was the goal until a few years ago. This explains why the target levels of <140/90 mmHg were introduced in the analysis of the most recently published national surveys. It is hoped that the BP control rate will be improved in Europe in response to the increasing acceptance of the <140/90 mmHg goals of therapy.

It may be tempting to establish a "hit parade" for the BP control rates observed in hypertensive patients from various countries. This, however, should be avoided. Surveys may greatly differ in the way they were conducted (mode of selection of subjects, site and number of BP measurements), which renders direct comparisons difficult and potentially misleading.

The decision to initiate antihypertensive therapy in a given patient or to intensify its treatment is usually based on repeated BP readings taken by a doctor. BP levels determined on a single occasion in the context of a survey can therefore not be expected to represent the "true" BP control rate in the community.

BP CONTROL RATE IN INTERVENTIONAL MORBIDITY-MORTALITY TRIALS PERFORMED IN EUROPE

European countries have contributed importantly to the realization of controlled morbidity–mortality trials in the field of hypertension (2). In the majority of these interventional trials the goal was to normalize DBP. In the most recent one, however, the aim was to normalize both SBP (<140 mmHg) and DBP (<90 mmHg). This was the case for instance in the CONVINCE trial (27). A total of 16,602 patients diagnosed as having hypertension and who had ≥1 additional cardiovascular risk factors were randomized to an average of 3 years to either a calcium antagonist based (controlled-onset extended release verapamil) or a ß-blocker based (atenolol). It is worth mentioning here a subanalysis of this trial in which the possible existence of regional differences in BP control was investigated (28). Figure 42.3, for instance, shows the proportion of hypertensives recruited in Western Europe ($n = 2{,}048$) and Eastern Europe ($n = 1{,}891$) who had their BP <140/90 mmHg at baseline when they were receiving previous antihypertensive therapy. It also shows the percentage of patients from the same regions having achieved the target BP during the trial. There was an impressive improvement in BP control in Western as well as Eastern Europe. This may reflect an increased motivation of doctors and patients having agreed to participate in a strictly controlled clinical trial. Another contributing factor may be the removal of economic barriers as the medications in the CONVINCE trial were provided free of charge. This latter factor probably played a major role in Eastern Europe, where not only was the BP control rate better (92.8%) compared to Western Europe (67%), but also the continuation rate on blinded study medication improved (87.6% versus 66.4%, respectively).

BP CONTROL RATE IN HYPERTENSIVE PATIENTS FOLLOWED BY PHYSICIANS IN DIFFERENT EUROPEAN COUNTRIES

There is a growing interest for studies addressing the issue of BP control in hypertensive patients followed by physicians in private practice or hospital hypertension units. Such studies are representative of the everyday clinical experience of physicians, showing how difficult it is to normalize BP in every hypertensive patient, even if at high cardiovascular risk, and help to identify barriers to the achievement of a satisfactory

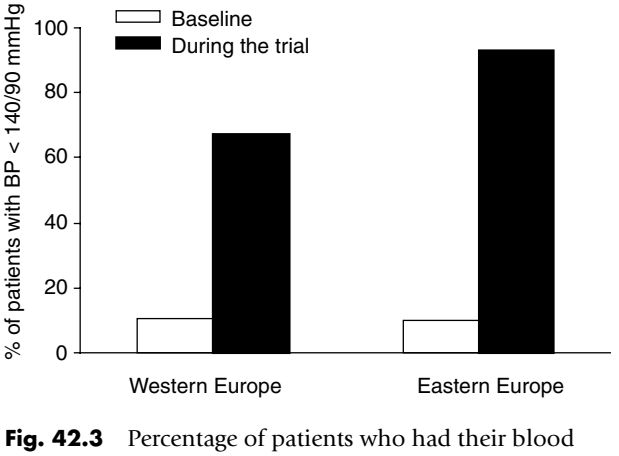

Fig. 42.3 Percentage of patients who had their blood pressure (BP) <140/90 mmHg at baseline when receiving previous antihypertensive therapy, and percentage of patients having achieved the target BP of <140/90 mmHg during the trial (average of the 18- and 24-month visits). *Source*: From Ref. 28.

BP control as well as possible strategies to improve it. That BP should be lowered below 140/90 mmHg in most hypertensive patients was clearly stated in the 1999 WHO/ISH guidelines (3). These recommendations were then progressively spread out in the majority of European countries. To give a chance for these recommendations to be well implemented, only studies whose data were collected since 1999 are reported here, the countries being ranked alphabetically:

BELGIUM

In a prospective cross-sectional survey, 253 general practitioners were asked to provide information on the first 15 men aged 55 years or older who showed up in their office (29). Data from 3,761 subjects were obtained. Out of them, 74% were considered to be hypertensive (of whom 20% had their BP ≥140/90 mmHg and 80% were on antihypertensive therapy). BP was <140/90 mmHg in 38% of the treated patients, and in 31% of all hypertensives. The hypertensive patients were classified into different risk categories according to the 1999 WHO/ISH guidelines (3). This could be done in 1,316 patients. The proportion of patients who were treated was 47%, 56%, and 86% in the medium, high, and very high risk groups, respectively. Among patients on antihypertensive therapy, BP was more frequently controlled in the medium (46%) than in the high (37%) and the very high risk groups (31%). The BP control rate was significantly better among treated patients with diastolic hypertension (defined as DBP ≥90 mmHg irrespective of SBP) than among treated patients with isolated systolic hypertension (SBP ≥140 mmHg and DBP <90 mmHg), at 53% and 33%, respectively (30).

FRANCE

A cross-sectional study was carried out in a sample of 3,153 general practitioners who were requested to give information on the first five hypertensive patients arriving in their office (31). Data from 14, 066 treated patients were available for analysis. These patients were divided into three groups according to the cardiovascular risk stratification proposed by the 1999 WHO/ISH guidelines. BP control (<140/90 mmHg) was seen less frequently in patients with the highest risk (27%) than in those with the medium (31%) and the lowest risk (43%) (Figure 42.4). A key observation was that the high risk patients more frequently received two or more drugs (56%) than their medium (44%) and low risk (34%) counterparts. Thus, patients who expected to benefit the most from BP normalization are also patients who are the most difficult to treat.

The BP control rate has also been evaluated in treated hypertensive patients known to have coronary heart disease (32). A total of 1,423 patients were recruited by general practitioners, and 2,596 by cardiologists. Normal BP (<140/90 mmHg) was observed more frequently among patients followed by cardiologists (40.8%) than among those followed in general practice (26.3%), and more often among patients in the lowest cardiovascular risk group (general practitioners: 42.2%; cardiologists: 56.1%) than in the highest cardiovascular risk group (general practitioners: 26.3%; cardiologists: 32.4%). Among patients with uncontrolled hypertension, 67.4% were receiving ≥2 drugs when followed in general practice, compared with 77.7% when followed in cardiological practice.

Recently, the results of an observational cross-sectional epidemiological study aiming to assess the determinants of hypertension control have been published (33). A total of 4,966 hypertensive patients aged >18 years were included, followed by 2,487 practitioners. The patients had to be pharmacologically treated with the same drug(s) for more than 1 month and less than 1 year. Half of them had two or more cardiovascular risk factors in addition to high BP. BP was controlled (<140/90 mmHg) in a small fraction of patients (18%). BP was <140/90 mmHg in only 15% of patients with coexisting diabetes ($n = 559$). Insufficient treatment was a main cause of the unsatisfactory BP control, as 48% of the patients were on monotherapy. Other factors independently associated with poor BP control were male gender and advanced age.

GERMANY

A cross-sectional prevalence study was conducted in a nationwide sample of primary care doctors ($n = 1,912$) who were asked to give information on a total of 43,549 patients; 17,485 of them were considered as having hypertension (40.1%): in 12,281 patients, the diagnosis was hypertension, and in the remaining 5,204, hypertension was associated with diabetes: 30.1% of the former and 27.3% of the latter had their BP < 140/90 mmHg. Among hypertensive patients, 57.4%, 79.6%, and 87.7% received antihypertensive therapy when aged from 16 to 40 years, 41 to 60 years, and over 60 years, respectively.

ITALY

The BP control rate achieved in hypertensive patients managed by specialist physicians had been studied in 131 outpatient centers located in northern (34.5%), central (28.1%), and

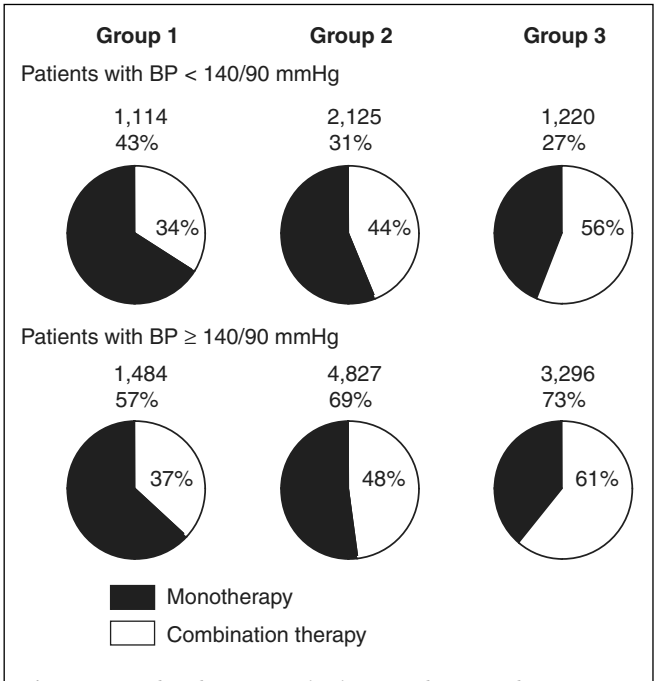

Fig. 42.4 Blood pressure (BP) control rate and management of hypertension according to cardiovascular risk category. *Source*: From Ref. 31.

southern Italy (37.4%) (34). Each center had the task of recruiting a minimum of 20 consecutive patients attending a routine visit. A total of 2,775 patients with a mean age of 61 years were included. Almost all these patients were receiving antihypertensive therapy (monotherapy: 36.9%; combination therapy: 56.9%). The prevalence of BP <140/90 mmHg was 37.5%. The control of SBP only was less frequent (40.2%) than the control of DBP only (64.4%). The total cardiovascular risk profile was calculated according to the 2003 European Society of Hypertesion–European Society of Cardiology (ESH–ESC) guidelines (4). Low–medium risk, high risk, and very high risk patients accounted for 37.3%, 34.2%, and 28.5% of the study population, respectively. The BP control rate was evaluated again 6 and 12 months later. Table 42.2 shows the percentage of patients with normal BP (<140/90 mmHg) at entry into the study and during the 6- and 12-month follow-up. The control rate was better in low-medium risk patients than in high and very high risk patients, and was better on the last than on the first visit. The improvement could hardly be explained by an intensification of drug consumption as the treatment remained unchanged during the course of the study in 78.3% of the patients, was stepped up in only 15.3% of the patients, and was even stepped down in 6.4% of the patients. An enhanced compliance with the prescribed treatment was thought to play a predominant role.

An observational study was performed by 1,800 general practitioners who were asked to recruit 10 consecutive patients aged 54 to 84 years (35). The diagnosis of hypertension was based on a BP ≥140/90 mmHg or the current use of antihypertensive drugs. A total of 12,792 patients were included in the study (5,280 were untreated and 7,512 treated). Overall BP control (BP <140/90 mmHg) occurred in 18.4% of subjects, with no relevant difference in relation to gender and age. Among treated hypertensives, 23.1% were diabetic. In these patients BP should optimally be lowered below 130/80 mmHg (4). Such a target was achieved in only 3% of cases, compared with 14.9% when considering a target of <140/90 mmHg.

SPAIN

A study was performed to assess the BP control rate among special subgroups of hypertensives treated in 47 hospital-based hypertension units nationwide (36). Out of the 4,049 analyzed patients, 48% were on monotherapy and 42% had BP <140/90 mmHg. The presence of diabetes (fasting blood glucose >126 mg/dL or current antidiabetic therapy), renal failure (serum creatinine >1.5 mg/dL in men and >1.4 mg/dL in women), and proteinuria (urinary protein excretion >300 mg/day) was observed in 893, 669, and 1,757 patients, respectively. In these patients, the 2003 ESH–ESC guidelines dictate pursuing the lowering of BP below 130/80 mmHg (4).

Table 42.2 Percentage of blood pressure control (<140/90 mmHg) at entry into the study and at months 6 and 12 of follow-up according to the cardiovascular risk category

	Entry	Month 6	Month 12
Low–medium risk	48.5%	50.4%	55.8%
High risk	34.6%	44.0%	51.3%
Very high risk	39.2%	44.0%	48.4%

Source: From Ref. 34.

This target was reached in only 10% of diabetics, 12% of patients with renal failure, and 12% of proteinuric patients.

The BP control rates achieved either conventionally (i.e., using office BP as a criterion) or with reliance on ambulatory BP monitoring have been compared in 12,897 hypertensive patients, recruited by 1,124 physicians from 210 primary healthcare clinics (37). There was less than 1-month interval between the office BP measurements and the 24-h ambulatory BP monitoring. Office BP was controlled (<140/90 mmHg) in 23.6% of patients. The daytime ambulatory BP control rate (<135/85 mmHg) was 51.6%. Among patients who had daytime ambulatory pressures ≥135/85 mmHg, only 5.4% had their office BP controlled. These observations are of interest: they indicate that the BP control rate in treated hypertensives is substantially better when relying on BP readings taken outside the medical setting rather than on standard office-based measurements. This is important since ambulatory BPs are known to reflect cardiovascular risk more closely than BPs determined in a medical setting.

A survey has been performed very recently in 5 Western European countries (38). The data were collected in 2004 using identical procedures, allowing valid comparisons between countries. The survey involved a nationally representative sample of physicians who were asked to provide information on 15 consecutive cardiovascular patients. Figure 42.5A shows the percentage of treated hypertensive patients who had BP <140/90 mmHg. There were large differences across some countries, but the control rates were overall clearly better than that previously reported in the same countries. Notably, only a small fraction of patients with inadequately controlled BP had their treatment modified (dose escalation, addition, or switch of drug), indicating that physicians' inertia may account for the persistence of high BP levels in many patients on antihypertensive therapy (Figure 42.5B).

Taken together, the recent studies described above show that there is still a large room for improvement in European countries with regard to the control of BP in hypertensive patients. This is true not only when the patients are treated by primary care physicians, but also when follow-up treatment is given to them in a specialized setting. Notably, however, the BP control rate observed in everyday practice is generally superior to that observed in population surveys, but inferior to that achieved in interventional morbidity-mortality trials. It should be pointed out that it is easier to control BP in hypertensives with low rather than in those with high cardiovascular risk, and that combination therapy is required in most hypertensive patients in order to bring BP to normal levels.

CONCLUSIONS

There is robust evidence that tight BP control in hypertensive patients allows maximal protection against cardiovascular and renal diseases (1,2). Owing to the availability of several classes of BP lowering drugs it is possible today to normalize BP in most hypertensives. Population surveys conducted in European countries revealed that many people with hypertension are treated but not controlled. This may be partly due to the fact that these surveys were performed at a time when the necessity of a strict BP control was not yet established and accepted by the healthcare professionals, including medical doctors. Large differences in BP control rates were observed among countries, reflecting, probably to a large

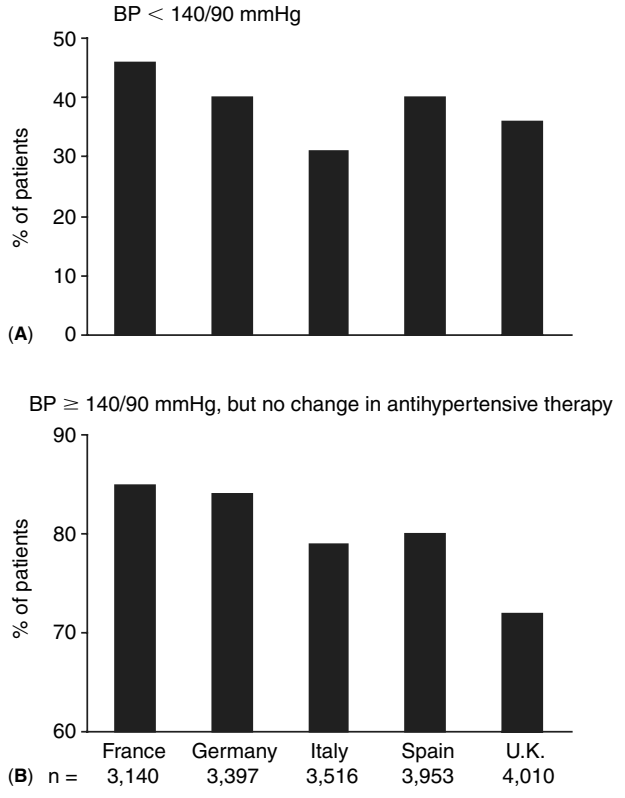

Fig. 42.5 (**A**) Percentage of hypertensive patients having their blood pressure (BP) controlled (BP <140/90 mmHg) during antihypertensive therapy. (**B**) Percentage of patients in whom antihypertensive treatment was not modified despite inadequately controlled hypertension (BP ≥140/90 mmHg). *Source*: From Ref. 38.

extent, the financial resources made available for the management of high BP. The BP control rate observed today in everyday practice is improving, but remains unsatisfactory. In order to normalize BP in most hypertensive patients, it appears necessary to extend the use of drug combinations. This is especially true in patients at high cardiovascular risk, in whom it is generally more difficult to bring BP under control than in those at low cardiovascular risk.

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HYPERTENSION IN THE VERY ELDERLY 43

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INTRODUCTION

One of the biggest risks for cardiovascular disease, whether or not it is related to hypertension, is increasing age. Nearly all people aged 75 years or over have a 5-year absolute cardiovascular risk of over 15% even if they do not smoke, are not diabetic, and have an acceptable total cholesterol to high-density lipoprotein (HDL) cholesterol ratio (1). One might argue that, as the absolute risk of a cardiovascular event in elderly individuals and, particularly, the very elderly is high simply due to their age, they would all benefit from treatment.

There is overwhelming evidence that antihypertensive treatment in patients up to the age of 80 is beneficial. Several well conducted randomized controlled trials published over the last 20 years (2–8) have shown consistent benefits with a reduction in stroke events of 25–47%, of cardiac events of 13–27%, and all cardiovascular events of 17–40%. There have also been several meta-analyses that have also shown consistent benefits (9–12). Subjects recruited to these trials represent older populations from Europe (West and East), United States, Australia, and China with diastolic, combined systolic and diastolic, and isolated systolic hypertension (ISH). Overall, there is a high benefit to risk ratio, and it is higher than that seen in younger patients.

Over the age of 80, the evidence is more confusing, both in terms of risk and benefit. Guidelines for the management of hypertension vary. The joint guideline from the European Society of Hypertension and European Society of Cardiology simply report the beneficial aspects from a meta-analysis (13) of subjects aged over 80 recruited to intervention trials (14). It does not report the possible adverse effects from the meta-analysis. Those from the British Hypertension Society state that benefits of BP-lowering therapy in people over the age of 80 years have not yet been established, although they reference the same meta-analysis (15). The American Joint National Committee (JNC) VII makes no mention of those over the age of 80 (16). The most recent guidelines in the United Kingdom from the National Institute of Health and Clinical Excellence state that one should "offer patients over 80 years of age the same treatment as other patients over 55, taking account of any comorbidity and their existing burden of drug use" (17). The guidelines quote that these recommendations are unchanged from those from 2004 when they qualified their statement with the comment that "patients over 80 years of age are poorly represented in clinical trials and the effectiveness of treatment in this group is less certain" (18). In 2004 they rated the level of certainty for this statement as level B (on balance of evidence, a pattern of care is recommended with caution.) although in the most recent guidelines it is now level A (there is robust evidence to recommend a pattern of care) despite no new trail evidence in that time.

Lack of clear evidence becomes increasingly relevant when one considers that although the number of individuals over the age of 65 continues to increase, it is the individuals over the age of 80 that are increasing the most rapidly. In several countries by the year 2020 the individuals over the age of 80 will account for more than 4% of the total population (19). In the 25 countries of the European Union the number of people over the age of 80 is expected to triple from 4.0% in 2004 to 11.4% in 2050, with the highest proportions expected in Italy (14.1%), Germany (13.6%), and Spain (12.8%) (19).

Those over the age or 80 can be considered as survivors, although like older adults in general, they are a very heterogeneous group. It is likely that at some age or certain level of comorbidity individuals will not survive long enough to gain substantial benefit from treatment, particularly not from an increase in life years. However, a reduction in disability, maintenance of independence, and quality of life would clearly be of benefit. This chapter reviews the current literature in regard to the individuals over the age of 80.

PATHOPHYSIOLOGY, EPIDEMIOLOGY, AND DIAGNOSIS

With increasing age there is a progressive decrease in vascular compliance due to thickening of the subendothelial layer within the arterial wall. This occurs as a result of an increase thickening of the intimal layer brought about by the migration of smooth muscle cells (20). There are age related increases in the content of lipids, collagen, and minerals, which contribute to a reduction in arterial distensibility (21). Due to this increase in arterial stiffness, pulse waves are reflected from the periphery more quickly resulting in reflected waves returning to the heart before the closure of the aortic valve. This results in a late peak in systolic central arterial pressure and as a result there is augmentation of the

systolic blood pressure (BP) peak. With the reduction in distensibility there is also a decrease in diastolic BP and thus a decrease in diastolic coronary blood flow (22). There are also age related decreases in blood volume and baroreceptor responses that contribute to alterations in BP regulation as well as reduced sympathetic function and a blunting of plasma renin activity (23,24).

Thus in most countries it is observed that BP increases with age. It should be noted that in some primitive societies this association with age has not been observed suggesting that it is not a simple sequelae of aging (25). Longitudinal studies such as the Framingham cohort provide strong evidence for the age-related change in BP. In Framingham systolic BP increased in a linear fashion with age and to a similar degree in both men and women, although men had a consistently higher level than women by about 5 mmHg (26). Different rates of change in BP were seen in the highly screened individuals of the Baltimore Longitudinal Study on Aging, although again no gender cross over was seen as can be the case in cross-sectional data (27). With regard to diastolic BP this increased to the age of 60 following which it plateaued in both sexes and then tended to decline again reflected the age-related changes mentioned. Given these changes it is obvious that there is a large increase in pulse pressure with age.

With this increase in BP with age, hypertension as defined as a BP of greater than 140 mmHg systolic or 90 mmHg diastolic is common. In the health survey for England (2000), which focused on older people it was noted that the mean pressures for those aged 80 or over was 146.5 mmHg systolic and 75.4 mmHg diastolic for men and 156.2 and 75.4 mmHg, respectively in women. 80% of men and 90% of women in this age group were considered hypertensive (28). It should be remembered that this prevalence data along with many other population surveys is based on casual recordings and thus the rates are likely to be an overestimate. The true level of the number of individuals with sustained hypertension is likely to be a third of these (29), none the less a significant proportion of this population group. Given the previously mentioned age-related changes in systolic BP and diastolic pressure, ISH is the commonest type of hypertension seen in the elderly and particularly the very elderly. For those hypertensive individuals aged over 80 approximately 65–70% have ISH with slightly higher rates in women than men (30).

With regard to making a diagnosis of hypertension in the very elderly, the usual precautions should be used—appropriate cuff size, position of the patient, quality of the equipment, etc. There is however a greater propensity for misdiagnosis in the very elderly for various reasons.

Firstly they show greater variability in BP, particularly for systolic BP (31). It has been shown that systolic BP can fall on average by 11 mmHg over three repeated measurements (32). Seasonal differences are more noticeable in with increasing age (33) and up to a fourfold increase in patients aged 65–74 years defined as being hypertensive in the winter compared to the summer has been noted (34). The white coat effect is also greater in the elderly, especially women. The difference between clinic and home measurements can be as much as 40 mmHg (35).

The occurrence of an auscultatory gap is also more common, especially in women and patients with ISH (36). It is important to check the BP in both arms as there can be as much as a 10 mmHg difference in systolic BP between arms. Due to the higher prevalence of orthostatic hypotension it is important to measure the BP both sitting/supine and standing. Atrial fibrillation is also more common effecting 1 in 10 of those aged 80 and has its own associated problems of measuring the BP accurately. Although rare (less than 2%), pseudohypertension, where the intra-arterial pressure is lower than the measured BP due to failure to occlude a heavily calcified vessel, can lead to inappropriate labeling as hypertensive and needs to borne in mind.

Finally postprandial hypotension is frequently forgotten and can be as great as 25 mmHg after a meal in institutional elderly patients (37). It can occur from 30 min to 2 h after a meal. It is important to check for other cardiovascular risk factors and comorbidities that would influence any drug choice and look for evidence of target organ damage. It is essential to take a full drug history including over the counter preparations (especially NSAIDs). Studies of nonsteroidal usage have been shown to produce a clinically significant increment in systolic BP of 5–10 mmHg in older adults (38).

The very elderly are most likely to have essential hypertension, with primary aldosteronism being rare and pheochromocytome even rarer. The possibility of a renovascular hypertension from renal artery stenosis should be remembered given the increase of this condition with increasing age. Renovascular hypertension usually presents with elevated systolic and diastolic BP, i.e., not the common form of hypertension seen in the very elderly.

RISK OF ELEVATED BP IN THE VERY ELDERLY

It is well established that increasing levels of BP carries an increased risk for cardiovascular morbidity and mortality in the general elderly population. It increases the risk of stroke, transient ischemic attacks, heart failure, coronary heart disease (CHD), peripheral vascular disease, renal impairment, cognitive impairment, and dementia. Systolic BP is a better predictor of events in the elderly than diastolic pressure and pulse pressure may be even better.

A meta-analysis by Staessen et al. showed that in intervention trials in the elderly systolic BP at entry was highly correlated with total mortality although the association with diastolic BP was negative (12). For each 10 mmHg increase in baseline systolic BP there was a significant 12% increase in stroke and 8% increase in cardiovascular events although only 4% for coronary events that was not significant. After parametric correction for regression dilution bias, the increased risk for a 10 mmHg increase in systolic BP was 26% for total mortality, 22% for stroke both of which were significant but again only a 7% increase for coronary events that was not significant. Of note was the finding that for any given level of systolic BP a lower diastolic BP was associated with a higher death rate indicating the importance of pulse pressure.

A recent review of BP and stroke (39) reiterated the continuous and log-linear association between the BP and risk of stroke with no evidence of a threshold below which levels of BP were no longer associated with a lower risk of stroke. The risk estimates were influenced by age. The proportional change in stroke risk was less in the elderly, especially the very elderly than in middle age, although the relationship did remain positive. At the age of 50–59 years a 10 mmHg lower systolic BP was associated with a 38% reduction in the risk of a stroke while at 80–89 years the reduction in risk was only 18%. In contrast in a study by Arboix et al. of 303

patients aged 85 years or more with an ischemic stroke, a history of hypertension was not identified as a risk factor in multivariate analysis (40). It should be noted that a comparison with an age-matched control was not performed. A 14-year follow-up of a Northern Italians aged 22–95 years did show hypertension to be a predictor of stroke mortality but only up to the age of 80 in women. The relative risk of hypertension was 4.78 before 70 years, 3.69 between 70–79 and 0.39 (not significant) aged 80 or more (41).

The William Hale research program has assessed 4008 individuals with a mean age of 71.8 years (28% being 75 years or more) without a previous diagnosis of cardiovascular disease over a mean of 11.1 years (42). Data from this cohort has shown that in the 75 and over group, elevated systolic BP increased the risk of a cardiovascular event, although diastolic BP was associated with a U-shaped risk with the lowest risk occurring around 80–90 mmHg. There was a slight decline in risk over 180 mmHg systolic but this may reflect the small numbers in the cohort in this age range with that level of BP.

In the Framingham study the risk of cardiovascular mortality and total mortality has been shown to increase smoothly with increasing systolic BP between the age of 45 and 74. An interesting reanalysis of this data by Port et al. (43) has suggested that neither all cause mortality nor cardiovascular mortality depended on systolic BP in a strictly increasing manner. The authors suggest that risk was independent of systolic BP for all pressures lower than a threshold at the 70th percentile. As systolic BP steadily increases with age the threshold increases with age, being 160 mmHg by the age of 65–74. Using the equation they propose, then for an 80 year old man the threshold would be 165 mmHg and for an 80 year old woman 170 mmHg. By the age of 90 the levels would be 170 and 180 mmHg, respectively.

Data from the Framingham study has also shown that for the age range 65–94 for both systolic and diastolic BP there was an increase in death from CHD (44). However, when the same data was broken down by different age groups a different result was obtained. Although there was an increase in CHD mortality for all age groups for systolic BP the degree of this effect was reduced in the 75–84 year age group. For diastolic BP there was an increase in CHD mortality in the age groups up to 74 years of age, but in the 75–84 year age group there was no significant increase. Diastolic BP has been shown to have no predictive power in the very elderly in the Framingham study.

Although at younger ages increasing BP is associated with increased mortality, over the age of 80 there is contrasting evidence (see Table 43.1). As far back as 1950 it was suggested that elevated BP was associated with increased mortality (45). Two U.K.-based studies in the 1970s generated mixed results with one suggesting an inverse relationship for men although not for women (46) and one showing no such relationship for either men or women (47). Similar results as this later U.K. study was reported in 1983 by Lindholm et al. (48) in a small Swedish cohort (49) and in 1988 by Ekbom et al. in a larger Swedish cohort (50).

However, in 1988, Mattila et al. reported that, in a Finnish cohort of 561 individuals aged 85 or more, the 5-year mortality was 72% in the normotensives compared to only 41% in those who were defined as being hypertensive. The inverse relationship was noted for both systolic and diastolic BP. Three publications from data acquired the Rancho again suggested an inverse relationship only for men and only for diastolic BP (51–53). The paradoxical relation of improved all-cause and cardiovascular survival in men aged 80 years or older with higher diastolic pressure was not explained by adjusting for a wide range of biologic and historical factors. It was also suggested that a fall in diastolic pressure of 5 mmHg was associated with poor survival in men after age 75 and that this risk was strongest in men who took antihypertensive medication.

Table 43.1 Results of population studies in the elderly relating BP to mortality

Trial	Year	Country	Age	No.	Event	Increase/decrease in events with increased BP			
						Male		Female	
						60+	75+	60+	75+
Frant and Greon (45)	1950	Holland	60+	110	Mort.	↑	↓	↑	↑
Fry (46)	1974	U.K.	60+	373	Mort.	↑	↓	0	0
Anderson and Cowan (47)	1976	U.K.	70–89	423	Mort.	—	0	—	0
Lindholm et al. (49)	1983	Sweden	70+	174	Mort.	—	0	—	0
Ekbom et al. (50)	1988	Sweden	60+	916	Mort.	0	—	0	—
Mattila et al. (48)	1988	Finland	85+	99M 462F	Mort.	—	↓↓	—	↓↓
Langer et al. (51–53)	1989–1993	U.S.A.	65+	4362	Mort.	↑	↓	↑	↑
Rastas et al. (54)	2006	Finland	85+	601	Mort.	—	↓↓	—	↓↓
van Bemmel et al. (55)	2006	Holland	85+	571	Mort.	—	↓↓	—	↓↓

Abbreviations: BP, blood pressure; F, female; M, male; Mort, mortality; —, not reported; 0, no effect; ↑, slight increase; ↓, slight decrease; ↓↓, marked decrease.

More recently Rastas et al. reported on the Vantaa 85+ study that in a cohort of 601 people over the age of 85 followed up for 9 years that low systolic BP (less than 140 mmHg) was associated with increased mortality in both men and women. This remained after adjusting for age, sex, functional status, and coexisting diseases (54). Also van Bremmel et al. reporting on the Leiden 85 plus cohort (55) found that at the age of 85 years and over, high BP was not associated with increased mortality, independently of the history of hypertension. Subjects with low systolic and diastolic BP (below 140/70 mmHg) were noted to have an increased mortality risk. This increased risk was particularly evident in those with a history of hypertension and was present even after correcting for underlying known vascular disease. Even though adjusting for markers of frailty, cognition and activities of daily living the association remained, albeit reduced.

Within all these studies the possibility of confounding exists. An inverse relationship between BP and mortality may not be the result of survival being reduced by a low BP but, rather, a low BP being an indicator of underlying cardiac disease or ill health. In the Hypertension in Elderly Patients screening study (56), although deaths from CHD showed a J-shaped curve, with the lowest death rate being for an untreated systolic BP of 160–179 mmHg, when patients with cardiac problems, asthma, diabetes, or any other serious disease were excluded, the increased mortality at lower pressures effectively disappeared. A community-based study of elderly people over the age of 85 from the Netherlands (57) reported an inverse relationship between BP and all cause mortality. For systolic BP, all cause mortality decreased from 85% in those with systolic pressures $<$125 mmHg to 59% in those with systolic pressures $>$200 mmHg. When adjusted for indicators of poor health, the decrease was no longer significant. No relation was noted between BP and mortality from cardiovascular disease or stroke after adjustment for age and sex, but, after adjustment for age sex and indicators of poor health, there was a positive relationship between diastolic BP and mortality from both cardiovascular disease and stroke.

A negative relationship between BP and total or cardiac mortality does not imply a negative relationship between BP and stoke incidence as strokes are not the major cause of death in the elderly. In the United Kingdom in 2004, for those aged 75–84, strokes account for 11% of deaths compared with 20% for ischemic heart disease and 27% for cancer, and for those aged over 85 the figures were 14%, 17%, and 14%, respectively (58).

Taking all the above into account there does remain the possibility that low BP is intrinsically harmful in the very elderly. The most likely cause for this is the high prevalence of CHD. Covert CHD is common in the very elderly. In a study of 490 patients aged 80 or over at the time of postmortem, 40% had a major coronary artery narrowed by a plaque more than 75% in cross-sectional area; 18% had one artery so narrowed; 21% had two arteries so narrowed; 21% had three arteries so narrowed; although only 29% reported clinical disease (59). The combination of the age-related changes in diastolic BP, along with further falls in diastolic pressure for whatever reason, on top of this diffuse coronary artery atheroma, has been long debated as the possible cause for the so-called "J-shaped curve" of increased cardiac events with low diastolic BP, i.e., reducing diastolic BP too much critically reduces the coronary flow occurs during diastole increasing the risk of a cardiac event.

Another possible factor may be orthostatic hypotension. This increases in prevalence with age with rates in older individuals of 6–30% depending on the characteristics of the population being studied (60–63). Both systolic and diastolic orthostatic hypotension have been found to be predictive of increased mortality in the elderly (64) and diastolic of myocardial infarction (MI) (65). Orthostatic hypotension is also a risk factor for falls, which carry significant morbidity and mortality (63). It has also been shown that orthostatic hypotension can give rise to reduced cerebral perfusion and thus predispose very elderly subjects to ischemic cerebral symptoms and even lacunar strokes and may impair cognitive function (66,67). Related to this, postprandial hypotension, which again is more common in the elderly, has been shown to predict mortality in older frailer individuals (68).

Having assessed the risk of elevated BP, one needs to consider the benefits of lowering BP. Even if the very elderly are survivors and high BP may be evidence of a well-preserved myocardium, that does not mean that a good outcome cannot be further improved upon.

EVIDENCE FOR THE BENEFIT OF TREATMENT IN THE VERY ELDERLY

As mentioned, there have been several intervention trials in the elderly published in the last 20 years (2–7), which have conclusively proven the benefit of treating individuals up to the age of 80. However, the data for those aged 80 or more remains limited (see Table 43.2).

The Medical Research Council trial in the elderly (4) and the Hypertension in Elderly Patient in primary care trial (2) excluded patients over the ages of 75 and 80, respectively. The European Working Party on high BP in the elderly trial (EWPHE) (3) recruited patients of any age over 60. The oldest patient in the trial was 97 but only 155 (18.4%) patients out of the 840 recruited were over the age of 80, the mean age being 72. The trial showed a significant reduction of 27% in all cardiovascular deaths, 38% in cardiac deaths, 36% in all

Table 43.2 Summary of intervention trials in the elderly

HEP (C+W) (2)	EWPHE (3)	MRC (4)	STOP-H (5)	SHEP (6)	Syst-Eur (7)
No patients over 80	155 (18.4%) of patients over 80	No patients over 80	269 (16.5%) of patients over 80	650 (13.7%) of patients over 80	441 (9.4%) of patients over 80
	No benefit		No benefit	Decrease in non-fatal stroke events	Decrease in non-fatal stroke events
				Fatal events not decreased	Fatal events not decreased

nonfatal cardiovascular events, and 36% in total stroke events. No benefit from treatment was shown in the age group over 80, but this may have been due to the low numbers.

The Swedish trial in old patients with Hypertension (STOP-H) (4) recruited patients aged 70 to 84 years of age. Of the 1,627 patients recruited, 269 (16.5%) were over the age of 80. The results of the trial showed a significant reduction of 73% in fatal strokes, 38% in nonfatal strokes, 47% in total stroke events, 40% in all cardiovascular events, and 43% in all cause mortality. Again no benefit from treatment was demonstrated in the age group over 80.

Of the 4,736 patients in the Systolic Hypertension in the Elderly Programme trial (SHEP) (7), 650 (13.7%) were aged 80 or over. The results of the trial showed a significant reduction of 37% in nonfatal strokes, 40% in nonfatal MIs, 33% in all nonfatal cardiac events, 36% in all stroke events, and 32% in all cardiovascular events. In the age over 80 there was a 45% reduction in stroke incidence but no decrease in fatal events.

In the Systolic Hypertension in Europe trial (Syst-Eur) (5) 4,695 patients were recruited and, of these, 441 (9.4%) were aged 80 or over. The results of the trial showed a significant reduction of 44% in nonfatal strokes, 42% in all strokes, 33% in nonfatal cardiac events, 26% in all cardiac events, and 31% in all cardiovascular events. When the results were broken into three age strata (60–69, 70–79, and ≥80) they suggested that, for total and cardiovascular mortality, but not for the combined fatal and nonfatal endpoints, the benefits of active treatment were absent in patients over the age of 80 (see Table 43.3) (69).

A subgroup meta-analysis of patients over the age of 80 in randomized controlled trials of antihypertensive trials has been published (13). Data were collected on 1,670 patients (874 received active treatment and 796 controls). Stroke (fatal and nonfatal) was used as the primary outcome with death from all causes, cardiovascular events and heart failure secondary ones. In total there were 134 strokes (57 in the active treatment group and 77 in the control). The corresponding figures for total mortality were 468 (245 active, 223 control). Overall, the results revealed a significant reduction of 34% in fatal and nonfatal strokes, 22% in all cardiovascular events and 39% in heart failure. There was no treatment benefit for cardiovascular death and a nonsignificant 6% (−5 to 18) relative excess of death from all causes. When just double-blind studies were considered the relative excess of death from all causes rose to 14% and was just significant (0–31). The authors point out the positive results were not robust as addition of data from only one hypothetical trial of proper design with no treatment effect would be enough to make the results nonsignificant.

A meta-analysis by Wang et al. (70), assessing systolic and diastolic BP lowering as determinants of cardiovascular outcome, reported a 42% reduction in strokes (fatal and nonfatal) and 28% reduction in all cardiovascular events in those over the age of 80. Again, with regards to total mortality there was a slight increase of 4%, although this was not significant. No benefit was seen for cardiovascular mortality.

Table 43.3 Subgroup analysis by age of patients recruited to Syst-Eur

Age	n	Hazard ratio for total mortality	Hazard ratio for all strokes
60–69	2,501	0.59[a]	0.46[a]
70–79	1,753	0.58	0.54[a]
≥80	441	1.11	0.67
All	4,695	0.86	0.58[a]

[a]$p < .05$. *Source*: Ref. 69.

The only trial to date to focus on the very elderly is the Hypertension in the Very Elderly Trial (HYVET) pilot. This recruited 1,283 patients aged 80 or over. This trial was a PROBE design with two treatment arms and a control group receiving no treatment. Although, the pilot was designed to assess and test the feasibility of performing an intervention trial in the over 80s, the main results have been published (71). They were in line with the subgroup meta-analysis suggesting a benefit in the reduction of strokes but a trend toward an increase in total mortality. In the combined actively treated groups, the reduction in stroke events relative hazard rate was 0.47 (0.24–0.93) while the possibility of excess deaths with active treatment was 1.23 (0.75–2.01). The authors suggested that treatment of 1000 patients for 1 year may reduce stroke events by 19 (9 nonfatal), but may be associated with 20 extra nonstroke deaths. The HYVET main trial is currently ongoing (72–75) and has randomized over 3,700 patients over the age of 80 (i.e., more than twice the number of patients included in the subgroup analysis) and will hopefully go a long way to elucidating what the risk to benefit ratio is from treating the very elderly.

Recent large trials (76–78) have included patients over the age of 80 but have been comparative trials comparing one treatment or treatment regime against another. Such trials can tell us that perhaps one class or combination of antihypertensive agents is better than other but does not inform us if initiating treatment in the first place is beneficial. The Study on Cognition and Prognosis in the Elderly (SCOPE) (79) did start off as a placebo-controlled trial but unfortunately by the end of the trial 84% of the control group were taking active medication.

What might be behind this possible increase in mortality with treatment is not clear. Possibilities may include an increase in arrhythmias due to changes in serum potassium, an increase in orthostatic hypotension, and the subsequent mortality associated with this, as already mentioned. The possibility of lowering BP too much with antihypertensive treatment could be argued as another possibility. However, a meta-analysis of individual patient data from seven randomized clinical trials showed an increased risk of events in patients with low BP in both treated and untreated cohorts, suggesting that the risk was not related to antihypertensive treatment but more likely poor health leading to low BP, and thus increased mortality (80). In the SHEP study (6), actively treated patients had a reduction in systolic BP from a mean of 171 to 142 mmHg and of diastolic from 77 to 68 mmHg yet still achieved a significant 27% reduction in MI. 60% of patients had baseline ECG abnormalities and, in these, the reduction in CHD events was 31%. The mean BP was still high, and therefore these results may not necessarily be extrapolated to subjects with lower systolic and diastolic pressures. For example, a post-hoc analysis from the International Verapamil–Trandolopril Study (INVEST) (81) of 22,576 patients (mean age 65) with hypertension and CHD showed that the risk of all cause mortality and MI (although not stroke) progressively increased with low BP, particularly below 110/70 mmHg. A J-shaped relationship between BP and stroke in treated hypertensives has been reported based on data from the Rotterdam study (82). Concern has also been raised as to whether lowering BP too much in those with

established cerebrovascular disease may have detrimental effects, particularly with regard to precipitation of lacunar infarctions and subcortical ischemia due to reductions in cerebral perfusion (83).

Overall, the current data seems to suggest a trade-off between a reduction in stroke and cardiovascular events against a possible adverse effect of increased mortality. There is the possibility that there may be additional benefits with regards to antihypertensive medication. As stated, it is now regarded that elevated BP, particularly in midlife, is a risk factor for cognitive decline and dementia, both of an Alzheimer's and vascular type (84,85). There is some evidence to suggest that treatment with antihypertensive medication may reduce the risk of dementia. The SHEP (86) and MRC (87) studies did not show any benefit. The Perindopril Protection against Recurrent Stroke Study (PROGRESS) (88), in which 48% of the 6,105 patients were hypertensive found a protective effect of treatment but only in those who had both a previous stroke or transient ischemic attack and concurrent stroke during the trial. SCOPE (79) also found no effect of treatment.

The trial that generates the most noticeable results is Syst-Eur (89,90). The extended follow of patients from the trial suggests that long-term antihypertensive treatment based on a calcium channel blocker (CCB) reduced the risk of dementia by 55% from 7.4 to 3.3 per 1,000 patient years. After adjustment for sex, gender, education, entry BP the relative hazard rate was 0.38 (0.23–0.64), suggesting treatment of a 1,000 patients for 5 years would prevent 20 (7–33) cases of dementia. A recent meta-analysis by Feigin et al. (91) suggested that antihypertensive treatment may be beneficial with an overall reduction in dementia of 20% although this was not quite significant and there was a noticeable heterogeneity between the trials. Further studies are needed in this area, but, should a benefit be found, this may provide additional reasons for treating the very elderly given the have high rates of dementia at this age.

How should one, therefore, manage someone who is 80 and hypertensive? If they are already on treatment when they reach 80, then there seems to be no reason why medication should be stopped, unless the patient is suffering from adverse effects of the treatment. For the patient noted to be hypertensive for the first time after the age of 80, then, as Goodwin (92) suggests, it will be a case of embracing complexity until further evidence is provided. Treatment decisions should be judged on a case-by-case basis, taking into account the level of BP, the amount of comorbidity, as well as the wishes of the patient having informed of them of some of the dilemma's surrounding the decision-making process.

Lifestyle modifications (salt restriction, weight reduction, increased levels of exercise, moderation of alcohol intake) can be suggested, but there is little or no evidence of benefit in this age group. It is worth noting that salt sensitivity increases with age and salt restriction would be prudent and beneficial (93,94). With regard to which medication, using the general adage of "start low go slow" is sensible. A firm idea of what target to aim for once treatment has been initiated is useful, and below 150/80 mmHg is a pragmatic one.

There are few significant differences in the reduction of cardiovascular events if BP is controlled between different classes of antihypertensives (95). CCBs have been suggested to be better at preventing strokes than angiotensin-converting enzyme (ACE) inhibitors (95,96), and this may be particularly relevant in the very elderly where there is evidence to support a reduction in strokes with treatment in this age group. The trial that has recruited the most over 80s, although it did not have a placebo arm, is the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) with 2,168 (6.8%) being 80 or over (76). ALLHAT came out in favor of thiazide-type diuretics overall. No separate analysis by age group has yet been published. The recently published Anglo-Scandinavian Cardiac Outcomes Trial-BP Lowering Arm (ASCOT-BPLA) was in favor of a CCB-based arm over one based on a β-blocker, although patients over the age of 80 were excluded from the trial (97). With regard to adverse effects apart from specific class effects these have already been alluded to above.

CONCLUSIONS

It may well be that treatment of hypertensive patients over the age of 80 is a balance between benefit in terms of a reduction in stroke and heart failure, both a major cause of disability in this age group, and the possible adverse effect of an increase in mortality. Even if this is shown to be the case, a very elderly individual may well wish to accept a risk of increased mortality if a disabling stroke can be prevented. Data from the Health Survey for England 2001 showed 62% of hypertensive individuals aged 80 or more were being treated, albeit only 19% were controlled (28). Evidence from New Zealand suggests even higher rates of treatment in this age group (98).

The guidelines for the treatment of hypertension have tended to extrapolate data from studies in younger patients or do not give a full account of the issues and data relating to the very elderly. It would be inappropriate to withhold treatment simply on the basis of age, but it does behove the scientific community to try and generate a sound basis for making clinical decisions. It can be challenging to engage the elderly and, particularly, the very elderly in research (99), but this is something that should be pursued given the demographic changes occurring. It is not wise to assume that the benefits to younger patients enrolled in clinical trials can be extrapolated to frailer older individuals (100). Those over 80 are a group of survivors, but a very heterogeneous one, and are unlikely to benefit importantly from an increase in life years gained. A reduction in disability, maintenance of independence, and quality of life would be of benefit. Hopefully, the results from the HYVET trial, which are expected within the next 2 years, will go a long way to clarify the benefits of treatment and the level of risk of treating this group of the population.

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HYPERTENSION IN ACUTE STROKE 44

Terence J Quinn, John L Reid

INTRODUCTION—HYPERTENSION AND STROKE

The importance of high blood pressure (BP) in acute stroke has been recognised for some time. As early as the 18th century physicians were attempting management of the condition through large volume venesection (1). The role of hypertension in the etiology of cerebrovascular disease is now well established from actuarial data and prospective epidemiology (2,3). There is a log-linear relationship between increasing arterial pressure and first ever stroke (4), a similar relationship appears to hold for recurrent stroke (5). A rise of mean BP of 10 mmHg leads to a 30% increase in ischaemic stroke risk (6). The corresponding risk of intracerebral haemorrhage is greater still (7). More recently large scale randomised controlled trials have confirmed the importance of reducing BP in primary and secondary prevention of stroke and other cardiovascular diseases (8). There is now overwhelming evidence that regardless of class of agent used, relative BP reduction has a significant early and long-term effect on reducing stroke risk (9). Newer antihypertensive agents may have important class specific beneficial effects in stroke prevention in addition to their BP reducing actions (8).

In the acute phase of stroke the role of high (or low) BP and the need for pharmacological intervention remains far less clear. Debate and controversy as to best management continues. The field has been dominated by strongly held views, conflicting and contradictory results of small scale interventions but little or no robust outcome evidence. Ongoing trials will hopefully provide answers in the near future.

BP PROFILE IN ACUTE STROKE

METHOD OF BP MEASUREMENT

BP measurement technique can have a major influence on subsequent results (10). Much of the earlier literature on BP profile in acute stroke was based on suboptimal methods of measurement. The limitations of casual BP measurement in the emergency setting are well recognised (11). Single BP measurements in acute stroke may be even less reliable due to altered baroreceptor sensitivity causing a state of labile arterial pressure (12). Use of continuous or beat to beat BP measurement permits a more informative representation of BP trends (13). Automatic intermittent non invasive recording provides similar data and avoids the observer bias of manual recording. A substantial body of literature is now available that has utilised these more advanced measures providing more reliable information on BP in a range of stroke syndromes (14).

Any discussion of BP in acute stroke requires an agreed definition of "normal" BP. Most recent studies have adopted the World Health Organisation definition of hypertension (15) i.e., BP greater than 140/80 mmHg. Patients with lower pressures are defined as hypotensive. However, pressures of less than 140/80 will include a substantial proportion of "normotensive" individuals. Targets for optimal BP vary depending on age and comorbidity. Given the high frequency of pre-existing cardiovascular disease and hypertension in acute stroke patients it could be argued that this fixed definition of hypertension is less clinically relevant than an individualised target BP.

INCIDENCE OF HYPERTENSION AND HYPOTENSION IN ACUTE STROKE

The large scale acute intervention studies provide useful information on the incidence of hypertension in acute stroke. Two multi-centre trials that did not have BP lowering as a primary aim, are the International Stroke Trial (IST) (16) with 19,435 patients and the Chinese Acute Stroke Trial (CAST) (17) with 21,106 patients. In IST hypertension incidence was 80%. Mean systolic blood pressures (SBP) in the range of 160.1 mmHg (SD, 27.5 mmHg) were measured at approximately 20 hours post stroke (see Figure 44.1). The CAST recorded an incidence of hypertension of 75% within the first 48 hours with average SBP of 157 mmHg. Within the acute stroke hypertensive population, there is a consistent subgroup of patients with markedly elevated blood pressures (SBP greater than 180 mmHg), 28% of IST and 25% of CAST.

In view of the inclusion and exclusion criteria utilised in such trials, caution should be exercised when applying the data to a non selected population. Patients with BP over 220/120 and patients with cardiovascular co-morbidity are

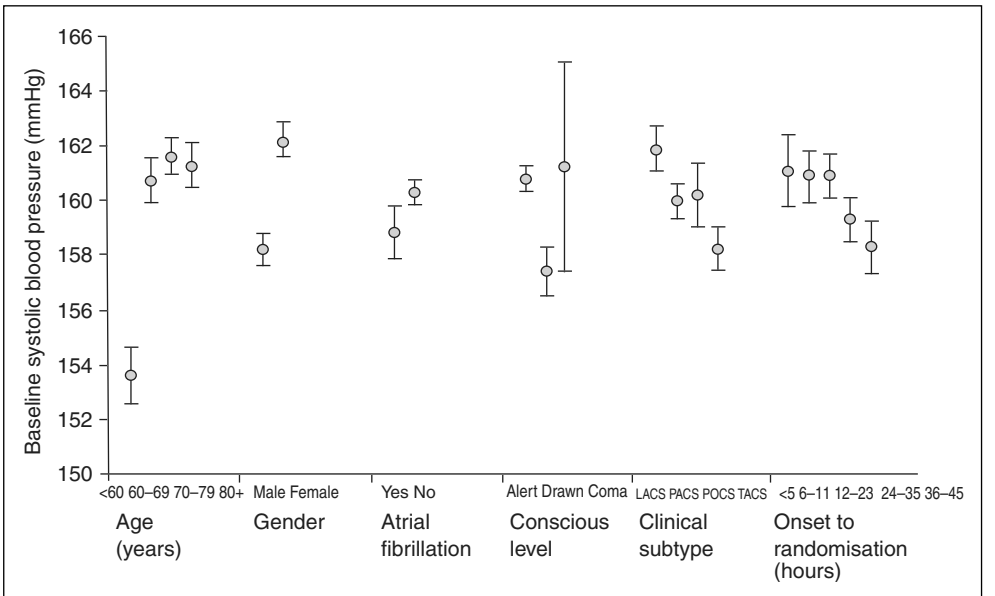

Fig. 44.1 Blood pressures recorded in the international stroke trial (subgroup analysis). *Source*: From Ref. 62.

excluded from most trials. Thus the above figures may underestimate the true incidence of hypertension after acute stroke. It is, however, reassuring that prospective observational studies confirm the findings of the large trials. In the Copenhagen Stroke Study, elevated BPs were recorded in 77% of consecutive acute stroke patients with mean BPs of 162/89 mmHg (18). Similar incidence and BP levels have been recorded in other studies (19,20).

Hypertension in acute stroke due to intracerebral haemorrhage has an estimated incidence of 90% (21). Some but not all studies have reported that BP is higher in patients with intracerebral haemorrhage than ischaemic stroke (22,23).

Although less common than hypertension, hypotension in acute stroke is also recognised as an important entity. Reversing the WHO criteria for hypertension, 18% of patients in the IST were hypotensive (16), in CAST a higher incidence of hypotension was found at 25% (17). The Athens Acute Stroke Registry (20) used a lower and perhaps more clinically relevant definition of hypotension, recording 10.5% of all strokes with a SBP less than 120 mmHg, while 2.2% of strokes had a SBP less than 100 mmHg. In these studies few patients with intracerebral haemorrhage had hypotension.

NATURAL HISTORY OF BP IN ACUTE STROKE

BP becomes elevated in the first minutes after stroke onset. Immediate paramedic measured BP revealed SBP of over 160 mmHg in greater than a third of patients (24). Thereafter, there is a gradual reduction in BP. Wallace and Levy were the first to note a spontaneous normalisation of BP, recording significant reductions in BP in the first ten days (25). More recent work has confirmed this finding but suggests that much of the reduction in BP is achieved within the first 24 hours (22), perhaps even within the first 90 min (24). Higher admission BP predicts a more rapid fall (26). Most studies report that the spontaneous fall in BP is arrested by around day seven (22). Thus most stroke physicians use the second week after an event as the starting point for commencing evidence based secondary preventive antihypertensive therapy. BP drops have been recorded in the days after intracerebral haemorrhage, but evolve over a more prolonged time period (22).

Acute BP changes in stroke vary according to stroke subtype, possibly suggesting differing underlying mechanisms. In an Italian study, highest pressures were found in lacunar and then atherothrombotic stroke types (27) Subsequent normalisation of BP was rapid in these two groups. In cardioembolic stroke the acute rise in BP was less marked and subsequent BP reduction more prolonged. The timing and degree of BP fluctuation may relate to the state of the cerebral vasculature. Spontaneous reductions in arterial BP can occur as occluded cerebral arteries are recanalised with no significant drop if artery remains blocked (28).

Although the global trend is for a gradual reduction in BP after stroke, this is not universal. In the Glycine Antagonist in Neuroprotection trial (GAIN), 6% of patients increased BP by 30% in the first week (29). It is estimated that up to one third of patients remain hypertensive in the first weeks after the event (22).

PATHOPHYSIOLOGY OF ACUTE BP CHANGE

No single mechanism has been found to account for the rise in BP in early stroke. A number of potential mechanisms have been proposed and a multifactorial etiology seems likely. Reported associations with acute hypertension include: age; (30) alcohol consumption (22); delay to admission (31); high initial disability (29); non-caucasion ethnicity (32); and increased body weight (33). Risk factors for hypotension include ischaemic heart disease and atrial fibrillation (18). As with any risk predictor, association does not confirm causation.

Hypertension

In ischaemic stroke the strongest association with acute BP elevation is previous history of hypertension (33). Previously hypertensive patients have a significantly higher pressure post

stroke than those previously normotensive (19). Over half of patients presenting with stroke have a previous history of hypertension (26); the percentage is higher for intracerebral bleeds (34). However, admission BP is not simply a reflection of poor BP control in the community; around 50% of acute stroke patients are already receiving antihypertensive medication at the time of admission (35). The spontaneous reduction in pressures in the majority of patients after stroke (25) suggests that an acute rise in pressure occurs in all groups regardless of baseline BPs.

Raised intracerebral pressure

The "Cushing reflex" of systemic hypertension in response to raised intracranial pressure could theoretically contribute to early hypertension, however the data does not support this. No association is seen between larger lesions and increased pressure (29,36). Furthermore arterial pressure rises early in the course of a stroke (24), yet significant rises in intracranial pressure are a more gradual process.

Neuroendocrine

High plasma and urinary levels of catecholamines suggest the importance of acute stroke related activation of the sympathetic nervous system (37). However, in a comparative study "normotensive" patients post stroke had similar elevations of catecholamines to hypertensives (38). Plasma levels of cortisol are also increased in acute stroke, with a failure of the normal suppression of cortisol by an exogenous steroid challenge, suggesting a central derangement of the normal hypothalamic-pituitary-adrenal homeostasis (38). Serial measurements of ACTH post event confirm loss of the usual feedback regulation (39). The renin angiotensin system and endogenous nitric oxide may also contribute to BP changes. As discussed later, blockade of the renin system and augmentation of nitric oxide are important therapeutic approaches used to modify BP in acute stroke.

Topography of lesion

It has been proposed that the site of the stroke lesion may alter BP through effects on vasomotor centres (40). A number of brain areas that control BP have been suggested by experimental work. However, imaging studies have failed to demonstrate a consistent link between lesion site and BP profile (41).

Environmental factors

A "white-coat" phenomenon, with the psychological stress of hospitalisation with stroke directly increasing BP has been proposed (42). An early study added weight to this theory by demonstrating that rises in BP were more closely related to the time of hospitalisation than the onset of symptoms (19). Although at time of publication this "white coat" effect was widely accepted there are now a number of reasons to believe that it is of limited importance after stroke. Patients admitted with other medical diagnosis do not have the same large rise of BP seen in acute stroke (43), while hospital in-patients who develop stroke do show a further rise in BP (44). The use of continuous BP monitoring should partially reduce environmental stressor bias on BP. When 24 hour monitoring has been used a significant rise in pressure is still demonstrated (45).

Alcohol

A link between alcohol consumption and admission hypertension has been postulated but has not been proven. There is no difference in admission BPs of light and heavy drinkers, although patients with the highest alcohol consumption have a greater SBP decline in the days post stroke (22). This phenomenon of rapidly falling BP in the context of previous alcohol excess is not specific to stroke patients (46).

Comorbidity

Non-cerebral complications such as urinary retention, myocardial ischaemia and infection are common immediately post stroke (47) and are likely to further indirectly influence BP (up or down) (48).

BP INTERVENTION IN ACUTE STROKE

EFFECT OF ACUTE BP ON OUTCOME

The continuing debate on the benefits and risks of intervention in acute stroke hypertension is fuelled by lack of consensus on the effect of acute BP changes on clinical outcomes (49,50). A relationship between acute hypertension and subsequent mortality has been postulated for decades (51). The majority of observational studies have found a relation between rising BP and outcome in both ischaemic stroke (52,53) and primary intracerebral haemorrhage (54). However, some groups have argued a beneficial effect of elevated SBP (55,56) and diastolic blood pressure (DPB) (Figures 44.2A and 44.2B) (57). Others have argued that BP has no effect on outcomes (58), that a significant effect is only seen in comatose patients (42) or that the effect of BP on outcome is lost in the elderly (59).

A meta-analysis of 32 studies examining the relationship between outcome and initial BP reported a statistically significant relationship between poor outcome and high SBP and DBP (60) This was true for all stroke types, although the relationship was strongest for primary intracerebral haemorrhage. Overall odds of death were increased two-fold in the hypertensive population. Lack of statistical power probably accounts for the conflicting results previously reported (61).

No randomised controlled trials were included in the above analysis. A similar relationship between admission BPs and subsequent outcome is found in the large trials. IST confirms increasing rate of death and dependency both in short term and longer term follow up is associated with higher BP (16). For patients with SBP above 150 mmHg, the risk of early death increased by 3.8% for every 10-mmHg increase in pressure (62).

Although most reports on outcomes have focussed on the hypertensive group, poorer outcomes in patients with initial hypotension have also been reported. In the IST study patients with an SBP $<$150 mmHg had, for every 10-mmHg fall in BP, an increased risk of early death of 17.9% and an increased risk of death or dependency at six months of 3.6% (62). The Athens Stroke Registry data gives an increased relative risk of 1-month and 1-year mortality of 28.2% for every 10 mmHg decrease in SBP below 130 mmHg (20).

Thus the relationship between outcome and BP does not appear to be a simple linear one, rather a "U "shaped distribution of outcomes is suggested. Different nadirs have been found for BP and optimal outcome (20,62). This is a reflection of differing background levels of hypertension in the populations studied, the "U "curve for outcome is shifted right in patients with previous hypertension (20) The previously

nonhypertensive group had best outcomes at 121–140 mmHg SBP, while the hypertensive group had a nadir around 140–160 mmHg SBP.

Some authors have claimed that the apparent U shaped distribution for outcome is artefactual, biased by the use of single casual BP measurements (14). Using non-invasive 24-hour BP monitoring, increasing death and dependency had a linear relationship with increasing systemic pressure with no level of hypotension correlating with poor outcomes (52). Although informative, studies using advanced BP recordings do not have the statistical power of the multicentre trials previously cited.

Other haemodynamic variables such as heart rate (63) and mean arterial pressure (64) also have a predictive power in acute stroke. Examining a variety of parameters in parallel it was found that a linear relationship existed between poor outcome and heart rate, SBP, mean BP, pulse pressure, mean arterial pressure, pulse pressure index and rate pressure product (65) Beat to beat BP variability and altered cardiac baroreceptor sensitivity have also been shown to be a powerful predictor of outcome after stroke (66), with an odds ratio for poor outcome of 1.38 for every 1 mmHg increase in mean arterial BP variability, independent of absolute BP level.

Several mechanisms have been proposed for the effect of hypertension on stroke outcome including early recurrence, hemorrhagic transformation, or worsening cerebral oedema (67). Of these, an increased rate of stroke recurrence is best supported by the available data. Recurrent ischemic stroke within 14 days is independently associated with increasing BP (16,20). In IST for every 10-mmHg increase in SBP the frequency of early recurrence increased by 4.2% (16). The role of hypertension in cerebral oedema is less clear. An association between initial systolic hypertension and subsequent oedema has been noted (60), but data are conflicting (16,29). In animal studies haemorrhagic transformation of stroke is associated with increasing BP, but this association has yet to be proven in man outwith the context ofthrombolysis (69–71). In primary intracranial bleeds risk of haematoma expansion is increased twofold in the hypertensive group (62). A plausible mechanism being increased cerebral blood flow raising intracranial pressure and stimulating vasogenic oedema and further bleeding (72).

The link between acute hypotension and poor outcome is likely to relate to coexistent pathology including aspiration pneumonia and other sepsis (73). In addition increased prevalence of coronary artery disease and congestive cardiac

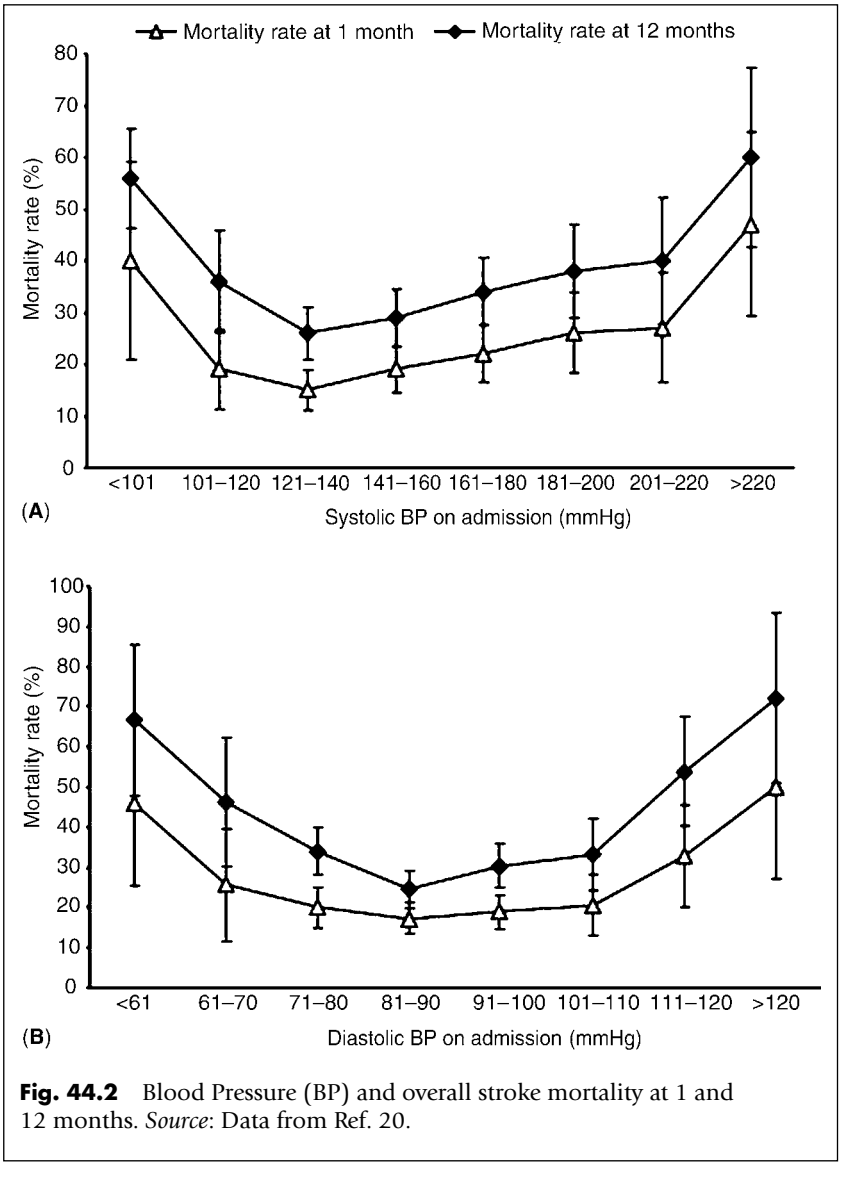

Fig. 44.2 Blood Pressure (BP) and overall stroke mortality at 1 and 12 months. *Source*: Data from Ref. 20.

failure has been found in the patient groups with hypotension post stroke (18). Systemic hypotension can worsen the stroke insult itself as low cardiac output and subsequent hypoperfusion of the brain is associated with larger infarcts (74). A non-significant trend towards early reinfarction has also been reported in the hypotensive group (62).

CEREBRAL AUTOREGULATION

In health cerebral blood flow is maintained at a constant 50 ml/100g/min in the face of wide variations in systemic pressure (75). This process of cerebral autoregulation is driven by dynamic changes in cerebral vascular resistance. In normotension the process is efficient with lower and upper limits in the range 50–150 mmHg mean arterial pressure (76). In chronic hypertension this range is shifted upwards to higher arterial pressures, a process that is only partially reversible with standard antihypertensive treatment (77). Following an acute stroke cerebral auoregulation is lost, such that cerebral blood flow is directly dependant on systemic arterial pressure. Normal autoregulatory control is not regained for weeks (78).

Given that during acute stroke cerebral perfusion is dependant on arterial BP, hypertension at this time could be viewed as compensatory and possibly protective. During the acute event an "ischaemic penumbral" area of underperfused but still potentially viable brain tissue may surround the infarcted core (79). Theoretically, artificially raising BP may further improve cerebral blood flow to the penumbra and "salvage" brain tissue. Artificial BP elevation can increase cerebral blood flow in acute stroke (79). In animal models raising arterial pressure has been associated with improved outcomes (80). In clinical practice induced hypertension has been used in the management of subarrachnoid haemorrhage and after head trauma with some success (81).

The converse may also be true and lowering BP acutely could worsen cerebral ischemia, this may be especially important in the context of atheroma stenosis of cerebral arteries (82). Case reports of poor outcomes associated with over aggressive BP reduction are common (83,84), and large spontaneous drops in pressure may be associated with increased mortality (85).

Unfortunately experimental and clinical data provides equally compelling arguments against BP elevation in acute stroke (Table 44.1). In animal studies actively raising BP worsens cerebral oedema (86). As already discussed, systemic hypertension correlates with poor outcomes likely mediated through increased stroke recurrence. In a cohort with high prevalence of ischaemic heart disease and left ventricular dysfunction there is potential for serious adverse cardiac events when maintaining or eliciting hypertension through inotropic or volume expansion therapy (87).

INTERVENTIONS TO MANAGE BP IN ACUTE STROKE

Although it is frequently commented that there is little evidence on the benefits of active intervention in acute stroke hypertension, it is more accurate to state that there is little good quality evidence. A recent Cochrane review cited more than 80 separate studies, of these the majority were underpowered, with sub-optimal BP measurement technique, and heterogenous outcome scales (88).

Pressor agents

A number of early case reports suggested a beneficial effect of artificially raising BP in acute ischaemic stroke (89,90). The most commonly studied agent is phenylephrine, others include volume expansion; norepinephrine, dobutamine, dopamine, fludrocortisone and midrodine (87). Retrospective analysis of patients treated with phenylephrine suggests that this agent can induce controlled hypertension and that in a subgroup of patients with severe carotid artery stenosis this can be beneficial (91). A recent systematic review of twelve studies examining induced hypertension found generally positive results, however heterogeneity and small patient numbers did not allow for any meaningful meta-analysis (87). Of the various agents reviewed, side effect profiles preclude their safe widespread use in a stroke population (92). Not surprisingly there have been no reports of trials assessing the use of pressor agents in intracerebral haemorrhage.

Calcium channel blockers

In acute stroke the most frequently studied class of antihypertensives are the calcium channel blockers. The dihydropyridine agent nimodipine has beneficial effects when administered acutely in subarrachnoid haemorrhage

Table 44.1 Arguments for and against active manipulation of acute stroke hypertension

Arguments for active treatment of hypertension of in acute stroke	Arguments against active treatment hypertension in acute stroke
Proven benefit in primary and secondary prevention trials.	Acute hypertension in stroke is transient in majority of patients.
Increased rate of stroke recurrence in acutely hypertensive group.	Poor outcomes noted in patients with large reductions in blood pressure.
Possible increased risk of haemorrhagic transformation and cerebral oedema in acutely hypertensive group.	Loss of cerebral autoregulation leaves perfusion of ischaemic area dependant on arterial pressure.
Acute hypertension can preclude other evidence based treatments e.g., thrombolysis.	Possible deleterious effects in context of stenosed intracranial arteries.
Beneficial effects of certain antihypertensives beyond blood pressure actions.	Certain antihypertensive agents proven to be harmful when administered acutely in stroke.

and is widely used (93). This beneficial effect is not solely dependant on prevention of vasospasm, and possible neuroprotective properties have been postulated (94). Neuronal ischaemia is associated with neurotoxic influx of calcium into cells. Pharmacological modulation of T-type and L-type channels could potentially halt the neurotoxic ion flux, a theory supported by laboratory and animal studies (95).

Clinical benefits have been less impressive in acute stroke trials. A number of small studies have reported conflicting effect on outcomes. The most recent Cochrane review studied twenty eight trials (7,521 patients) (96). A dose dependent decrease in BP was evident, with a non-significant trend towards poorer outcomes in treated patients. Intravenous administration was significantly associated with negative outcomes in a dose dependant fashion. Two large scale placebo controlled trials of intravenous nimodipine (97) (L-type calcium channel antagonist) and flunarizine (98) (T-type calcium channel antagonist) were stopped early due to concerns over poor outcomes in the treatment arms. Previous reviews claiming a beneficial effect of nimodipine if used in the hyperacute stage are not supported by current evidence (96). Functional imaging work suggests a possible mechanism for the deleterious effect, with the hypotension induced by calcium channel agents causing global decreases in cerebral blood flow (77) and poor perfusion of the ischaemic penumbra (99).

Betablockers

As with nimodipine, there was initial interest in the use of betablockers in acute stroke following the report of a beneficial effect of propranolol in subarrachnoid haemorrhage (100). Again there are theoretical benefits to acute betablockade, including lowered metabolic requirements of brain tissue and protection against cardiac dysrhthymia. Certain betablockers may have additional anti-inflammatory potentially neuroprotective effects (101). Unfortunately as with calcium channel agents clinical data did not confirm any beneficial effect. In the placebo controlled low dose betablockade in acute stroke trial (BEST) the active arms showed a significant reduction in BP with associated increased early and late mortality (102).

The combined alpha and beta receptor antagonist labetolol was used to actively lower BP in the NINDS rt-PA stroke trial, intravenous boluses being given to patients with SBP over 180 mmHg or DBP over 105 mmHg (103). Although the thrombolysis group showed an overall survival advantage, within this group the patients receiving labetalol had less favourable outcomes (104). A pilot study suggesting a possible role for labetalol in haemorrhagic stroke, has not been followed by a confirmatory large scale placebo controlled trial (105). The long duration of beta blockade and potential postural hypotension from the alpha blocking component make labetolol less attractive for use in acute stroke than other intravenous agents. It should be noted that in animal models there is a pronounced decrease in cerebral blood flow in response to labetolol (106).

Diuretics

Following the publication of the PROGRESS trial thiazide and related diuretics in low doses are increasingly used in secondary prevention of stroke (9). In the acute stroke setting bendrofluazide in the short term did not lower BP and had no effect on outcomes compared to placebo (107). In the tertiary analysis of the GAIN study, treatment with a diuretic was associated with increased mortality and poor functional outcomes (29). The population receiving early bendrofluazide is likely biased. The agent can only be given orally and dysphagia is common in the immediate period post event (47).

Nitrate oxide donors

Nitric oxide is an endogenous vasodilator that has a number of roles that theoretically could be advantageous in ischaemic stroke: inhibition of platelet aggregation (108); altered white cell function (109) and blocking potentially neurotoxic NMDA activity (110). Differing isoforms of nitric oxide synthase are present in brain tissue. It has been shown in experimental work that inducible nitric oxide synthase (iNOS) and neuronal nitric oxide synthase (nNOS) products are harmful in brain ischaemia. In contrast nitric oxide produced by the endothelial isoform (eNOS) is beneficial (112, 113). Selective NOS inhibitors can reduce infarct size in animals without adverse effects on cerebral blood flow (114). At present there is no selective nitric oxide synthase inhibitor available for clinical use.

Transdermal glyceryl trinitrate (GTN), intravenous GTN, and sodium nitroprusside (SNP) have been studied in the acute setting. In small scale controlled trials transdermal GTN reduced arterial BP in a dose dependent manner achieving reductions of mean 23 mmHg peripheral SBP (115). These significant BP reductions were made without compromising cerebral blood flow (116). Studies to date have not been powered to detect a treatment effect but further studies are in progress.

Although a powerful antihypertensive, concern over potential accumulation of cyanide has limited the use of SNP clinically. Initial work in non-stroke patients suggested that BP control with SNP was at the expense of raised intracranial pressure (116). However, more recent work with SNP in stroke has demonstrated maintained or improved cerebral blood flow to the ischaemic penumbra (117). In large intravenous doses SNP may have an antiplatelet effect making it inappropriate for use in intracerebral haemorrhage (118).

Drugs affecting the renin–angiotensin system

There is increasing evidence for organ specific effects of angiotensin converting enzyme (ACE) from both experimental work (119) and high profile clinical trials (9,120). A role for the renin–angiotensin system in dynamic cerebral autoregulation, was first reported in animal studies (121) and this has subsequently been supported by clinical work (122). Placebo controlled trials of the ACE inhibitor perindopril given acutely to hypertensive stroke patients revealed significant reductions in systemic pressure with no consequent reduction in cerebral blood flow (123). The lack of effect on cerebral blood flow despite systemic pressure changes remains apparent even in patients with significant carotid artery disease (124). The ACE inhibitor studies to date have not been powered to detect any outcome effects.

Early laboratory evidence suggested angiotensin II receptor blockers (ARB) share the beneficial effects of ACE inhibitors and may have additional benefits (125). The Losartan Intervention for Endpoint Reduction (LIFE) trial reported a 25% reduction in stroke in hypertensives on a losartan based regimen compared to an atenolol regimen (126). In rat models of ischaemia activation of angiotensin II receptors has been shown to improve recovery (127). Early use of

losartan in acute stroke has been shown to have no deleterious effects on cerebral perfusion in man (128). The evaluation of acute candesartan therapy in stroke survivors (129) (ACCESS) study assessed candesartan (another ARB) in hypertensive acute stroke patients. The trial was stopped prematurely, following concern over imbalance of endpoints. No significant effects on BP were noted between treatment and placebo arms. However, there was a significant reduction in 12 month mortality (2.9% candesartan vs. 2% placebo) related to differing cardiac event rates (9.8% candesartan vs. 18.7% placebo). Further studies are underway to explore the relevance of these findings.

Agents with secondary BP effects

A number of medications studied in acute stroke have additional BP modulating effects that may influence outcomes. Although used for its antiplatelet properties, the hypotensive actions of dipyridamole may partly account for its positive effect on outcomes post stroke (29). Streptokinase has a well characterised hypotensive effect that may contribute to its poor efficacy compared to other thrombolytic agents (130). Pentoxyphyline, magnesium sulphate, naftidrofuryl and piracetam all have potential to lower BP (88). For reasons not well understood, BPs are lower in patients treated with glucose/potassium/insulin (GKI) infusions compared to standard physiological saline (131). For all these agents the lower BPs that can be achieved have not been proven to have a significant effect on outcomes (131).

Of agents that have secondary BP raising effects, the haemoglobin based oxygen carrying solution diasprin cross linked haemoglobin was found to elicit a dose dependent pressor response, however, three month mortality was unfavourable when tested in acute stroke (132). Separate reviews of vasoconstrictor theophylline derivatives (133); amphetamine (134) and haemodilution (135) in acute stroke found no significant difference in outcomes, although these agents were not exclusively used in the acute phase of stroke and no detailed analysis of BP was made.

A PRAGMATIC APPROACH TO BP MANAGEMENT IN ACUTE STROKE

The lack of high quality evidence on the effects of BP manipulation in acute stroke is reflected in the wide variation in current clinical practice. A degree of geographical variation is evident, for example nimodipine is still widely used in acute stroke in care in China (96). Within countries variation in practice also exists, a questionnaire study of UK stroke physicians found no consensus on management of hypothetical patients with abnormal BP. A greater number chose to artificially raise low BP than treat high pressure; however the majority would continue previously prescribed antihypertensives (136). A similar Canadian study found wide variation in treatment of hypertension with frequent use of non-evidence based therapies (137).

The mode of administration of any BP intervention demands some consideration. The agent should be suitable for patients with dysphagia, as up to 50% of patients will have swallowing difficulties following the acute event (47). Topical, transdermal or sublingual agents have been explored although, dose titration can be challenging, and in the case of nitrates tolerance can develop (113). Intravenous agents offer easy dose titration but require more monitoring and associated catheters and intravenous lines may limit mobility and attempts at early rehabilitation. The agent used should also offer rapid onset with a smooth BP profile, avoiding precipitous drops in BP—which have been shown to correlate with poor outcomes (138).

Guidelines have been issued on the management of extremes of BP in acute stroke. Recommendations are to actively lower BP if consistently above 220 mmHg SBP or

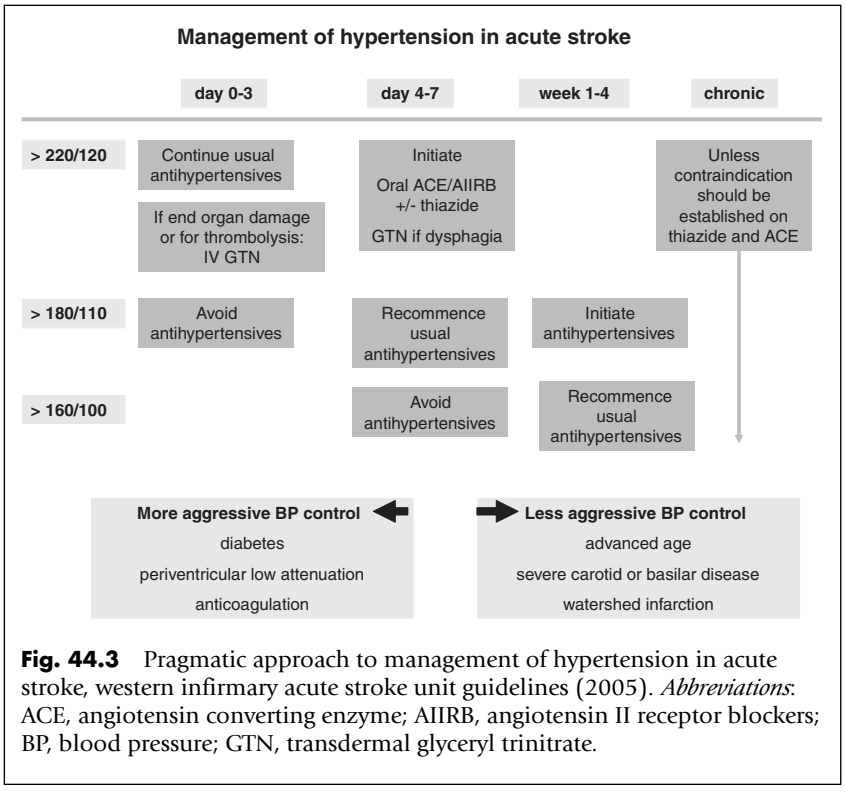

Fig. 44.3 Pragmatic approach to management of hypertension in acute stroke, western infirmary acute stroke unit guidelines (2005). *Abbreviations*: ACE, angiotensin converting enzyme; AIIRB, angiotensin II receptor blockers; BP, blood pressure; GTN, transdermal glyceryl trinitrate.

Table 44.2 Ongoing trials of acute BP management in stroke

Trial	Active intervention
Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS)	Oral/sublingual lisinopril; oral/sublingual labetalol Phenylepherine
Efficacy of Nitric Oxide in Stroke (eNOS)	Transdermal GTN Continuation of previous antihypertensives
Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS)	Continuation of previous antihypertensives
Scandanavian Candesartan Acute Stroke Trial (SCAST)	Oral Candesartan

Abbreviations: BP, blood pressure; GTN, transdermal glyceryl trinitrate.

120 mmHg DBP. Triggers for treatment are lower if intracerebral haemorrhage is present or if there is evidence of end organ damage, when pressures over 200 mmHg SBP and 100 mmHg DBP warrant treatment. No specific agent is recommended, 138 although because of the practical issues of dysphagia and the need for rapid onset and offset of action intravenous or transdermal GTN is one of the more widely used treatments.

In our acute stroke unit we have devised pragmatic guidelines for the management of BP in acute stroke. These guidelines make use of the limited evidence available and are designed for use by physicians faced with clinical decisions on hypertensive stroke patients. If pressures of more than 220 mmHg SBP or 120 mmHg DBP are recorded for thirty minutes or more, intravenous GTN by continuous infusion is considered, with target pressure reduction of 5–15%. Close monitoring of BP and clinical state is essential during the period of active BP manipulation. With the advent of thrombolysis, thresholds for treatment of hypertension in eligible patients are lower still. It has been shown that bleeding complication rates increase with acute uncontrolled hypertension and as such pharmacological therapy with intravenous GTN would be considered for pressures above 180 mmHg SBP or 105 mmHg DBP. We will follow this policy until we have definitive evidence from the controlled trials. (Figure 44.3)

THE FUTURE

Building on the evidence that we have available, large scale multicentre randomised placebo controlled trials investigating management of acute stroke hypertension are currently recruiting (Table 44.2). The results of such studies will make the background for evidence based guidance.

CONCLUSION

Meta-analysis and large scale trials confirm that acute stroke hypertension is common and associated with poor outcomes. Although observational studies have given us good data on the natural history of BP change in stroke, the pathophysiological changes that drive this phenomenon are yet to be fully explained. Similarly, it remains unclear whether acute BP changes should be treated and, if so, how this should be done. Clinical trials to date have suggested some agents that may be harmful and have not provided sufficient evidence for an optimal treatment regimen. Some of the confusion regarding acute treatment relates to the multiple potential effects of antihypertensive medication beyond BP lowering. Current guidelines are based on limited evidence, and are essentially pragmatic. Ongoing, large-scale, randomised, controlled trials should, in the near future, provide an evidence base for acute management of BP in acute stroke.

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COMPLIANCE TO TREATMENT IN HYPERTENSION 45

Serap Erdine, Margus Viigimaa

INTRODUCTION

Despite the well-known beneficial effects of lowering high blood pressure (BP), an important contributor to overall cardiovascular risk, the control of hypertension is far from being optimal, not only in the developing world but also in developed countries (1–3). Even in randomised controlled trials, where patient's motivation and physician expertise are ensured, it has been difficult to achieve optimal BP, despite the significant difference in the observed response rates (4). Among the several factors responsible for suboptimal control rates in hypertension, patient adherence, i.e., patient compliance, and persistence to treatment play crucial roles in achieving target BP values (5,6). Not surprisingly, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has identified poor medication-taking behavior (specifically, adherence) as one of the main causes of failure to control BP in patients with hypertension (7). It is not only enough that patients take their medications regularly, but also continue to do so in the long-term in chronic diseases, such as hypertension, to avoid cardiovascular morbidity and mortality.

DEFINITION AND EPIDEMIOLOGY

DEFINITION

Stated by the 2003 World Health Report as "the single most important modifiable factor that compromises treatment outcome across diseases," patient compliance or, synonymously, patient adherence is the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a healthcare provider, whereas, medication persistence represents the accumulation of time from initiation to discontinuation of therapy (Figure 45.1) (8,9). The WHO (World Health Organization) report has emphasized the need to differentiate adherence from compliance, the main difference being that adherence requires the patient's agreement to recommendations, while most of the authors believe both terms should be used synonymously (7,8,10). The term "concordance" has been suggested as a broader term in which patients' medication-taking behavior matches healthcare recommendations (11).

Persistence is measured in terms of time, whereas medication adherence is reported in terms of the percentage of prescribed doses taken per defined period of time. Medication adherence is a dynamic parameter that varies over time. It has been demonstrated that medication-taking behavior often improves during the scheduled clinic visit and presents a decrease immediately after the physician's appointment; this is called the "White coat compliance pattern" (12).

When monitored electronically, 50–60% of all patients have been shown to be fully compliant. Those who follow at least 80% of the prescribed regimen (30–40% of all patients) are considered partially compliant. And patients with periods of poor adherence, "drug holidays," or those with levels of compliance less than 80% of the prescribed treatment, are considered non-compliant (5–10% of all patients) (13,14).

EPIDEMIOLOGY

It is estimated that adherence rates are approximately 50%, with a great variation ranging between 0 and 100% (15). In a quantitative review, a mean adherence rate of 76.6% to medical recommendations has been reported for cardiovascular disease (16). As has been demonstrated in this review and other studies, adherence to medical treatment and lifestyle advice is inadequate (17). Fewer than 60% of 8,406 managed care patients on concomitant antihypertensive and lipid lowering therapy have achieved adherence with their antihypertensive treatment over a one-year period, measured by prescription fill of 80% or greater (18). While physicians claim that 70% of their patients adhere to treatment, 81% of patients claim they always take their medication (19).

Indeed, medication-taking behavior can vary considerably in the hypertensive patient population. The wide range of adherence rates in published studies is presumably a reflection not only of the range of methodologies and antihypertensive agents that have been used, but also of the number and complexity of reasons for poor compli-ance (9).

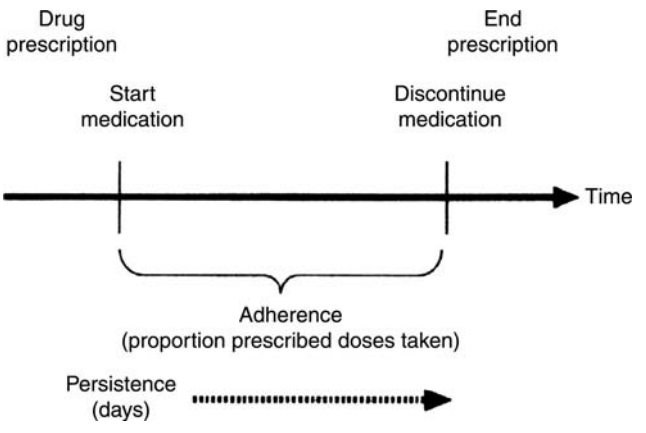

Fig. 45.1 Assessment of patient adherence to antihypertension treatment.

Persistence with antihypertensive therapy is also far from being optimal. It has been demonstrated that persistence decreased in the first 6 months after the start of the antihypertensive treatment and declined in the next 4 years (20). While 78% of patients with newly diagnosed hypertension were persistent at 1 year and only 46% at 4.5 years, the corresponding figures were 97% and 82% in patients with established hypertension, respectively (21). Compliance and persistence rates decrease substantially after 12 months. Among patients still on therapy after the first year, 50% stop therapy within the next 2 years (22). In this retrospective cohort study of new users of antihypertensive medication, 39% of patients used antihypertensive therapy continuously during 10 years of follow-up, 39% permanently discontinued therapy, and 22% discontinued temporarily and restarted therapy. Throughout 10 years of follow-up, more men than women used antihypertensive therapy continuously, however, for both men and women, persistence decreased over time.

CAUSES OF NON-COMPLIANCE

Compliance is a multidimensional phenomenon determined by the interplay of five sets of factors:

- Patient related
- Condition related
- Therapy related
- Health system related
- Social/economic related

PATIENT-RELATED FACTORS ASSOCIATED WITH POOR COMPLIANCE

Among the patient characteristics that may influence adherence, demographic factors, such as age, gender, and ethnicity, may play a role. Although the role of age is controversial, elderly people being more adherent than the younger in some studies and less compliant in others, age is not an independent predictor of compliance to treatment (15,18,23). In general, younger patients have a tendency to stop their medication due to the feeling of well-being, whereas older patients discontinue due to adverse effects (24). Although women have been found to be less adherent than men in some studies, generally more women adhere to their antihypertensive treatment (18,23,24). Evidence has suggested that depression may reduce medication adherence and is a modifiable factor (23). Patient's motivation and physician–patient relationship, namely open and trusting partnership, are important determinants of patient compliance.

CONDITION RELATED

From the perspective of the patients, hypertension is asymptomatic, and they do not feel unwell. As a result of this, patients are relatively unconcerned about having high BP. Being asymptomatic for a considerable time and due to the fact that patients are unaware of the long-term complications of hypertension, there exists a risk for hypertensive patients to be poor compliers. Rate of progression or severity of the disease and availability of the drugs are also among the condition-related factors (8).

SOCIAL/ECONOMIC RELATED

Lower socioeconomic status, i.e., cost of treatment, is a big consideration—particularly relevant in the developing world (8). Level of education and unemployment are also important risk factors for poor adherence (8).

HEALTH SYSTEM RELATED

Health system related issues, such as delivery of care, financing, and providing proper pharmaceutical management also play an important role in the promotion of adherence (8).

THERAPY RELATED

Drug intolerability or side effects, treatment turbulence or frequent changes in antihypertensive medication, initial choice of drug therapy, complexity of the treatment regimen, frequency of daily dosage, number of concurrent medications either for accompanying cardiovascular diseases or else, and high costs of treatment effects are the therapy-related factors which have a great influence on poor adherence (9,20,25).

Side effects associated with antihypertensive drugs are important, particularly among younger patients and elderly hypertensives under multidrug treatment (9,24,26). The Rational Evaluation and Choice in Hypertnsion (REACH) survey has demonstrated that 22% of the non-compliant patients did not adhere to treatment because of side effects, 34% reported unacceptable side effects, 78% told their doctors of experienced side effects, and 9% spontaneously stopped their medication (27). It is of great concern that some physicians often prefer the use of lower doses, taking the risk of inadequate BP control, to avoid the incompliance due to adverse effects (28). The solution to this important problem could be the prescription of antihypertensive drugs with favorable tolerability profiles that are well tolerated, or fixed-combination treatment strategy, as advocated by most hypertension guidelines, to achieve target BP values (29). One other advantage of fixed-dose combination treatment would be the simplification of treatment, a crucial factor to improve compliance and persistence (30). Data from several analysis have shown that patients on antihypertensive treatment with favorable tolerability and once daily dosing had greater medication persistence rates at 1 year than those treated with other classes of antihypertensive agents (23,30). The inverse relationship between adherence and the prescribed number of doses per day has been demonstrated by several studies (31,32). Simplifying a drug regimen by eliminating even one pill has been shown to improve adherence in a number of studies (18).

Multiple cardiovascular therapies and number of concurrent medications have also been shown to have a great impact on patient adherence and persistence to therapy. A retrospective, cohort study of individuals on antihypertensive and lipid lowering therapy have clearly demonstrated that the number of other medications a patient was taking in the pre-treatment year was strongly and inversely associated with adherence with concomitant therapy (18).

CAUSES AND CONSEQUENCES OF POOR COMPLIANCE

CAUSES OF NON-COMPLIANCE

IMPACT ON BP CONTROL AND CARDIOVASCULAR OUTCOMES

According to the WHO, "Adherence (compliance) to therapies is a primary determinant of treatment success. Poor adherence (compliance) attenuates optimum clinical benefits and therefore reduces the overall effectiveness of health systems" (8). Compliance with antihypertensive therapy improves BP control (<140/90 mmHg), thus preventing the risk of adverse cardiovascular outcomes. A retrospective review of medical and pharmacy claims over a 4-year period showed that patients with high levels of medication adherence were 45% more likely to achieve BP control than those with medium or low compliance (33). DiMatteo et al. reported that patients who adhered to their antihypertensive medication were three times more likely to achieve good BP control than those who were non-adherent (34). It has been well established that patients whose hypertension is uncontrolled are more likely to have target organ damage and a higher long-term cardiovascular risk when compared to those with good control of BP (35).

ECONOMIC CONSEQUENCES OF POOR COMPLIANCE WITH ANTIHYPERTENSIVE THERAPY

Discontinuing or switching antihypertensive therapy is associated with significant cost burden due to extra medical consultations, unnecessary escalation in drug treatment, i.e, higher doses or increased number of drugs (within class and across classes), decrease in productivity and loss of working days, and increase in hospitalizations.

A retrospective analysis has demonstrated that poor adherence causes an average loss of 3.5 work days per year (36). It has also been shown that poorly compliant patients incurred an additional annual cost of US$ 873 per patient (37).

Better compliance with antihypertensive drugs leads to a decreased risk of hospitalization. A retrospective cohort observation of 137,277 patients which evaluated the effects of medication compliance on all-cause medical costs has not only shown that hospitalization rates were significantly lower for patients with high medication adherence, but also all-cause medical costs (outpatient services, emergency room services, and hospitalization due to any cause) were considerably higher in patients with lower levels of compliance (38).

In conclusion, non-compliance and poor persistence are significant burdens in the treatment of hypertension that lead to:

- Suboptimal BP control
- Suboptimal CV protection
- High economic burden

Improved adherence can lead to higher rates of treatment success, fewer diagnostic procedures, fewer hospitalizations, and lower mortality rates.

HOW TO ASSESS AND IMPROVE COMPLIANCE TO TREATMENT

ASSESSMENT OF COMPLIANCE

In recent years, research efforts have focused on the use and evaluation of methods for measuring adherence. There are many methods that one can use to determine whether an individual has been taking the prescribed pills as directed. Table 45.1 compares various feasible methods used to measure adherence to antihypertensive medication.

SELF-REPORT

Research has shown that the simple, direct question, "Have you missed any pills in the last week?" has a 50% specificity and 87% sensitivity for adherence at least over the week (39). The utility of this single question is improved if the question is put to the patient's significant other, who is sometimes more truthful, and less affected by transference. More elaborate questioning systems and several multi-item questionnaires have been developed with the explicit aim of ascertaining antihypertensive medication adherence (14). In an effort to facilitate the identification of barriers to adequate compliance, Morisky et al. (40) developed a multi-item scale to assess patient adherence to BP medication regimens in the outpatient setting. For several of these self-report tools, high reliability and validity have been reported (14,41).

A recent study (42) showed that results from a brief self-report tool were associated with timing compliance as

Table 45.1 Feasible methods of measuring medication adherence in outpatient clinical settings

	Source of information	Advantages	Disadvantages
Self-reports	Patient completion of survey	Simple Economical Information on social, situational, behavioral factors that affect adherence	Recall bias May overestimate compliance May elicit socially acceptable responses
Electronic adherence monitoring; (e.g., Medication Event Monitoring System (MEMS)	Patient use of system	Provides information on daily intake and dosing Provides information enabling analysis of long-term patterns Potentially captures white-coat adherence	Medication consumption assumed but not confirmed Expensive Can be intrusive (patient must carry) Device can fail Inaccurate if subject to interference by patient or other devices
Pharmacy refill rates	Administrative database	Objective Captures amount and frequency of medications obtained by patient Reflects patient's decision to remain on drug Provides information on average adherence over time	Medication consumption assumed, but not confirmed Incomplete data if patient orders by mail, uses several pharmacies, receives free samples Lag time for data availability
Pill counts	Patient brings medications remaining for time period	Objective	Medication consumption assumed, but not confirmed Reliant on patient to bring in pills May overestimate adherence (e.g., pill dumping/sharing)
Pharmacological methods	Determination of serum and urinary concentrations of drugs	Objective, higher sensitivity and specificity	Difficult to use in standard practice

Source: Adapted from Ref. 14.

a measure of adherence obtained through electronic monitoring (MEMS) in patients taking BP lowering medication. Level 1 of the self-report was described as "I always take all of my tablets at the same time of day" and level 6 as "I take hardly any of my blood pressure tablets". A drop to a lower level (i.e., from level 1 to level 2 or from level 2 to level 3–6 combined) was associated with a decrease in timing compliance of 5 percentage points. The self-report tool appears to perform well, irrespective of the number of drugs taken.

However, self-report has some relevant limitations. It has been shown, that self-reporting frequently underestimates rates of adherence (43). Measurement of compliance by questioning the patient leads to over-estimation of the number of tablets taken when compared to an electronic pill counting device (44).

ELECTRONIC MONITORING DEVICES

Electronic monitoring is recognized as the gold standard of measurement of compliance. The electronic pill counter or MEMS may be considered as the best existing system for measurement of compliance (45). This consists of a standard pill box that has a microprocessor which can register the date and hour of the opening of the container. This allows us to monitor the amount of time between doses of drug and the change in compliance with time. There are, however, several inconveniences, such as cost and opening of the drug container, correlated with compliance.

Electronic devices to monitor medication adherence are reported to be highly reliable. Although MEMS has been reported to be acceptable to patients and effective in identifying "white coat compliers" in research studies, limitations to its use in the outpatient setting include cost, device failure, and potential for patients to manipulate the device, resulting in inaccurate measurements (14).

PHARMACY REFILL RATES

Pharmacy refill rates have been used as measures of medication adherence in several studies. Very important is the assessment of pharmacy records, which are usually highly computerized and lend themselves well to determining when and how many pills were received by a particular patient. Choo et al. (46) reported that pharmacy dispensing records and pill count were each highly correlated with dose-count adherence assessed by electronic monitoring.

Pharmacy refill rate reflects patients' decision to continue with therapy without the influences of pharmaceutical company promotion and sampling to physicians. The important limitation to the use of refill rates in the outpatient setting is the lag time for data availability, which can take 2–6 months, depending on country and prescription habits.

PILL COUNTS

In the daily practice, a physician can easily assess a patient's adherence by counting the pills remaining in a pill bottle, and comparing this number with the expected consumption. Pill counting systems have also been successfully used. Recent study reported significant correlations between pill count and compliance as measured by MEMS in a clinical study to enhance patient adherence (47). This method is objective and straightforward in the outpatient setting.

However, there are several limitations of this method. Measurement of compliance by counting remaining pills leads to over-estimation of the number of tablets taken when compared to an electronic pill counting device (44). Problems such as pill dumping or pill sharing may also overestimate adherence. So, pill counts are prone to patient manipulation. Additionally, patients must remember to bring in their pills for counting, which may be perceived as intrusive to the patient (14).

PHARMACOLOGICAL METHODS

Pharmacological measures determine serum and urinary concentrations of drugs or using biological markers integrated into the tablets. Pharmacological methods give percentages of non-compliance which are higher than found by other measures. They are generally thought to have a higher sensitivity and specificity, but remain difficult to use in standard practice (44).

Measuring drug metabolites in blood is fraught with error because patients can take the medication only when they are due to be tested (43). This is known as "white coat adherence". So, even pharmacological methods are not always precise in assessment of compliance to antihypertensive treatment.

ASSESSMENT USING ANCILLARY PROPERTIES OF DRUGS

Many physicians are accustomed to using the ancillary pharmacological properties of antihypertensive drugs to estimate adherence to medications. Long-term administration of thiazide-type diuretics often results in increased serum concentrations of uric acid, and this can be used as a surrogate marker for adherence to this important type of antihypertensive drug. Alpha- and beta-blockers are particularly good examples, since they routinely cause an orthostatic BP drop, and at least relative bradycardia, respectively (39).

METHODS OF IMPROVING COMPLIANCE

A key factor contributing to poor BP control is suboptimal adherence to prescribed therapy. Despite numerous studies conducted over the last 50 years to identify the best method for increasing patient compliance, no single intervention has emerged as superior to the others (14).

In clinical practice, treatment compliance may be as low as 50%, which is much lower than that generally observed in the clinical trial setting where tighter controls and monitoring reduce non-compliance (6,48). Furthermore, in addition to issues regarding compliance with antihypertensive therapy, long-term persistence (remaining on therapy) is also problematic.

Methods of improving adherence to antihypertensive treatment are shown in Table 45.2.

PATIENT EDUCATION

A study in 1997 by Bailey et al. (49) showed that 78% wished to know the effects of irregular treatment compliance and 90% wished to know of side effects, 60% wanted to know about possible drug interactions and 82% the causes of arterial hypertension. Providing both written and oral instructions and patient education materials about the medications is recommended.

A recent study has demonstrated that there was a 17.5% absolute increase in the BP control in the patient education group (50). Another study has shown that improvement in the management of hypertension in the "Manage it well!" program is the consequence of better education (51). Counseling from the healthcare provider about the regimen is useful, but some studies show an even bigger improvement in adherence when the advice comes from another party (nurse, dedicated educator, or pharmacist).

Most hypertensive patients have no symptoms. Thus, it is difficult to get them to accept treatment or life-style changes, which prevent cardiac events in the long-term. Hypertension is often considered as a consequence of stress, anxiety,

Table 45.2 Methods of improving adherence to medications

Provide both verbal and written instructions and patient education materials
Motivate patients to ensure that they adhere to treatment
Simplify the dosage regimen (minimizing frequency of administration, once-a-day dosing, if possible)
Minimize the number of pills
Select drugs that are well tolerated
Be sensitive to cost of pills (attempt to minimize out-of-pocket costs)
Co-operate with pharmacists and nurses
Use reminders (manual and computer-based)
Cuing medication consumption to activities of daily living (e.g., caring for teeth)
Patient self-monitoring
Involve family and significant others
Pill organizers
Electronic pill cap monitors, "alarm clocks"
Computer-based reminder systems, remote home monitoring systems

Source: Adapted from Refs. 6 and 39.

or nervousness by the patient. Thus many think that no treatment is necessary apart from sedatives or anxiolytics. Furthermore, some patients consider that this diagnosis is synonymous with the arrival of old age and thus reject the treatment.

SIMPLIFY THE DOSAGE REGIMEN

Steps should be taken (if possible) to simplify the regimen: once daily pills that can be taken without regard to meals are generally favored. Reducing the number of pills (by using combination pills) can be useful. Eisen et al. (45) showed, that compliance went from 83.6% for a single daily dose to 59% for a three times a day dosage. The legibility of the prescription is also very important since this is generally the only written information given to the patient explaining how he should take the treatment.

In a recent meta-analysis of eight studies and 11,485 observations, Iskedjian et al. (32) reported that the average adherence for once-daily dosing was significantly higher than for multiple daily dosing. Reducing the number of daily doses appears to be effective in increasing adherence to BP-lowering medication and should be tried as a first-line strategy.

SELECT DRUGS THAT ARE WELL TOLERATED

The undesirable effects of treatment are major obstacles to good compliance. The more frequent and handicapping they are, the less motivated the patient. In addition, in hypertension, these side effects occur in patients without clinical manifestations of their condition.

An increasingly important side-effect of antihypertensive treatment is erectile dysfunction (ED). ED is significantly correlated with advancing age and has a higher prevalence among men with chronic conditions such as hypertension. The prevalence of ED has been estimated to be 17% in untreated hypertensive men and 25% in treated hypertensive men, compared with 7% of normotensive men (52). Treatment of ED with sildenafil improved adherence in patients taking common long-term medications who were previously non-adherent (53).

Several studies show that the level of compliance differs according to the therapeutic class of the antihypertensive. ARB-s have the best level of compliance followed by converting enzyme inhibitors, calcium blockers, beta blockers, and diuretics.

BE SENSITIVE TO COST OF PILLS

A potential barrier to medication adherence is the high cost. Attempting to minimize the out-of-pocket costs for pills is useful in two ways. It makes the important point to the patient that the prescriber is trying to save the patient money, and it helps to stabilize resources spent on healthcare.

Generic substitution is an important opportunity to reduce the costs of pharmaceutical care. However, pharmacists and physicians often find that patients and brand-name manufacturers have doubt about the equivalence of the substituted drug.

This may be reflected by decreased adherence to therapy.

Recent study demonstrated that generic substitution of antihypertensive drugs does not lead to lower adherence or more discontinuation and cardiovascular disease-related hospitalizations compared with brand-name therapy (54). When a less-expensive antihypertensive generic equivalent becomes available, generic substitution should be considered to achieve economic benefits.

PILL ORGANIZERS

Segmented pill containers (e.g., a container with four columns and seven rows, into which are dispensed the appropriate number of pills for each morning, noon, dinner, and night-time for the week) have improved adherence.

PATIENT SELF-MONITORING

The patient can be asked to measure his own BP. Patient self-monitoring often has a beneficial effect on adherence, especially in hypertension. Home BP monitors typically reveal higher BPs after patients have omitted their medications for a few doses, and many patients are favorably impressed that improved adherence leads to generally lower BPs. This provides motivation to continue taking the medications as prescribed.

Several studies showed that compliance has significantly increased with self-measurements and large proportion of the patients who were non-compliant at the beginning of the study became so (44).

INVOLVING FAMILY MEMBERS AND SIGNIFICANT OTHERS

Involving family members and significant others in BP measurements and pill taking generally improves adherence, although some patients do not appreciate the decrease in autonomy when others become partially responsible for their BP (39).

Recently, depression was added to the list of factors associated with non-compliance with antihypertensive medications and family members are important in this aspect (24).

PHARMACISTS AND NURSES

Other health care professionals, such as pharmacists or nurses, have a role to play in compliance as they have special contact with the patient and often the patient confides in them. The nurse can serve as reinforcement for the treatment plan that physicians prescribe for hypertensive patients. Nurses can educate patients on the importance of adherence (55). The involvement of nurses, who may have more time than a physician to discuss potential side effects of medication, has been shown to improve treatment compliance (56).

ELECTRONIC PILL CAP MONITORS, "ALARM CLOCKS"

Electronic pill cap monitors can be rented to check the adherence of patients. Adherence to therapy may be increased by follow-up reminders or telephone contacts. Several companies now make "alarm-clocks" that ring when pill taking is scheduled, and do not stop ringing until the pill bottle is opened. For longer-term drug therapies, several methods of improving adherence have been proven, but have not become popular because of their cost.

COMPUTER-BASED REMINDER SYSTEMS, REMOTE HOME MONITORING SYSTEMS

Computer-based reminder systems are effective, but expensive if the person does not already have a computer. Hypertensive

patient remote home monitoring systems (e.g., Docobo) can significantly increase treatment compliance (57).

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ANTIHYPERTENSIVE TREATMENT IN PATIENTS WITH HEART FAILURE

46

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INTRODUCTION

Hypertension is a major risk factor for the development of cardiac failure because it can lead to the development of coronary heart disease and because it is a risk factor for the development of left ventricular hypertrophy (LVH) (1). Treatment of hypertension in heart failure depends on the type of heart failure present. In systolic dysfunction, where blood pressure (BP) is usually low due to damage to the left ventricle (LV), the task is to reduce the preload and afterload, so as to relieve LV function and to reduce symptoms and signs of congestive heart failure (CHF). However, in diastolic dysfunction, the main task is to reduce heart rate (and prolong diastole) and lower BP, which again leads to the regression of ventricular hypertrophy (2).

Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, thiazide diuretics, and aldosterone antagonists are all well-established compounds for the treatment of hypertension, post-myocardial infarction (MI), and heart failure (Table 46.1). Furthermore, these drugs also seem efficacious in preventing heart failure in patients with hypertension. Calcium antagonists are possibly less effective in the prevention and treatment of CHF, and should be avoided as a first-line therapy in patients with hypertension and heart failure unless especially indicated, e.g., verapamil or diltiazem in patients with supraventricular tachycardia, including rapid atrial fibrillation, for treatment of resistant hypertension, in patients with hypertrophy and diastolic dysfunction, or in patients with coronary ischemia (4).

Patients with severe heart failure with an LV ejection fraction (LVEF) <40% are excluded from the majority of trials on hypertension. Therefore, these treatment recommendations are based on the results of trials including heart failure patients, not exclusively hypertensive patients, although a large proportion of the study populations (frequently about 50%) consist of patients with hypertension as an important underlying cause of the heart failure. Primary preventive trials of hypertensives in patients without overt heart failure at the outset are also included. Advanced coronary heart disease and atrial fibrillation are common denominators in a relatively large proportion of the patients, which of course must be taken into consideration when making decisions about almost any aspect of the treatment of these patients (Table 46.1); however, this is not the primary focus of this paper.

TRIAL EVIDENCE IN FAVOR OF TREATMENT WITH ACE INHIBITORS

Based on data from major studies, such as Studies of Left Ventricular Dysfunction (SOLVD), Survival and Ventricular Enlargement (SAVE), Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), Trandolapril Cardiac Evaluation (TRACE), and Acute Infarction Ramapril Efficacy (AIRE), ACE inhibitors are considered the gold standard for the treatment of heart failure.

The SOLVD trial enrolled 2,569 patients with chronic heart failure and an LVEF ≤35% (5). Patients were randomly assigned to receive placebo ($n = 1{,}284$) or enalapril ($n = 1{,}285$). The results indicated that the addition of enalapril to conventional therapy significantly reduced mortality and hospitalizations for heart failure in patients with chronic CHF and reduced LVEF. The CONSENSUS study, a double-blind, randomized trial, also found enalapril to have favorable effects compared with conventional heart failure treatment (6). This was the first trial to show the beneficial effects of ACE inhibitors, reporting a 31% reduction in 1-year mortality in the enalapril group compared to the placebo group. In the double-blind randomized SAVE study, 1,116 patients with post-myocardial infarction heart failure received placebo and 1,115 patients received captopril. All-cause mortality was significantly reduced in the captopril group compared with the placebo group (20% versus 25%; $p = 0.019$). The captopril group also had lower risks for the following (7): death from cardiovascular causes, development of severe heart failure, CHF requiring hospitalization and recurrent MI.

Similar favorable effects have been shown in studies such as the TRACE study. In this randomized, double-blind, placebo-controlled study, patients with an enzyme-verified acute MI (AMI) and an LVEF less or equal 35% were randomized to

Table 46.1 Antihypertensive drugs and benefits in specific cardiac diseases

Class of drug	Congestive heart failure	Coronary heart disease	Atrial fibrillation	Left ventricular hypertrophy
ACE inhibitors	First line	Add on	Add on	Alternative to ARBs
ARBs	Alternative to ACE inhibitors	Add on	Add on	First line
Loop diuretics	If fluid retention, and always if high creatinine	If high creatinine	If high creatinine	If high creatinine
Thiazides	Add on	Add on	Add on	Add on
Beta-blockers	Add on	First line	First line	Add on
Aldosterone antagonists	Add on	Add on	No specific indication	Add on
Verapamil, diltiazem	Usually not indicated	Alternative first-line therapy, but not combined with beta-blockers	Alternative first-line therapy, but usually not combined with beta-blockers	Add on
Dihydropyridine CCBs	Add on	Alternative first line	No specific indication	Add on
Alpha-blockers	No specific indication	No specific indication	No specific indication	Add on

Abbreviations:ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers.
Source: Adapted from Ref. 3.

receive either trandolapril or placebo. Of the total study population, 23% had a history of hypertension. The authors concluded that ACE inhibition after AMI complicated with LV dysfunction was of greater benefit to patients with a history of arterial hypertension ($p = 0.03$) (8). The AIRE study investigators enrolled 2,006 patients with post-myocardial cardiac failure, postulating that the ACE inhibitor ramipril would lengthen survival in these patients. In the group randomized to receive ramipril ($n = 1{,}014$), mortality from all causes was 17%, whereas, in the group that received placebo ($n = 992$), it was 23% ($p = 0.002$). Analysis revealed a risk reduction in the secondary outcomes death, severe/resistant heart failure, MI, or stroke (9).

In total, approximately 7,000 patients have been evaluated in placebo-controlled trials on ACE inhibitors, showing consistent improvement in cardiac function, symptoms, and clinical status, with a reduction in all-cause mortality of 20–25%, and decrease of 20–25% in the combined risk of death or hospitalization (10). The European Society of Cardiology (ESC) thus recommends ACE inhibitors as a first-line therapy (Table 46.1) in patients with a reduced LV systolic function (<40–45%) with or without symptoms (11). ESC recommends ACE inhibitors as the initial therapy in the absence of fluid retention. In patients with fluid retention, ACE inhibitors should be given together with diuretics. According to the guidelines updated in 2005, ACE inhibitors should be initiated in patients with signs or symptoms of heart failure, even if transient, after the acute phase of MI, even if the symptoms are transient, to improve survival, symptoms, and functional capacity, and to reduce re-infarctions and hospitalizations.

There is no data on the effect of ACE inhibitors on mortality in patients with diastolic dysfunction or heart failure with preserved LV systolic function. As ACE inhibitors reduce BP and have a documented effect on regression of LVH, which is common in patients with heart failure and diastolic dysfunction, they may be beneficial in the treatment of hypertension in this subgroup of patients.

Adverse effects of ACE inhibitors include hypotension, syncope, cough, renal failure, and hyperkalemia. ACE inhibitors are contraindicated in the presence of bilateral renal artery stenosis and angio-edema during previous ACE inhibitor therapy. Regular monitoring of renal function is recommended.

THE NEED FOR TREATMENT WITH DIURETICS

Diuretics are essential for the symptomatic treatment of heart failure (Table 46.1). Diuretics reduce the preload and afterload, resulting in reduced pulmonary and peripheral congestion and improvement of dyspnea (12,13). While loop diuretics are mostly used in patients with decompensated heart failure presenting with ankle edema or pulmonary congestion, diuretics of the thiazide type prove more effective in the treatment of hypertension and prevention of heart failure, particularly in combination with other antihypertensive drugs, as discussed below.

TRIAL EVIDENCE IN FAVOR OF TREATMENT WITH ANGIOTENSIN RECEPTOR BLOCKERS

The effects of angiotensin II are mediated by two receptors, denoted angiotensin I and angiotensin II. Stimulation of the angiotensin I receptor is associated with water and sodium retention, and increased aldosterone, vasopressin, and endothelin secretion, all of which increase BP (14). ARBs inhibit the renin–angiotensin–aldosterone system (RAAS) and lower BP.

The ARB valsartan not only reduces the BP as efficaciously as ACE inhibitors—as shown in Valsartan in Acute Myocardial Infarction Trial (VALIANT) (15)—the results of Valsartan Heart Failure Trail (Val-HeFT) indicate that it also has a crucial role in the treatment of heart failure (16–18). Val-HeFT—a major trial comparing valsartan with placebo when added to standard therapy for patients with heart failure—found that, compared with placebo, valsartan significantly improved LVEF and reduced the incidence of atrial fibrillation, both of which are important in the prevention of heart failure. Valsartan further reduced the combined endpoint of mortality and hospitalizations due to heart failure.

Evaluation of Losartan in the Elderly (ELITE) was a randomized double-blind study that compared the effect of losartan with that of captopril. The patients enrolled were

aged more than 65 years and had NYHA class II–IV heart failure and an LVEF <40% (19). The primary endpoint was a tolerability measure of an increase in serum creatinine which was found to be the same in both groups. Fewer patients in the losartan group discontinued therapy, and no patients discontinued the medication as a result of coughing as a side effect. In this study of elderly heart failure patients, mortality associated with losartan was unexpectedly lower than that associated with captopril. The ELITE II tested whether losartan was superior to captopril in improving survival. Approximately half the patients stratified for beta-blocker use received losartan, the other half received captopril. There were no significant differences in the primary or secondary endpoints between the two groups, but losartan was significantly better tolerated.

The Candesartan in Heart Failure–Assessment of Reduction in Mortality and Morbidity (CHARM) investigators (20) studied patients with an LVEF less than 40% who were not receiving ACE inhibitors due to previous intolerance (21) or who were currently receiving ACE inhibitors (22), and patients with an LVEF >40% (23). Patients randomly received candesartan ($n = 3,803$) or placebo ($n = 3,796$). Candesartan was shown to be well tolerated and significantly reduced cardiovascular deaths and hospital admission for heart failure both in the Alternative and the Added group though the findings in patients with diastolic dysfunction (Preserved group) did not reach the level of statistical significance.

The ESC recommends ARBs to be used as an alternative to ACE inhibitors in symptomatic patients intolerant to ACE inhibitors (Table 46.1), to improve morbidity and mortality in patients with LV systolic dysfunction (11). They also state that ARBs can be considered in combination with ACE inhibitors in patients who remain symptomatic to reduce mortality and hospital admission for heart failure. As reported in the guidelines updated in 2005, ARBs and ACE inhibitors seem to show similar efficacy in terms of reducing morbidity and mortality in CHF. In AMI with signs of heart failure or LV dysfunction, ARBs and ACE inhibitors have similar or equivalent effects on morbidity and mortality.

One of the common side effects of ACE inhibitors is a dry, irritating cough; however, several trials have shown a much lower incidence of cough with ARBs than with ACE inhibitors. The incidence of cough in trials with valsartan is similar to that with placebo (24). Another important advantage of ARBs is an exceptionally good tolerability profile, which may improve treatment compliance (25).

TRIAL EVIDENCE IN FAVOR OF TREATMENT WITH ALDOSTERONE RECEPTOR ANTAGONISTS

Aldosterone promotes the retention of sodium, the loss of magnesium and potassium, sympathetic activation, parasympathatic inhibition, myocardial and vascular fibrosis, baroreceptor dysfunction, vascular damage, and impairs arterial compliance (26–30). Randomized Aldactone Evaluation Study (RALES) showed the importance of aldosterone receptor antagonists in the treatment of heart failure (31). RALES was a double-blind study that enrolled patients with severe heart failure and a reduced LVEF of no more than 30%, who were receiving treatment with traditional heart failure medications (ACE inhibitor, loop diuretic, and, in most cases, a digitoxin). Approximately half of the patients were randomized to receive spironolactone (25 mg/day); the other half received placebo. The trial showed a 30% reduction in the risk of death among the patients receiving the aldosterone antagonist. The frequency of hospitalization for worsening heart failure was 35% lower among this group of patients, who also showed a significant improvement in heart failure symptoms. These results indicate that aldosterone receptor antagonists are highly relevant for the treatment of heart failure.

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) Investigators assigned patients with AMI complicated by LV dysfunction and heart failure to receive either eplerenone ($n = 3,313$) or placebo in addition to optimal medical therapy (3,319 patients) (32). There was a significantly lower death rate among the patients receiving eplerenone (478 versus 554 deaths; $p = 0.008$).

The ESC recommends aldosterone receptor antagonists in addition to ACE inhibitors, beta-blockers, and diuretics in advanced heart failure with systolic dysfunction, to improve survival and morbidity (Table 46.1). Aldosterone receptor antagonists are also recommended in addition to ACE inhibitors and beta-blockers in heart failure after MI with LV systolic dysfunction and signs of heart failure or diabetes, to reduce mortality and morbidity (11).

The potential for serious hyperkalemia is a cause for the infrequent use of aldosterone receptor antagonists. The incidence of serious hyperkalemia in the RALES trial was minimal in both groups of patients; however, gynecomastia or breast pain was reported in 10% of men treated with spirinolactone, as compared with 1% of men in the placebo group (31). After the publication of RALES, there was an increase in the rate of prescription for spironolactone. An analysis of the rate of prescription of spironolactone and the rate of hospitalization for hyperkalemia in patients before and after the publication of RALES showed an increased mortality rate in patients treated with spironolactone. Thus, to reduce the complication of hyperkalemia associated with spironolactone it is important with more judicious use and close laboratory monitoring (33).

TRIAL EVIDENCE IN FAVOR OF TREATMENT WITH BETA-RECEPTOR BLOCKERS

The introduction of beta-blockers has undoubtedly been a major recent change in the management of chronic heart failure. Not long ago, beta-blockers were considered to be inadequate and were contraindicated in the treatment of heart failure. However, data emerging from recent studies provide evidence that beta-blockers have an incremental value in patients with chronic heart failure. Heart failure is characterized by changes in many neurohormonal mechanisms and an activation of the sympathetic and RAAS. Beta-blockers have shown to reduce adrenergic drive, improve autonomic balance, and reduce ventricular wall stress (34,35).

Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) compared the beta-blocker nebivolol with placebo in elderly patients >70 years with history of hospital admission for heart failure or known to have an LVEF <35% (36). The patients in the SENIORS study closely resembled the general population of patients with heart failure, with a mean age of 76 years and patients with both

systolic and diastolic dysfunction. The results showed that nebivolol significantly reduces the risk of all-cause mortality or cardiovascular hospital admission compared with placebo. In Carvediol or Metoprolol European Trial (COMET) patients with CHF, previous admission for a cardiovascular reason, an LVEF <35%, and with optimally treatment with diuretics and an ACE inhibitor (37) were randomized to receive either carvedilol (target dose 25 mg twice daily) or metoprolol (target dose 50 mg twice daily). The results suggest that carvediol extends survival compared with metoprolol.

The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) Investigators analyzed the long-term efficacy of carvedilol on morbidity and mortality in patients with LV dysfunction after AMI (38). All-cause mortality was lower in the carvedilol group than the placebo group (12% versus 15%; $p = 0.03$). There was also a reduction in the frequency of cardiovascular mortality and non-fatal MIs in the treatment group. Cardiac Insufficiency Bisoprolol Study (CIBIS II) investigated the efficacy of bisoprolol in decreasing all-cause mortality in heart failure (39). This was a multicenter, double-blind, randomized trial in which 2,647 patients in NYHA class III or IV with an LVEF less or equal 35%, receiving standard therapy with diuretics and ACE inhibitors, were enrolled to receive either bisoprolol or placebo. The trial was stopped early because bisoprolol showed a significant mortality benefit compared with placebo (11.8% versus 17.3%; $p < 0.0001$). There were also significantly fewer sudden deaths among patients on bisoprolol than among those on placebo. In MERIT-HF patients were randomized to receive metoprolol CR/XL (12.5 or 25 mg/day) or placebo. Metoprolol improved survival, reduced the number of hospitalizations due to heart failure, and improved NYHA class (40).

The European guidelines recommend beta-blockers to be considered in all patients with heart failure from ischemic or non-ischemic cardiomyopathies and reduced LVEF on standard treatment, including diuretics, and ACE inhibitors, unless there is a contraindication (11). They also recommend beta-blockers in addition to ACE inhibitors following an AMI in patients with LV systolic dysfunction with or without symptomatic heart failure, to reduce mortality (Table 46.1). Based on the results of the SENIORS study, they have also stated that beta-blockers reduce the number of hospital admissions, improve the functional class, and reduce worsening of heart failure. This beneficial effect has been consistently observed in subgroups of different age, gender, functional class, LVEF, and ischemic or non-ischemic etiology. Based on the results of COMET they further write: "Differences in clinical effects may be present between different beta-blockers in patients with heart failure." Accordingly, only bisoprolol, carvediol, metoprolol, and nebivolol can be recommended.

TRIAL EVIDENCE IN FAVOR OF TREATMENT WITH CALCIUM ANTAGONISTS

Calcium antagonists of the long-acting dihydropyridine class have been tested in patients with CHF in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) and PRAISE II studies and in the Vasodilator–Heart Failure Trial (V-HeFT) II or III studies with felodipine (17,41). None of these studies showed significant effects on mortality and morbidity in patients with reduced LV systolic function. Thus, calcium antagonists are not recommended for the treatment of patients with CHF and reduced LV function (4,41,42).

However, in hypertensive patients with preserved LV systolic function they might be useful add-on drugs to ACE inhibitors or ARBs and beta-blockers (Table 46.1).

In INVEST hypertensive patients with coronary artery disease were randomized to receive either the calcium antagonist verapamil or a non-calcium antagonist atenolol. Trandolapril and/or hydrochlorothiazide were administered to achieve BP goals according to international guidelines. The clinical effect was found to be the same in the two groups (43).

HYPERTENSION, CORONARY HEART DISEASE, AND CHF

BP level affects the risk of a recurrent event in patients with coronary heart disease (44), and hypertension is frequently a past or present clinical problem in patients with CHF (45). However, only a few trials have tested the effects of BP lowering in patients with coronary heart disease or CHF. The Hypertension Optimal Treatment (HOT) study showed a significant reduction in strokes with a lower target BP in hypertensive patients with a history of ischemic heart disease, and found no significant evidence of increased coronary heart disease risk at low diastolic BP (46,47). Beta-blockers, ACE inhibitors, and antialdosterone compounds are well known to prevent cardiovascular events and prolong life in patients after an AMI and with heart failure (31,32,48–51), but how much of the benefit is due to concomitant BP lowering and how much is due to specific drug actions has never been ascertained. There are data to support the use of ARBs as alternatives to ACE inhibitors in CHF, or in combination with ACE inhibitors (16,19). The role of calcium antagonists in the prevention of coronary events has been indicated by Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which showed a long-acting dihydropyridine to be equally effective as the other antihypertensive compounds (52). Calcium antagonists are possibly less effective in the prevention of CHF, as suggested in both ALLHAT (52) and in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial (53,54), and should not be considered as a first- or second-line treatment unless particularly indicated (e.g., verapamil or diltiazem in patients with tachyarrhythmia). Patients with typical LVH will probably benefit from most antihypertensive drugs, though ARBs would be the first choice based on the experience in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study (55).

CONCLUSIONS

The European hypertension guidelines recommend treatment of hypertension in patients with heart failure, frequently complicated with coronary heart disease and atrial fibrillation, to echo the heart failure guidelines and to introduce BP-lowering drugs that simultaneously deal with the concomitant diseases (56,57). In summary, drugs of choice are (Table 46.1) ACE inhibitors, ARBs, diuretics, beta-blockers, and aldosterone receptor antagonists (3). Alpha-blockers and calcium antagonists are likely safe as add-on treatment in most

patients if needed for indications other than heart failure, e.g., resistant hypertension, prostatic hyperplasia, ischemic heart disease, or tachyarrhythmia. Several of these drugs may be needed in combination to achieve the target BP, which is (when assessed by measurements in the office and with patients in the seated position) a stable BP <130/80 mmHg in these patients with established heart disease (56,57).

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2007 ESH–ESC PRACTICE GUIDELINES FOR THE MANAGEMENT OF ARTERIAL HYPERTENSION

47

ESH–ESC Task Force on the Management of Arterial Hypertension[a]

These practice guidelines on the management of arterial hypertension are a concise summary of the more extensive ones prepared by a Task Force jointly appointed by the European Society of Hypertension and the European Society of Cardiology.

These guidelines have been prepared on the basis of the best available evidence on all issues deserving recommendations; their role must be educational and not prescriptive or coercive for the management of individual subjects who may differ widely in their personal, medical and cultural characteristics.

The members of the Task Force have participated independently in the preparation of these guidelines, drawing on their academic and clinical experience and by objective examination and interpretation of all available literature. A disclosure of their potential conflict of interest is reported on the websites of the ESH and the ESC.

1. DEFINITION AND CLASSIFICATION OF HYPERTENSION

Blood pressure has a unimodal distribution in the population as well as a continuous relationship with CV risk.

For practical reasons the term "hypertension" is used in daily practice and patients are categorized as shown in Table 47.1. However the real threshold for defining "hypertension" must be considered as flexible, being high or low based on the total CV risk of each individual.

2. TOTAL CARDIOVASCULAR (CV) RISK

- All patients should be classified not only in relation to the grades of hypertension but also in terms of the total CV risk resulting from the coexistence of different risk factors, organ damage and disease.
- Decisions on treatment strategies (initiation of drug treatment, BP threshold and target for treatment, use of combination treatment, need of a statin and other non-antihypertensive drugs) all importantly depend on the initial level of risk.
- There are several methods by which total CV risk can be assessed, all with advantages and limitations. Categorization of total risk as low, moderate, high, and very high added risk has the merit of simplicity and can therefore be recommended. The term 'added risk' refers to the risk additional to the average one.
- Total risk is usually expressed as the absolute risk of having a CV event within 10 years. Because of its heavy dependence on age, in young patients absolute total CV

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Table 47.1 Definitions and classification of blood pressure (BP) levels (mmHg)

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

Isolated systolic hypertension should be graded (1,2,3) according to systolic blood pressure values in the ranges indicated, provided that diastolic values are <90 mmHg.

risk can be low even in the presence of high BP with additional risk factors. If insufficiently treated, however, this condition may lead to a partly irreversible high risk condition years later. In younger subjects treatment decisions should better be guided by quantification of relative risk, i.e. the increase in risk in relation to average risk in the population.

- Using rigid cut-offs of absolute risk (e.g. >20% within 10 years) in order to decide on treatment is discouraged.

3. STRATIFICATION OF TOTAL CV RISK

In the Figure 47.1 total CV risk is stratified in four categories. Low, moderate, high and very high risks refer to 10 year risk of a fatal or non-fatal CV event. The term "added" indicates that in all categories risk is greater than average. The dashed line indicates how the definition of hypertension (and thus the decision about the initiation of treatment) is flexible, i.e. may be variable depending on the level of total CV risk.

4. CLINICAL VARIABLES THAT SHOULD BE USED TO STRATIFY TOTAL CV RISK

Table 47.2 Factors influencing prognosis

Risk factors	Subclinical organ damage
Systolic and diastolic BP levels Levels of pulse pressure (in the elderly) Age (M > 55 years; W > 65 years) Smoking Dyslipidaemia -TC > 5.0 mmol/l (190 mg/dl) or: -LDL-C > 3.0 mmol/l (115 mg/dl) or: -HDL-C: M < 1.0 mmol/l (40 mg/dl) W < 1.2 mmol/l (46 mg/dl) or: -TG > 1.7 mmol/l (150 mg/dl) Fasting plasma glucose 5.6–6.9 mmol/l (102–125 mg/dl) Abnormal glucose tolerance test Abdominal obesity (waist circumference >102 cm (M), >88 cm (W)) Family history of premature CV disease (M at age <55 years; W at age <65 years)	Electrocardiographic LVH (Sokolow-Lyon >38 mm; Cornell >2440 mm/ms or: Echocardiographic LVH[a] (LVMI M ≥ 125 g/m², W ≥ 110 g/m²) Carotid wall thickening (IMT > 0.9 mm) or plaque Carotid-femoral pulse wave velocity >12m/sec Ankle/Brachial BP index <0.9 Slight increase in plasma creatinine: M: 115–133 μmol/l (1.3–1.5 mg/dl) W: 107–124 μmol/l (1.2–1.4 mg/dl) Low estimated glomerular filtration rate[b] (<6 ml/min/1.73 m²) or creatinine clearance[c] (<60 ml/min) Microalbuminuria 30–300 mg/24 h or albumin-cratinine ratio: ≥22 (M); or ≥31 (W) mg/g cratinine
Diabetes mellitus	**Eatablished CV or renal disease**
Fasting plasma glucose ≥7.0 mmol/l (126 mg/dl) on repeated measurement or: Postload plasma glucose >11.0 mmol/l (198 mg/dl) Note: the cluster of three out of 5 risk factors among abdominal, obesity, altered tasting plasma glucose, BP ≥ 130/85 mmHg. low HDL cholesterol and high TG (as defined above) indicats the presence of metabolic syndrome.	Cerebrovascular disease: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack Heart disease: myocardial infarction; angina; coronary revascularization; heart failure Renal disease: diabetic nephropathy; renal impairment (serum creatinine M > 133;W > 124 μmol/l); proteinuria (>300 mg/24 h) Perpheral artery disease Advanced retinopathy: haemorrhages or exudates, papilloedama

[a]Risk maximal for concentric (wall thickness/radius ratio≥0.42)
LVH (left ventricular hypertrophy).
[b]MDRD formula.
[c]Cockroft Gault formula.
Abbreviations: BP, blood pressure; C, cholesterol; CV, cardiovascular disease; IMT, intima-media thickness; M, men; TG, triglycerides; W, women.

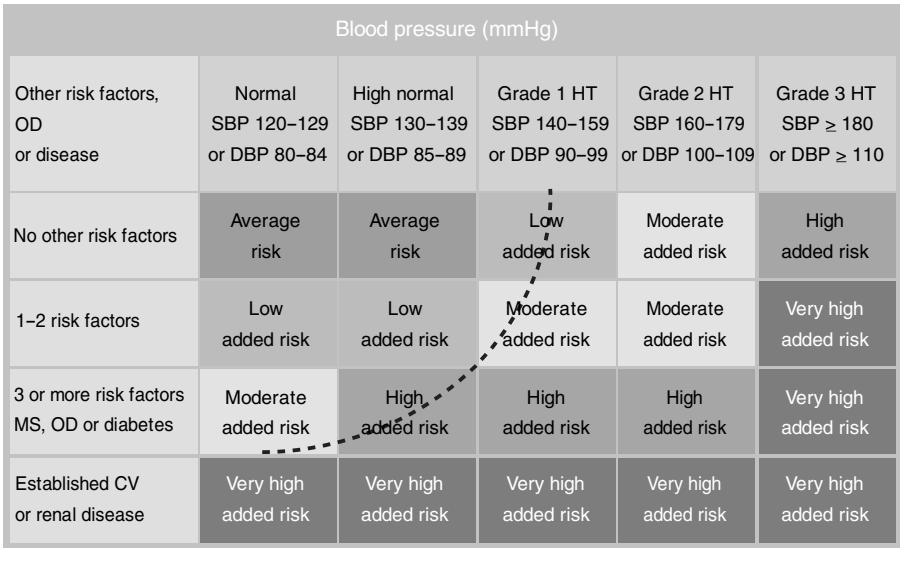


Fig. 47.1 Stratification of CV risk in four categories of added risk. *Abbreviations*: CV, cardiovascular; DBP, diastolic blood pressure; HT, hypertension; MS, metabolic syndrome; OD, subclinical organ damage; SBP, systolic blood pressure.

5. DIAGNOSTIC EVALUATION

AIMS

- Establishing BP values
- Identifying secondary causes of hypertension
- Searching for
  - other risk factors;
  - subclinical organ damage;
  - concomitant diseases;
  - accompanying CV and renal complications.

PROCEDURES

- repeated BP measurements
- family and clinical history
- physical examination
- laboratory and instrumental investigations.

6. BLOOD PRESSURE (BP) MEASUREMENT

When measuring BP, care should be taken to:

- Allow the patients to sit quietly for several minutes;
- Take at least two measurements spaced by 1–2 minutes;
- Use a standard bladder (12–13 cm long and 35 cm wide) but have a larger bladder available for fat arms and a smaller one for thin arms and children;
- Have the cuff at the level of the heart, whatever the position of the patient;
- Deflate the cuff at a speed of 2 mmHg/s;
- Use phase I and V (disappearance) Korotkoff sounds to identify SBP and DBP, respectively;
- Measure BP in both arms at first visit to detect possible differences due to peripheral vascular disease. In this instance, take the higher value as the reference one;
- Measure BP 1 and 5 min after assumption of the standing position in elderly subjects, diabetic patients, and when postural hypotension may be frequent or suspected;
- Measure heart rate by pulse palpation (at least 30 sec).

7. AMBULATORY AND HOME BP MEASUREMENTS

AMBULATORY BP

- Although office BP should be used as the reference, ambulatory BP may improve prediction of CV risk in untreated and treated patients.
- 24-h ambulatory BP monitoring should be considered, in particular, when
  - considerable variability of office BP is found
  - high office BP is measured in subjects otherwise at low total CV risk
  - there is a marked discrepancy between BP values measured in the office and at home
  - resistance to drug treatment is suspected
  - hypotensive episodes are suspected, particularly in elderly and diabetic patients
  - sleep apnoea is suspected
  - office BP is elevated in pregnant women and pre-eclampsia is suspected

Normal values for 24 hour average BP are lower than for office BP, i.e. $<$125–130 mmHg systolic and $<$80 mmHg diastolic. Normal values of daytime BP are $<$130–135 mmHg systolic and $<$85 mmHg diastolic.

HOME BP

- Self-measurement of BP at home is of clinical value. Home BP measurements should be encouraged in order to:
  - provide more information on the BP lowering effect of treatment at trough, and thus on therapeutic coverage throughout the dose-to-dose time interval
  - improve patient's adherence to treatment regimens
  - understand technical reliability/environmental conditions of ambulatory BP data
- Self-measurement of BP at home should be discouraged whenever:
  - it causes anxiety to the patient
  - it induces self-modification of the treatment regimen
- Normal values for home BP are lower than for office BP, i.e. $<$130–135 mmHg systolic and $<$85 mmHg diastolic.

PARTICULAR CONDITIONS

ISOLATED OFFICE HYPERTENSION (WHITE COAT HYPERTENSION)

Office BP persistently $\geq$140/90 mmHg

Normal daytime ambulatory ($<$130–135/85 mmHg) or home ($<$130–135/85 mmHg) BP

In these subjects CV risk is less than in individuals with raised office and ambulatory or home BP but may be slightly greater than that of individuals with in and out-of-office normotension

ISOLATED AMBULATORY HYPERTENSION (MASKED HYPERTENSION)

Office BP persistently normal ($<$140/90 mHg)

Elevated ambulatory ($\geq$125–130/80 mmHg) or home ($\geq$130–135/85 mmHg) BP

In these subjects CV risk is close to that of individuals with in and out-of-office hypertension.

8. DIAGNOSTIC EVALUATION: MEDICAL HISTORY AND PHYSICAL EXAMINATION

FAMILY AND CLINICAL HISTORY

1. Duration and previous level of high BP
2. Indications of secondary hypertension
3. Risk factors
4. Symptoms of organ damage
5. Previous antihypertensive therapy (efficacy, adverse events)
6. Personal, family, environmental factors.

PHYSICAL EXAMINATIONS

1. Signs suggesting secondary hypertension
2. Signs of organ damage
3. Evidence of visceral obesity.

9. LABORATORY INVESTIGATION

ROUTINE TESTS

- Fasting plasma glucose
- Serum total cholesterol
- Serum LDL-cholesterol
- Serum HDL-cholesterol
- Fasting serum triglycerides
- Serum potassium
- Serum uric acid
- Serum creatinine
- Estimated creatinine clearance (Cockroft-Gault formula) or glomerular filtration rate (MDRD formula)
- Haemoglobin and haematocrit
- Urinalysis (complemented by microalbuminuria dipstick test and microscopic examination)
- Electrocardiogram.

RECOMMENDED TESTS

- Echocardiogram
- Carotid ultrasound
- Quantitative proteinuria (if dipstick test positive)
- Ankle-brachial BP Index
- Fundoscopy
- Glucose tolerance test (if fasting plasma glucose >5.6 mmol/L (100 mg/dL)
- Home and 24 h ambulatory BP monitoring
- Pulse wave velocity measurement (where available).

EXTENDED EVALUATION (DOMAIN OF THE SPECIALIST)

- Further search for cerebral, cardiac, renal and vascular damage. Mandatory in complicated hypertension.
- Search for secondary hypertension when suggested by history, physical examination or routine tests: measurement of renin, aldosterone, corticosteroids, catecholamines in plasma and/or urine; arteriograms; renal and adrenal ultrasound; computer-assisted tomography; magnetic resonance imaging.

10. SEARCHING FOR SUBCLINICAL ORGAN DAMAGE

Due to the importance of subclinical organ damage as an intermediate stage in the continuum of vascular disease and as a determinant of total CV risk, signs of organ involvement should be sought carefully by appropriate techniques:

HEART

Electrocardiography should be part of all routine assessment of subjects with high BP in order to detect left ventricular hypertrophy, patterns of "strain", ischaemia and arrhythmias. Echocardiography is recommended when a more sensitive method of detection of left ventricular hypertrophy is considered useful as well as assessment of left ventricular systolic function. Geometric patterns can be defined echocardiographically, of which concentric hypertrophy carries the worse prognosis. Diastolic dysfunction can be evaluated by transmitral Doppler.

BLOOD VESSELS

Ultrasound scanning of the extracranial carotid arteries is recommended when detection of vascular hypertrophy or asymptomatic atherosclerosis is deemed useful. Large artery stiffening (leading to isolated systolic hypertension in the elderly) can be measured by pulse wave velocity. It might be more widely recommended if its availability were greater. A low ankle-brachial BP index signals advanced peripheral artery disease.

KIDNEY

Diagnosis of hypertension-related renal damage is based on a reduced renal function or an elevated urinary excretion of albumin. Estimation from serum creatinine of glomerular filtration rate (MDRD formula, requiring age, gender, race) or creatinine clearance (Cockroft-Gault formula, requiring also body weight) should be routine procedure. Urinary protein should be sought in all hypertensives by dipstick. In dipstick negative patients low grade albuminuria (microalbumniuria) should be determined in spot urine and related to urinary creatinine excretion.

FUNDOSCOPY

Examination of eye grounds is recommended in severe hypertensives only. Mild retinal changes are largely non-specific except in young patients. Haemorrhages, exudates and papilloedema, only present in severe hypertension, are associated with increased CV risk.

BRAIN

Silent brain infarcts, lacunar infarctions, microbleeds and white matter lesions are not infrequent among hypertensives, and can be detected by MRI or CT. Availability and costs do not allow indiscriminate use of these techniques. In elderly hypertensives, cognitive tests may help to detect initial brain deterioration.

The Table 47.3 summarizes availability, prognostic value and cost of procedures to detect subclinical organ damage.

Table 47.3 Availability, prognostic value and cost of some markers organ damage (scored from 1 to 4 pluses)

Markers	CV predicitive value	Availability	Cost
Electrocardiography	++	++++	+
Echocardiography	+++	+++	++
Carotid Intima-Media Thickness	+++	+++	++
Arterial stiffness [Pulse wave velocity]	+++	+	++
Ankle-Brachial index	++	++	+
Coronary calcium content	+	+	++++
Cardiac/Vascular tissue composition	?	+	++
Circulatory collagen markers	?	+	++
Endothelial dysfunction	++	+	+++
Cerebral lacunae/White matter lesions	?		++++
Est. Glomerular Filtration Rate or Creatinine Clearance	+++	++++	+
Microalbuminuria	+++	++++	+

11. EVIDENCE ON THE BENEFIT OF ANTIHYPERTENSIVE TREATMENT

- Placebo controlled trials have provided uncontroversial evidence that BP lowering reduces fatal and non-fatal cardiovascular events. Beneficial effects have been found when treatment is initiated with a thiazide diuretic, a β-blocker, a calcium antagonist, an ACE-inhibitor or an angiotensin receptor blocker.
- Trials comparing different antihypertensive drugs have not been able to conclusively demonstrate that for the same reduction in BP different antihypertensive drugs (or drug combinations) reduce to different degree CV events. These trials (and their meta-analysis and meta-regressions) underline the crucial role of BP lowering in reducing all kinds of CV events, i.e. stroke, myocardial infarction and heart failure, independently of the agents used.
- BP-independent effects related to use of specific drugs have been reported for cause-specific events, e.g. stroke, heart failure and coronary events, but these effects are smaller than the dominant effect of BP lowering
- BP-independent effects attributable to specific drugs have been more consistently shown for events that occur earlier in the continuum of CV disease, e.g. protection against subclinical organ damage and prevention of high risk conditions such as diabetes, renal failure and atrial fibrillation.

12. INITIATION OF BP LOWERING THERAPY

- Initiation of BP lowering therapy should be decided on two criteria:
  - The level of SBP and DBP
  - The level of total CV risk
  - This is detailed in the Figure 47.2 which considers treatment based on lifestyle changes and anti-hypertensive drugs with, in addition, recommendations on the time delay to be used for assessing the BP lowering effects.

The following points should be emphasized:

- Drug treatment should be initiated promptly in grade 3 hypertension as well as in grade 1 and 2 when total CV risk is high or very high.
- In grade 1 or 2 hypertensives with moderate total CV risk drug treatment may be delayed for several weeks and in grade 1 hypertensives without any other risk factor for several months. However, even in these patients lack of BP control after a suitable period should lead to initiation of drug treatment.
- When initial BP is in the high normal range the decision on drug intervention heavily depends on the level of risk. In the case of diabetes, history of cerebrovascular, coronary or peripheral artery disease, the recommendation to start BP lowering drugs is justified by the results of controlled trials. Subjects with BP in the high normal range in whom total CV risk is high because of a subclinical organ damage should be advised to implement intense lifestyle measures. In these subjects BP should be closely monitored and drug treatment considered in the presence of a worsening of the clinical condition.

13. GOALS OF TREATMENT

- In hypertensive patients, the primary goal of treatment is to achieve maximum reduction in the long-term total risk of CV disease.
- This requires treatment of the raised BP per se as well as of all associated reversible risk factors.
- BP should be reduced to at least below 140/90 mmHg (systolic/diastolic), and to lower values, if tolerated, in all hypertensive patients.
- Target BP should be at least $<$130/80 mmHg in patients with diabetes and in high or very high risk patients, such as those with associated clinical conditions (stroke, myocardial infarction, renal dysfunction, proteinuria).
- Despite use of combination treatment, reducing systolic BP to $<$140 mmHg may be difficult and more so if the target is a reduction to $<$130 mmHg. Additional difficulties should be expected in the elderly, in patients with diabetes, and in general, in patients with CV damage.
- In order to more easily achieve goal BP, antihypertensive treatment should be initiated before significant CV damage develops.

14. LIFESTYLE CHANGES

- Lifestyle measures should be instituted, whenever appropriate, in all patients, including those who require drug treatment. The purpose is to lower BP, to control other risk factors and to reduce the number or the doses of antihypertensive drugs.
- Lifestyle measures are also advisable in subjects with high normal BP and additional risk factors to reduce the risk of developing hypertension.

Blood pressure (mmHg)					
Other risk factors, OD or disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥ 180 or DBP ≥ 110
No other risk factors	No BP intervention	No BP intervention	Lifestyle changes for several months then drug treatment if BP uncontrolled	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes + immediate drug treatment
1–2 risk factors	Lifestyle changes	Lifestyle changes	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes + immediate drug treatment
≥ 3 risk factors, MS or OD	Lifestyle changes	Lifestyle changes and consider drug treatment	Lifestyle changes + drug treatment	Lifestyle changes + drug treatment	Lifestyle changes + immediate drug treatment
Diabetes	Lifestyle changes	Lifestyle changes + drug treatment	Lifestyle changes + drug treatment	Lifestyle changes + drug treatment	Lifestyle changes + immediate drug treatment
Established CV or renal disease	Lifestyle changes + immediate drug treatment	Lifestyle changes + immediate drug treatment	Lifestyle changes + immediate drug treatment	Lifestyle changes + immediate drug treatment	Lifestyle changes + immediate drug treatment

Fig. 47.2 Initiation of antihypertensive treatment.

- The lifestyle measures that are widely recognized to lower BP and/or CV risk, and that should be considered are:
  - smoking cessation
  - weight reduction (and weight stabilization)
  - reduction of excessive alcohol intake
  - physical exercise
  - reduction of salt intake
  - increase in fruit and vegetable intake and decrease in saturated and total
  - fat intake
- Lifestyle recommendations should not be given as lip service but instituted with adequate behavioural and expert support, and reinforced periodically.
- Because long-term compliance with lifestyle measures is low and the BP response highly variable, patients under non-pharmacological treatment should be followed-up closely to start drug treatment when needed and in a timely fashion.

15. CHOICE OF ANTIHYPERTENSIVE DRUGS

- The main benefits of antihypertensive therapy are due to lowering of BP per se
- Five major classes of antihypertensive agents–thiazide diuretics, calcium antagonists, ACE-inhibitors, angiotensin receptor blockers and ß-blockers–are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination. ß-blockers, especially in combination with a thiazide diuretic, should not be used in patients with the metabolic syndrome or at high risk of incident diabetes.
- In many patients more than one drug is needed, so emphasis on identification of the first class of drugs to be used is often futile. Nevertheless, there are conditions for which there is evidence in favour of some drugs versus others either as initial treatment or as part of a combination.
- The choice of a specific drug or a drug combination, and the avoidance of others should take into account the following:
  - The previous favourable or unfavourable experience of the individual patient with a given class of compounds.
  - The effect of drugs on CV risk factors in relation to the CV risk profile of the individual patient.
  - The presence of subclinical organ damage, clinical CV disease, renal disease or diabetes, which

may be more favourably treated by some drugs than others.
  - The presence of other disorders that may limit the use of particular classes of antihypertensive drugs.
  - The possibilities of interactions with drugs used for other conditions.
  - The cost of drugs, either to the individual patient or to the health provider. However, cost considerations should never predominate over efficacy, tolerability, and protection of the individual patient.
- Continuing attention should be given to side-effects of drugs, because they are the most important cause of non-compliance. Drugs are not equal in terms of adverse effects, particularly in individual patients.
- The BP lowering effect should last 24 hours. This can be checked by office or home BP measurements at trough or by ambulatory BP monitoring.
- Drugs which exert their antihypertensive effect over 24 hours with a once-a-day administration should be preferred because a simple treatment schedule favours compliance.

16. CONDITIONS FAVOURING THE USE OF SOME ANTIHYPERTENSIVE DRUGS VERSUS OTHER

Subclinical organ damage	
LVH	ACEI, CA, ARB
Asymptomatic atherosclerosis	CA, ACEI
Microalbuminuria	ACEI, ARB
Renal dysfunction	ACEI, ARB
Clinical event	
Previous stroke	any BP lowering agent
Previous MI	BB, ACEI, ARB
Angina pectoris	BB, CA
Heart failure	diuretics, BB, ACEI, ARB, Anti-aldosterone agents
Atrial fibrillation	
Recurrent	ARB, ACEI
Permanent	BB, non-dihydropiridine CA
Tachyarrhythmias	BB
ESRD/proteinuria	ACEI, ARB, loop diuretics
Peripheral artery disease	CA
LV dysfunction	ACEI
Condition	
ISH (elderly)	diuretics, CA
Metabolic syndrome	ACEI, ARB, CA
Diabetes mellitus	ACEI, ARB
Pregancy	CA, methyldopa, BB
Black people	diuretics, CA
Glaucoma	BB
ACEI induced cough	ARB

LVH = left ventricular hypertrophy; ISH = Isolated systolic hypertension; ESRD = renal failure; ACEI = ACE-inhibitors; ARB = angiotensin receptor antagonists; Ca = calcium antagonists; BB = beta-blockers.

17. CONTRA-INDICATIONS TO USE CERTAIN ANTIHYPERTENSIVE DRUGS

	Compelling contra-indications	Possible contra-indications
Thiazide diuretics	Gout	Metabolic syndrome Glucose intolerance Pregnancy
Beta-blockers	Asthma A-V block (grade 2 or 3)	Peripheral artery disease Metabolic syndrome Glucose intolerance Athletes and physically active patients Chronic obstructive pulmonary disease
Calcium antagonists (dihydropyridines)		Tachyarrhythmias Heart failure
Calcium antagonists (verapamil, diltiazem)	A-V block (grade 2 or 3) Heart failure	
ACE-inhibitors	Pregnancy Angioneurotic oedema Hyperkalaemia Bilateral renal artery stenosis	
Angiotensin receptor antagonists	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	
Diuretics (antialdosterone)	Renal failure Hyperkalaemia	

18. MONOTHERAPY VERSUS COMBINATION THERAPY

- Regardless of the drug employed, monotherapy allows to achieve BP target in only a limited number of hypertensive patients.
- Use of more than one agent is necessary to achieve target BP in the majority of patients. A vast array of effective and well tolerated combinations is available.
- Initial treatment can make use of monotherapy or combination of two drugs at low doses with a subsequent increase in drug doses or number, if needed.
- Monotherapy could be the initial treatment for mild BP elevation with low or moderate total CV risk. A combination of two drugs at low doses should be preferred as the first step in treatment when the initial BP is in the grade 2 or 3 or total CV risk is high or very high with mild BP elevation.
- Fixed combinations of two drugs can simplify the treatment schedule and favour compliance.
- In several patients BP control is not achieved by two drugs, and a combination of three of more drugs is required.
- In uncomplicated hypertensives and in the elderly, antihypertensive therapy should normally be initiated gradually. In higher risk hypertensives, goal BP should be achieved more promptly, which favours initial combination therapy and quicker adjustment of doses.

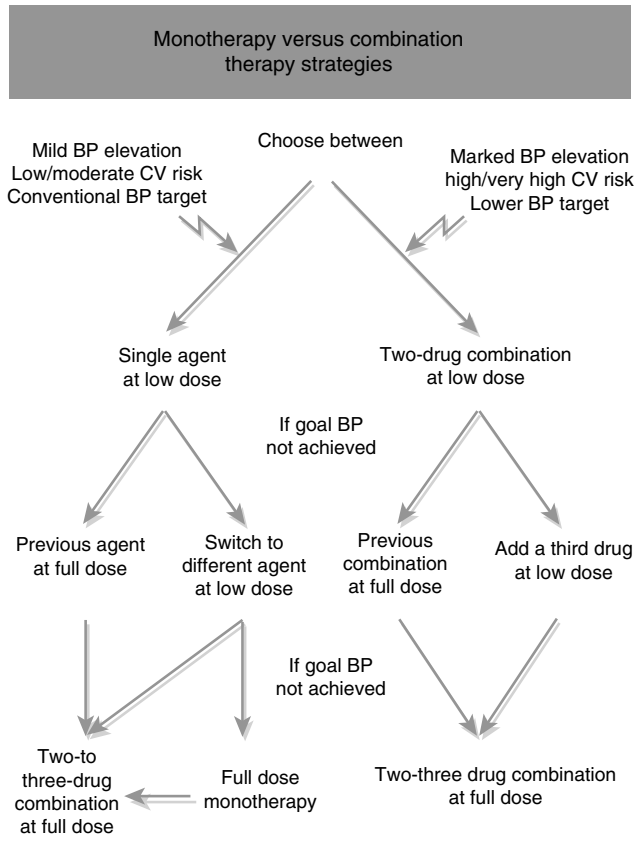
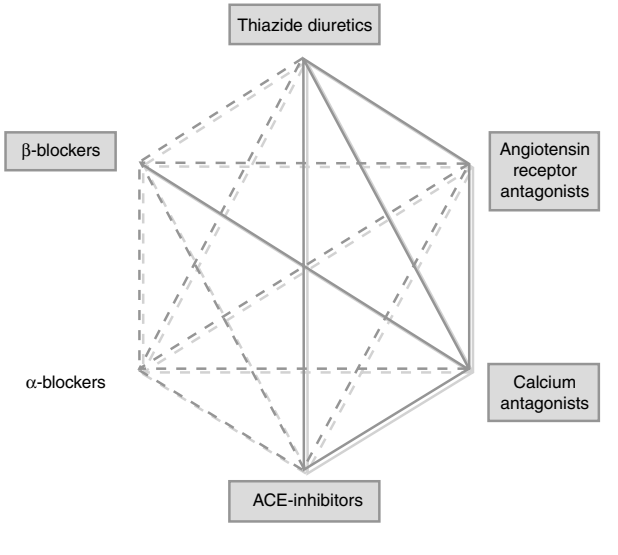


Fig. 47.3

19. POSSIBLE COMBINATIONS BETWEEN SOME CLASSES OF ANTIHYPERTENSIVE DRUGS



The preferred combinations in the general hypertensive population are represented as thick lines.

The frames indicate classes of agents proven to beneficial in controlled intervention trials.

Fig. 47.4

20. ANTIHYPERTENSIVE TREATMENT IN SPECIAL GROUPS

Antihypertensive treatment may differ from the one recommended in the general hypertensive population, in special groups of patients or in specific clinical conditions. The specific requirements under these circumstances are detailed below.

ELDERLY PATIENTS

- Drug treatment can be initiated with thiazide diuretics, calcium antagonists, angiotensin receptor antagonists, ACE-inhibitors, and ß-blockers, in line with general guidelines. Trials specifically addressing treatment of isolated systolic hypertension have shown the benefit of thiazides and calcium antagonists but subanalysis of other trials also show efficacy of angiotensin receptor blockers.
- Initial doses and subsequent dose titration should be more gradual because of a greater chance of undesirable effects, especially in very old and frail subjects.
- BP goal is the same as in younger patients, i.e. <140/90 mmHg or below, if tolerated. Many elderly patients need two or more drugs to control blood pressure and reductions to <140 mmHg systolic may be difficult to obtain.
- Drug treatment should be tailored to the risk factors, target organ damage and associated cardiovascular and non-cardiovascular conditions that are frequent in the elderly. Because of the increased risk of postural hypotension, BP should always be measured also in the erect posture.
- In subjects aged 80 years and over, evidence for benefits of antihypertensive treatment is as yet inconclusive. However, there is no reason for interrupting a successful and well tolerated therapy when a patient reaches 80 years of age.

DIABETIC PATIENTS

- Where applicable, intense non-pharmacological measures should be encouraged in all patients with diabetes, with particular attention to weight loss and reduction of salt intake in type 2 diabetes.
- Goal BP should be <130/80 mmHg and antihypertensive drug treatment may be started already when BP is in the high normal range.
- To lower BP, all effective and well tolerated drugs can be used. A combination of two or more drugs is frequently needed.
- Available evidence indicates that lowering BP also exerts a protective effect on appearance and progression of renal damage. Some additional protection can be obtained by the use of a blocker of the renin-angiotensin system (either an angiotensin receptor antagonist or an ACE-inhibitor).
- A blocker of the renin-angiotensin system should be a regular component of combination treatment and the one preferred when monotherapy is sufficient.

- Microalbuminuria should prompt the use of antihypertensive drug treatment also when initial BP is in the high normal range. Blockers of the renin-angiotensin system have a pronounced antiproteinuric effect and their use should be preferred.
- Treatment strategies should consider an intervention against all CV risk factors, including a statin.
- Because of the greater chance of postural hypotension, BP should also be measured in the erect posture.

PATIENTS WITH RENAL DYSFUNCTION

- Renal dysfunction and failure are associated with a very high risk of CV events.
- Protection against progression of renal dysfunction has two main requirements: a) strict blood pressure control (<130/80 mmHg and even lower if proteinuria is>lg/day); b) lowering proteinuria to values as near to normal as possible.
- To achieve the BP goal, combination therapy of several antihypertensive agents (including loop diuretics) is usually required.
- To reduce proteinuria, an angiotensin receptor antagonist, an ACE-inhibitor or a combination of both are required.
- There is controversial evidence as to whether blockade of the renin-angiotensin system has a specific beneficial role in preventing or retarding nephro-sclerosis in non-diabetic non-proteinuric hypertensives, except perhaps in Afro-American individuals. However, inclusion of one of these agents in the combination therapy required by these patients appears well founded.
- An integrated therapeutic intervention (antihypertensive, statin and antiplatelet therapy) has to be frequently considered in patients with renal damage because, under these circumstances, CV risk is extremely high.

PATIENTS WITH CEREBROVASCULAR DISEASE

- In patients with a history of stroke or transient ischaemic attacks, antihypertensive treatment markedly reduces the incidence of stroke recurrence and also lowers the associated high risk of cardiac events.
- Antihypertensive treatment is beneficial in hypertensive patients as well as in subjects with BP in the high normal range. BP goal should be <130/80 mmHg.
- Because evidence from trials suggests that the benefit largely depends on BP lowering per se, all available drugs and rational combinations can be used. Trial data have been mostly obtained with ACE-inhibitors and angiotensin receptor antagonists, in association with or on the top of diuretic and conventional treatment, but more evidence is needed before their specific cerebrovascular protective properties are established.
- There is at present no evidence that BP lowering has a beneficial effect in acute stroke but more research is under way. Until more evidence is obtained antihypertensive treatment should start when post-stroke clinical conditions are stable, usually several days after the event. Additional research in this is necessary because cognitive dysfunction is present in about 15% and dementia in 5% of subjects aged ≥65 years.
- In observational studies, cognitive decline and incidence of dementia have a positive relationship with BP values. There is some evidence that both can be somewhat delayed by antihypertensive treatment.

PATIENTS WITH CORONARY HEART DISEASE AND HEART FAILURE

- In patients surviving a myocardial infarction, early administration of ß-blockers, ACE-inhibitors or angiotensin receptor blockers reduces the incidence of recurrent myocardial infarction and death. These beneficial effects can be ascribed to the specific protective properties of these drugs but possibly also to the associated small BP reduction.
- Antihypertensive treatment is also beneficial in hypertensive patients with chronic coronary heart disease. The benefit can be obtained with different drugs and drug combinations (including calcium antagonists) and appears to be related to the degree of BP reduction. A beneficial effect has been demonstrated also when initial BP is <140/90 mmHg and for achieved BP around 130/80 mmHg or less.
- A history of hypertension is common while a raised BP is relatively rare in patients with congestive heart failure. In these patients, treatment can make use of thiazide and loop diuretics, as well as of β-blockers, ACE-inhibitors, angiotensin receptor antagonist and antialdosterone drugs on top of diuretics. Calcium antagonists should be avoided unless needed to control BP or anginal symptoms.
- Diastolic heart failure is common in patients with a history of hypertension and has an adverse prognosis. There is at present no evidence on the superiority of specific antihypertensive drugs.

PATIENTS WITH ATRIAL FIBRILLATION

- Hypertension is the most important risk factor for atrial fibrillation. Atrial fibrillation markedly increases the risk of CV morbidity and mortality, particularly of embolic stroke.
- Increased left ventricular mass and left atrium enlargement are independent determinants of atrial fibrillation, and require intense antihypertensive therapy.
- Strict blood pressure control is required in patients under anticoagulant treatment to avoid intracerebral and extracerebral bleeding.
- Less new onset and recurrent atrial fibrillation has been reported in hypertensive patients treated with angiotensin receptor antagonists.
- In permanent atrial fibrillation, β-blockers and non-dihydropyridine calcium antagonists (verapamil, diltiazem) help controlling ventricular rate.

21. HYPERTENSION IN WOMEN

TREATMENT

Response to antihypertensive agents and beneficial effects of BP lowering appear to be similar in women and in men. However, ACE-inhibitors and angiotensin receptor antagonists should be avoided in pregnant and women planning pregnancy because of potential teratogenic effects during pregnancy.

ORAL CONTRACEPTIVES

Even oral contraceptives with low oestrogen content are associated with an increased risk of hypertension, stroke and myocardial infarction. The progestogen-only pill is a contraceptive option for women with high BP, but their influence on cardiovascular outcomes has been insufficiently investigated.

HORMONE REPLACEMENT THERAPY

The only benefit of this therapy is a decreased incidence of bone fractures and colon cancer, accompanied, however, by increased risk of coronary events, stroke, thromboembolism, breast cancer, gallbladder disease and dementia. This therapy is not recommended for cardioprotection in postmenopausal women.

HYPERTENSION IN PREGNANCY

- Hypertensive disorders in pregnancy, particularly pre-eclampsia, may adversely affect neonatal and maternal outcomes.
- Non-pharmacological management (including close supervision and restriction of activities) should be considered for pregnant women with SBP 140–149 mmHg or DBP 90–95 mmHg. In the presence of gestational hypertension (with or without proteinuria) drug treatment is indicated at BP levels >140/ 90 mmHg. SBP levels ≥170 or DBP ≥110 mmHg should be considered an emergency requiring hospitalization.
- In non-severe hypertension, oral methyldopa, labetalol, calcium antagonists and (less frequently) ß-blockers are drugs of choice.
- In pre-eclampsia with pulmonary oedema, nitroglycerine is the drug of choice. Diuretic therapy is inappropriate because plasma volume is reduced.
- As emergency, intravenous labetalol, oral methyldopa and oral nifedipine are indicated. Intravenous hydralazine is no longer the drug of choice because of an excess of perinatal adverse effects. Intravenous infusion of sodium nitroprusside is useful in hypertensive crises, but prolonged administration should be avoided.
- Calcium supplementation, fish oil and low dose aspirin are not recommended. However, low dose aspirin may be used prophylactically in women with a history of early onset pre-eclampsia.

22. THE METABOLIC SYNDROME

- The metabolic syndrome is characterized by the variable combination of visceral obesity and alterations in glucose metabolism, lipid metabolism and BP. It has a high prevalence in the middle age and elderly population.
- Subjects with the metabolic syndrome also have a higher prevalence of microalbuminuria, left ventricular hypertrophy and arterial stiffness than those without metabolic syndrome. Their CV risk is high and the chance of developing diabetes markedly increased.
- In patients with metabolic syndrome diagnostic procedures should include a more in-depth assessment of subclinical organ damage. Measuring ambulatory and home BP is also desirable.
- In all individuals with metabolic syndrome intense lifestyle measures should be adopted. When there is hypertension drug treatment should start with a drug unlikely to facilitate onset to diabetes. Therefore a blocker of the renin-angiotensin system should be used and followed, if needed, by the addition of a calcium antagonist or a low-dose thiazide diuretic. It appears desirable to bring BP to the normal range.
- Lack of evidence from specific clinical trials prevents firm recommendations on use of antihypertensive drugs in all metabolic syndrome subjects with a high normal BP. There is some evidence that blocking the renin-angiotensin system may also delay incident hypertension.
- Statins and antidiabetic drugs should be given in the presence of dyslipidemia and diabetes, respectively. Insulin sensitizers have been shown to markedly reduce new onset diabetes, but their advantages and disadvantages in the presence of impaired fasting glucose or glucose intolerance as a metabolic syndrome component remain to be demonstrated.

23. RESISTANT HYPERTENSION

DEFINITION

BP ≥ 140/90 mmHg despite treatment with at least three drugs (including a diuretic) in adequate doses and after exclusion of spurious hypertension such as isolated office hypertension and failure to use large cuffs on large arms.

CAUSES

- Poor adherence to therapeutic plan;
- Failure to modify lifestyle including:
  weight gain
  heavy alcohol intake (NB: binge drinking);
- Continued intake of drugs that raise blood pressure (liquorice, cocaine, glucocorticoids, non-steroid anti-inflammatory drugs, etc.);
- Obstructive sleep apnea;
- Unsuspected secondary cause;
- Irreversible or limited reversibility of organ damage;
- Volume overload due to:
  inadequate diuretic therapy

progressive renal insufficiency
high sodium intake
hyperaldosteronism.

TREATMENT

- Adequate investigation of causes
- If necessary, use of more than three drugs, including an aldosterone
- antagonist.

24. HYPERTENSIVE EMERGENCIES

- Hypertensive encephalopathy
- Hypertensive left ventricular failure
- Hypertension with myocardial infarction
- Hypertension with unstable angina
- Hypertension and dissection of the aorta
- Severe hypertension associated with subarachnoid haemorrhage or cerebrovascular accident
- Crisis associated with phaeochromocytoma
- Use of recreational drugs such as amphetamines, LSD, cocaine or ecstasy
- Hypertension perioperatively
- Severe pre-eclampsia or eclampsia

25. TREATMENT OF ASSOCIATED RISK FACTORS

LIPID LOWERING AGENTS

- All hypertensive patients with established CV disease or with type 2 diabetes should be considered for statin therapy aiming at serum total and LDL cholesterol levels of, respectively, <4.5 mmol/L (175 mg/dL) and <2.5 mmol/L (100 mg/dL), and lower, if possible.
- Hypertensive patients without overt CV disease but with high CV risk ($\geq$20% risk of events in 10 years) should also be considered for statin treatment even if their baseline total and LDL serum cholesterol levels are not elevated.

ANTIPLATELET THERAPY

- Antiplatelet therapy, in particular low-dose aspirin, should be prescribed to hypertensive patients with previous CV events, provided that there is no excessive risk of bleeding.
- Low-dose aspirin should also be considered in hypertensive patients without a history of CV disease if older than 50 years and with a moderate increase in serum creatinine or with a high CV risk. In all these conditions, the benefit-to-risk ratio of this intervention (reduction in myocardial infarction greater than the risk of bleeding) has been proven favourable.
- To minimize the risk of haemorrhagic stroke, antiplatelet treatment should be started after achievement of BP control.

GLYCAEMIC CONTROL

- Effective glycaemic control is of great importance in patients with hypertension and diabetes.
- In these patients dietary and drug treatment of diabetes should aim at lowering plasma fasting glucose to values 6 mmol/L (108 mg/dL) and at a glycated haemoglobin of $<6.5\%$.

26. PATIENTS' FOLLOW-UP

- Effective and timely titration to BP control requires frequent visits in order to timely modify the treatment regimen in relation to BP changes and the appearance of side-effects.
- Once the target BP has been reached, the frequency of visits can be considerably reduced. However, excessively wide intervals between visits are not advisable because they interfere with a good doctor-patient relationship, which is crucial for patient's compliance.
- Patients at low risk or with grade 1 hypertension may be seen every 6 months and regular home BP measurements may further extend this interval. Visits should be more frequent in high or very high risk patients. This is the case also in patients under non-pharmacological treatment alone due to the variable antihypertensive response and the low compliance to this intervention.
- Follow-up visits should aim at maintaining control of all reversible risk factors as well as at checking the status of organ damage. Because treatment-induced changes in left ventricular mass and carotid artery wall thickness are slow, there is no reason to perform these examinations at less than 1 year intervals.
- Treatment of hypertension should be continued for life because in correctly diagnosed patients cessation of treatment is usually followed by return to the hypertensive state. Cautious downward titration of the existing treatment may be attempted in low risk patients after long-term BP control, particularly if non-pharmacological treatment can be successfully implemented.

27. HOW TO IMPROVE COMPLIANCE WITH BLOOD PRESSURE LOWERING THERAPY

- Inform the patient of the risk of hypertension and the benefit of effective treatment.
- Provide clear written and oral instructions about treatment.
- Tailor the treatment regimen to patient's lifestyle and needs.
- Simplify treatment by reducing, if possible, the number of daily medicaments.
- Involve the patient's partner or family in information on disease and treatment plans.
- Make use of self measurement of BP at home and of behavioural strategies such as reminder systems.
- Pay great attention to side-effects (even if subtle) and be prepared to timely change drug doses or types, if needed.
- Dialogue with patient regarding adherence and be informed of his/her problems.

- Provide reliable support system and affordable prices.
- Arrange a schedule of follow-up visits.

Disclaimer: The ESH Guidelines represent the views of the ESH and were arrived at after careful consideration of the available evidence at the time they were written. Health professionals are encouraged to take them fully into account when exercising their clinical judgment. The guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patients, in consultation with that patient, and where appropriate and necessary the patient's guardian or carer. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

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Manual of

Hypertension

of the European Society of Hypertension

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Published under the auspices of the European Society of Hypertension

In the past few decades, hypertension has been the subject of a large number of books and manuals aimed at providing up-to-date reviews of the large amount of experimental and clinical studies performed in the pathogenesis, diagnosis, and treatment of the disease. The European Society of Hypertension approaches these issues in a different fashion, reflecting the authoritative opinion of the Society. The *Manual of Hypertension of the European Society of Hypertension* focusses on emerging new concepts that could affect the diagnostic and therapeutic approaches to the disease.

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