Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics

Second Edition

EDITED BY

William B. White, MD

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Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics

Clinical Hypertension and Vascular Diseases

William B. White, MD
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Second Edition

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Foreword

It is about 30 years since the development of the first practical non-invasive devices for repetitively measuring blood pressures in people undertaking their usual daily activities.

For those of us involved at the beginning of this technology, this important new book—comprehensively detailing the current state of the art—inevitably brings back memories of the early days when monitoring devices were large, complicated and uncertain. One of the first supporters of this science was NASA's manned space program. I still vividly recall engineers from a nearby device company borrowing my laboratory as they labored intently to prepare a blood pressure monitoring instrument, aided by the highly motivated astronaut who was to wear it during his forthcoming space mission. Remarkably, the prototype appeared to work at least as well in orbit as it did on the ground.

The concept of ambulatory blood pressure monitoring has always been beguiling. It certainly has provided insights into the physiology of blood pressure, including its diurnal changes. During the last several years the monitoring equipment has improved in important ways: it has become far simpler to use, more reliable in its operation and more flexible in gathering data.

From the point of view of the patient, reductions in the size and weight of the devices have added greatly to their practicality. Despite this progress, however, not all available automated technologies for monitoring blood pressure provide acceptable accuracy and reproducibility, and appropriately a major section of this text deals with the processes for validating and recommending these instruments.

This highly authoritative publication is the Second Edition of a work first published by Dr William White in 2000. Like its predecessor, it will become an indispensable source of information and reference in the field of ambulatory monitoring. Dr White is uniquely qualified for the task of bringing together and editing the contributions of the renowned group of experts who have joined him in writing this book. Not only has his own personal research contributed strongly to the knowledge that guides this discipline, but for many years he has been the Editor-in-Chief of *Blood Pressure Monitoring*, the principal peer-reviewed publication dealing with this area of clinical science.

There continues to be a notable expansion in the applications of blood pressure monitoring. Its use in clinical practice has grown significantly, particularly as official hypertension guidelines have now acknowledged its value for the accurate diagnosis of hypertension. This technology can be valuable in detecting white-coat hypertension, a condition where blood pressure is misleadingly high in the office or clinic, but normal when measured elsewhere. As well, patients with so-called masked hypertension, whose blood pressures are atypically low in the clinical setting, can be identified by this method.

One of the charms of ambulatory blood pressure monitoring is that it is one of the few medical tests that patients can largely interpret for themselves. Reviewing blood pressure values obtained over the 24 hour period allows patients, together with their physicians, to understand clearly whether or not they are hypertensive. And, if the evidence happens to point to the existence of hypertension, these informed patients will often become just as committed as their professional advisors to achieving effective treatment.

Whole-day monitoring data have also emerged as strong tools for exploring epidemiology. As the book discusses in detail, these measurements are more powerful in predicting major cardiovascular outcomes than conventional blood pressure readings. What's more, certain periods of the 24 hour pattern—for instance, the night-time readings, and whether they exhibit the expected physiologic reductions during sleep—can be of strong prognostic value. Even the rate-of-rise in blood pressure during the morning arousal period may be linked to the likelihood of major cardiovascular events. Research into the factors that regulate blood pressure profiles during the different portions of the day could ultimately lead to better-directed therapeutic strategies in hypertensive patients at risk.

Ambulatory blood pressure monitoring has become an indispensable part of studying drugs and potentially other treatments of hypertension. For a start, by ensuring that only truly hypertensive patients are included in clinical trials—thereby avoiding the dilutional effects on data of including patients with white coat hypertension—monitoring enhances the accuracy of quantifying blood pressure changes. Importantly, this technique virtually abolishes placebo effects. Additionally, its reproducibility reduces the number of patients needed to provide the statistical power for discriminating differences in achieved blood pressures among comparative treatment groups.

In many ways this book documents the maturing of ambulatory monitoring into an integral and vital part of clinical practice and research in hypertension. But it is far more than just a celebration of the great progress made in the field during recent years. Dr White brings us up to date with the insight and knowledge that can only come from one of the true pioneers and leaders in this work. For those who seek information about ambulatory blood pressure monitoring, and certainly for those who plan to use it, reading this new edition of William White's book will be an invaluable experience.

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Preface

The second edition of *Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics* is devoted to the topic of circadian variation in cardiovascular disease, with a special emphasis on the evaluation and treatment of hypertension. Clinical and device research related to self and ambulatory monitoring of the blood pressure and heart rate have led to significant advances in our ability to detect various clinical entities in patients with hypertension and its vascular complications. This research is important not only because hypertension is such a common problem among adults in industrialized countries, but also because the cardiovascular morbidity and mortality associated with the hypertensive disease process is so great.

Since the first edition of this book in 2000, research efforts in basic and clinical hypertension have continued to accelerate and work devoted to the measurement of blood pressure and blood pressure variability has also remained productive with new evaluations of devices, novel drug therapies, and outcomes research in cohort and population studies. During the past 6 years, numerous important research papers in the field of ambulatory blood pressure monitoring have been published and annual international consensus conferences have been held at the European and International Society of Hypertension meetings. Thus, it remains important and clinically relevant to devote a second edition of this book that updates research findings involving blood pressure monitoring and cardiovascular therapeutics.

The five chapters in Part I describe the methodology of self and ambulatory blood pressure monitoring in research and clinical practice. Dr. Pickering presents a comprehensive assessment of the utility of self blood pressure measurement for clinical practice by evaluating the validity of the devices, reviewing the epidemiologic data that are available, and discussing the potential for this technique in clinical trials and for the general management of patients. Drs. James and Mansoor describe the importance of diaries and physical activity recordings in cardiovascular disease. These techniques are crucial for obtaining meaningful data during ambulatory blood pressure recordings in clinical trials. Advances in actigraphy research have allowed investigators to pinpoint changes in physical activity that may directly impact on blood pressure

variability. Dr. Krishnan and I have written an overview of ambulatory monitoring of the blood pressure, including descriptions of device validation, patterns of blood pressure variation discovered with the advent of this technique, and usefulness of the methodology in clinical hypertension. Drs. O'Brien and Atkins have written a chapter on the importance of device validation and their reliability. The importance of device validation cannot be over-estimated as it eventually can have an effect on the overall validity of clinical trials using the recorders.

The seven chapters in Part II describe a number of advances in our understanding of the pathophysiology of the circadian biology of cardiovascular disorders. Drs. Portaluppi and Smolensky begin with an overview of the chronobiology of blood pressure regulation in humans. This chapter lays the groundwork for the rest of this section with its comprehensive discussion of the progress that has been made in research involving the chronophysiology of human disease with major emphases on hypertension, coronary artery disease, and stroke. Drs. Celis, Staessen, Palatini, Angeli, Schillaci and Verdecchia present a number of epidemiologic and prognostic studies that examine the importance of blood pressure and heart rate ability as determinants of cardiovascular morbidity and mortality. During the past decade, the field of ambulatory blood pressure monitoring has advanced dramatically owing to the completion and publication of major prospective studies that relate circadian blood pressure to cardiovascular outcomes. These studies show convincingly that ambulatory blood pressure values are independent predictors of cardiovascular morbidity and mortality. Drs. Sica and Wilson have examined the available data on the role of neurohormonal activity, salt sensitivity, and the renin–angiotensin system on blood pressure variability, especially as it relates to the blunting of the nocturnal decline in pressure.

Drs. Shea and Muller have reported on the circadian variation of myocardial infarction and cardiovascular death. These authors remind us of the need to identify acute causes of sudden death and myocardial infarction since coronary disease remains the leading cause of death in so many countries around the globe. Drs. Vagaonescu and Phillips conclude this section by providing a review of the data on the relationship between blood pressure variability and stroke, as well as discussing the seasonal and daily variations in the incidence of stroke.

The 4 chapters in Part III are all new in this Edition and focus on ambulatory blood pressure in special populations of patients with hypertension: Dr. Prisant covers the older patient who has systolic

hypertension from the perspective of a clinical cardiologist; Dr. Portman covers children and adolescents from the perspective of a pediatric nephrologists and hypertension specialist; Dr. Feldman evaluates data during pregnancy from the perspective of an expert in maternal-fetal medicine; Dr. Santos and Peixoto provide us with comprehensive data on patients with chronic kidney disease and those on dialysis from the perspective of nephrologists.

In Part IV, there are 3 chapters, including 1 new one for this second edition. The focus of the section is on the effects of antihypertensive drug therapy on the circadian variation of blood pressure, heart rate, and myocardial ischemia and the use of ambulatory monitoring in hypertension management. Dr. Lemmer has reviewed most of the available data on the effects of altering the timing of dosing of drugs (chronopharmacology) on circadian blood pressure variation; he provides data from the perspective of both the chronobiologist and the clinical hypertension specialist. I have provided an extensive review of the usefulness of ambulatory blood pressure monitoring during antihypertensive drug development. In addition to the obvious benefits of ambulatory blood pressure measurement from a quantitative and statistical point-of-view, ambulatory monitoring elucidates the efficacy of new antihypertensive therapies versus placebo. It also is an important tool to compare antihypertensive agents after registration of the drug has occurred. In the final chapter, Drs. Smith and Neutel, provide important information on use of ambulatory blood pressure monitoring in clinical practice. This is a pragmatic as well as an evidence-based chapter.

The experts contributing to this textbook have provided us with a comprehensive up-to-date view of a field in hypertension and vascular disease that is quite dynamic and always advancing. The progress that has been made since Drs. Perloff, Sokolow, and Cowans' seminal study on awake ambulatory blood pressure and cardiovascular outcome 24 years ago is truly remarkable. Just 15 years ago, most research in the field of ambulatory monitoring of the blood pressure was descriptive and did not even correlate the data to target organ disease. Thus, practicing physicians were not provided with enough useful information to have an impact on the day-to-day management of their patients. This certainly is no longer the case as after many years of outcomes studies that include target organ disease and events, ambulatory blood pressure monitoring has matured into a very useful methodology for clinical hypertension research as well as an important aid in the management of patients with hypertension and vascular disease.

I remain grateful for all of the outstanding chapters provided by my contributing authors, which greatly simplified my job as Editor. I am especially fortunate to have supportive colleagues such as Drs. Beatriz Tendler and Bruce Liang in the Pat and Jim Calhoun Cardiology Center at the University of Connecticut School of Medicine who helped in the practice and research program so diligently during the production of this book. Once again, Diane Webster from the Editorial office of Blood Pressure Monitoring at the University of Connecticut Health Center provided outstanding support in helping me to organize the manuscripts during the course of their production. Paul Dolgert and Jennifer Hackworth at Humana Press in New Jersey provided their broad expertise and invaluable guidance during the publishing process. Finally, I would like to extend my appreciation to my wife Dr. Nancy Petry and my children Bjornulf, Marte, and Elin for all of their love and support.

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I Out-of-Office Blood Pressure Monitoring

1 Self-Monitoring of Blood Pressure

Thomas G. Pickering, MD, Dphil

CONTENTS

From: *Clinical Hypertension and Vascular Disease: Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics*
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INTRODUCTION

Although the monitoring of antihypertensive treatment is usually performed using blood pressure readings made in the physician's office and having a blood pressure check is by far the most common reason for visiting a physician, it is neither a reliable nor an efficient process. Thus, physician's measurements are often inaccurate as a result of poor technique, often unrepresentative because of the white coat effect, and rarely include more than three readings made at any one visit. It is often not appreciated how big variations in blood pressure can be when measured in the clinic. In a study conducted by Armitage and Rose in 10 normotensive subjects, two readings were taken on 20 occasions over a 6-wk period by a single trained observer *(1)*. The authors concluded that "the clinician should recognize that the patient whose diastolic pressure has fallen 25 mm from the last occasion has not necessarily changed in health at all; or, if he is receiving hypotensive therapy, that there has not necessarily been any response to treatment." In addition, blood pressure can decrease by 10 mmHg or more within the time of a single visit if the patient rests, as shown by Alam and Smirk in 1943 *(2)*. There is also a practical limitation to the number or frequency of clinic visits that can be made by the patient, who may have to take time off work to make the visit.

ADVANTAGES AND LIMITATIONS OF SELF-MONITORING

The potential utility of hypertensive patients having their blood pressures measured at home, either by using self-monitoring or by having a family member make the measurements, was first demonstrated in l940 by Ayman and Goldshine *(3)*. They demonstrated that home blood pressures could be 30 or 40 mmHg lower than the physicians' readings and that these differences might persist over a period of 6 mo. Self-monitoring has the theoretical advantage of being able to overcome the two main limitations of clinic readings: the small number of readings that can be taken and the white coat effect. It provides a simple and cost-effective means for obtaining a large number of readings, which are at least representative of the natural environment in which patients spend a major part of their day. Self-monitoring has four practical advantages: it is helpful for distinguishing sustained from white coat hypertension, it can assess the response to antihypertensive medication, it can improve patient compliance, and it can reduce costs (Table 1).

Table 1
Advantages and Disadvantages of Self-Monitoring

Advantages
Elimination of white coat effect
Increased number of readings
Response to antihypertensive treatment assessed
Reduced costs
Improved compliance
Disadvantages
Limited prognostic data
May underestimate daytime pressure
Patients may misreport readings

The limitations of self-monitoring also need to be specified. First, readings tend to be taken in a relatively relaxed setting, so that they may not reflect the blood pressure occurring during stress; second, patients may misrepresent their readings; and, third, occasional patients may become more anxious as a result of self-monitoring.

Although the technique has been readily available for many years, it is taking a surprisingly long time to find its way into general clinical practice. There has been a recent explosion in the sale of devices for self-monitoring, few of which have been properly validated. Physicians are also endorsing the more widespread use of home monitoring, and national guidelines, such as those produced by the American Society of Hypertension *(4)*, are beginning to appear.

CHOICE OF MONITORS FOR HOME USE

When self-monitoring was first used, the majority of studies relied on aneroid sphygmomanometers *(5)*. In the past few years, automatic electronic devices have become increasingly popular, and the standard type of monitor for home use is now an oscillometric device, which records pressure from the brachial artery. These have several advantages, including freedom from observer bias and minimal training needed for patients to use them accurately. However, it is critical that patients use accurate devices for self-monitoring. Unfortunately, only a few have been subjected to proper validation tests, and several devices on the market have failed the tests. Two websites of nonprofit organizations list the currently validated monitors: the British Hypertension Society (http://www.bhsoc.org/blood_pressure_list.htm) and the dabl

Educational Trust (www.dableducational.org/). Monitors are available that record blood pressure from the upper arm, wrist, or finger.

Arm Monitors

Monitors that measure the blood pressure in the brachial artery with a cuff placed on the upper arm continue to be the most reliable. These monitors also have the additional advantage that the brachial artery pressure is the measure that has been used in all epidemiological studies of high blood pressure and its consequences. For the majority of patients, this is the preferred type of monitor.

Wrist Monitors

Wrist monitors are the most convenient to use and are preferred by many patients. They are also very compact. They have the potential advantage that the circumference of the wrist increases relatively little in obese individuals, so that there is less concern about cuff size. The smaller the diameter of the wrist in comparison with the upper arm, that less battery power that is needed to inflate them, and they also cause less discomfort for the patient. A potential disadvantage is that the wrist must be held at the level of the heart when a reading is being taken, which increases the possibility of erroneous readings. A recently introduced model (the Omron 637) avoids this problem by taking readings only when the wrist is held over the heart. It might be anticipated that the systolic pressure recorded at the wrist would be consistently higher than the pressure recorded from the upper arm, but this has not been a consistent finding. Experience with wrist monitors is relatively limited at present, and most of the monitors that have been tested have failed the validation studies (*see* www.dableducational.org/). They are, therefore, not generally recommended for routine clinical use.

Finger Monitors

Finger monitors incorporate a cuff encircling the finger and are easy to use and compact. To control for the hydrostatic effect of the difference between the level of the finger and the heart, it is recommended that the readings be taken with the finger held on the chest over the heart; even so, they are not accurate and none have passed validation tests. Their use should be discouraged.

Testing and Validation of Monitors

Patients should be advised to use only monitors that have been validated for accuracy and reliability according to standard international

testing protocols. The original two protocols that gained the widest acceptance were developed in the United States by the Association for the Advancement of Medical Instrumentation (AAMI) in 1987 and the British Hypertension Society (BHS) in 1990, with revisions to both in 1993. These required testing of a device against two trained human observers in 85 subjects, which made validation studies difficult to perform. One consequence of this has been that many devices still on the market have never been adequately validated. More recently, an international group of experts who are members of the European Society of Hypertension Working Group on Blood Pressure Monitoring have produced an international protocol that should replace the two earlier versions *(6)* and is easier to perform. Briefly, it requires comparison of the device readings (four in all) alternating with five mercury readings taken by two trained observers. Devices are recommended for approval if both systolic and diastolic readings taken are at least within 5 mmHg of each other for at least 50% of readings.

The fact that a device passed a validation test does not mean that it will provide accurate readings in all patients. There can be substantial numbers of individual subjects in whom the error is consistently greater than 5 mmHg with a device that has achieved a passing grade *(7)*. This may be more likely to occur in elderly *(8)* or diabetic patients *(9)*. For this reason, it is recommended that each oscillometric monitor should be validated on each patient before the readings are accepted. No formal protocol has yet been developed for doing this, but if sequential readings are taken with a mercury sphygmomanometer and the device as described next, major inaccuracies can be detected.

Checking Monitors for Accuracy

When patients get their own monitor it is very important to have them bring it in to the clinic to check their technique and also the accuracy of the monitor, even if it is a model that has passed the AAMI or BHS criteria previously described. The patient should be asked to take two readings with the monitor, followed by a mercury sphygmomanometer reading, a third reading with the monitor, and another mercury reading. The first monitor reading is likely to be higher than any of the others and is discarded. The averages of the two subsequent readings with the device and the mercury sphygmomanometer should be within 5 mmHg of each other. Figure 1 shows results from two patients evaluated by this protocol. In patient A, the readings with the device overlap the mercury readings, and the device can be considered to be

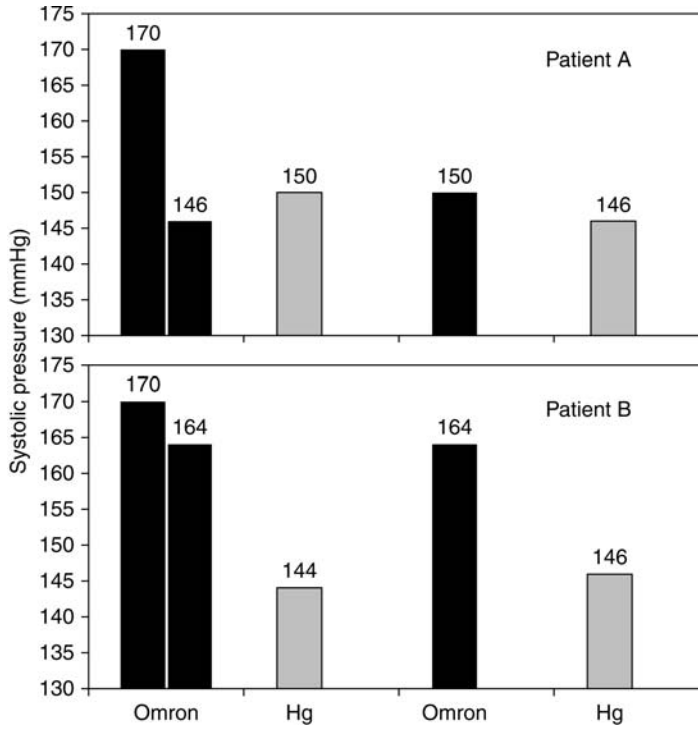

Fig. 1. Results of clinical testing of two devices for home monitoring in two patients. Bars show systolic pressure readings from the devices and a physician using a mercury sphygmomanometer.

accurate in that patient. In patient B, however, the device significantly underestimated the mercury readings.

Do Patients Provide Accurate Reports of Their Readings?

Some years ago a study of home glucose monitoring where patients were asked to keep a written record of their readings using a device that had a memory chip of which the patients were unaware found that there were substantial discrepancies between the readings reported by the patient and the actual readings stored in the device's memory, with a tendency to underreport extreme readings *(10)*. The availability of oscillometric devices with memory chips has enabled the same sort of study to be done with blood pressure readings, and so far two publications have appeared describing its use. Both *(11,12)* found that while the average values reported by the patients were generally similar to the true readings, there were substantial numbers of patients

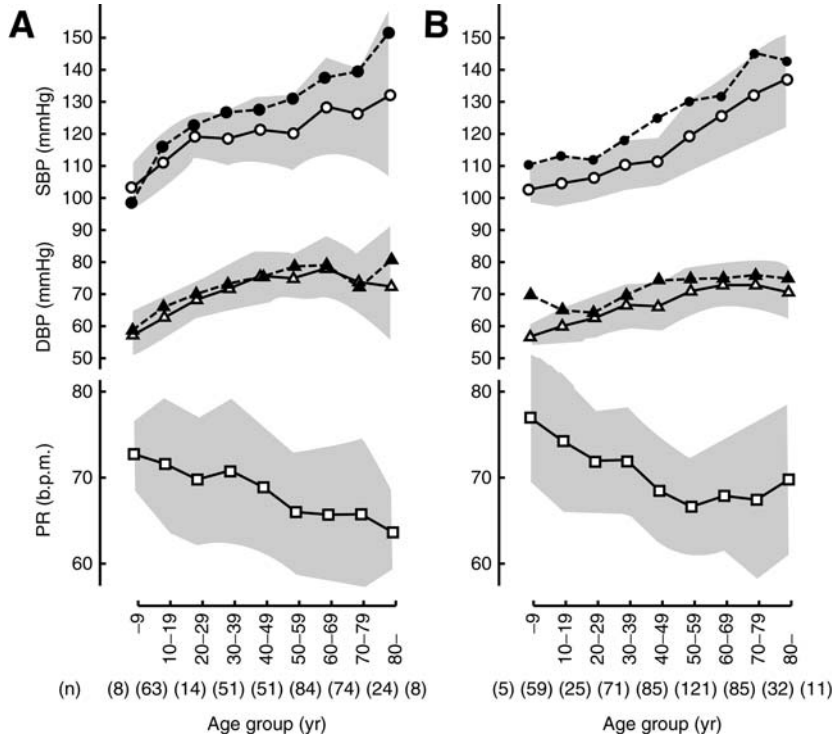

Fig. 2. Effects of age and gender on home blood pressure. Closed symbols show clinic readings; open symbols home readings. Shaded areas show range (1 SD): **(A)** men; **(B)** women. SBP and DBP, systolic and diastolic pressure; PR, pulse rate. (Reproduced with permission from ref. *15*.)

in whom the average discrepancy was at least 10 mmHg systolic and 5 mmHg diastolic, with a greater tendency to underreport than to overreport the values (as had been observed with glucose monitoring). Many of the latest generation of monitors have memory.

DEMOGRAPHIC FACTORS INFLUENCING HOME BLOOD PRESSURE LEVELS

Gender

Home blood pressure is lower in women than in men, as is true for clinic and ambulatory pressure. This has been well documented by the four large epidemiological studies (*see* Fig. 2) *(13–16)*. However, the clinic–home differences are generally the same in men and women.

Age

Age also influences home blood pressure, with all studies that evaluated this showing an increase. In the largest population study to investigate this, conducted in Ohasama, Japan, the increase with age was surprisingly small: thus, the average home pressure was 118/71 mmHg for men aged 20–29 yr, and 127/76 mmHg for men over 60 (Fig. 2) *(17)*. The published results almost certainly underestimate the true changes, because subjects on antihypertensive medications were usually excluded and the prevalence of hypertension increases with age. Another age-related change is the increase of blood pressure variability, as shown by the Ohasama study. The day-to-day variability of systolic pressure increases markedly with age in both men and women, whereas diastolic pressure is little affected and the variability of heart rate actually decreases.

ENVIRONMENTAL FACTORS INFLUENCING HOME BLOOD PRESSURE LEVELS

As with any other measure of blood pressure, the level of pressure that is recorded during home monitoring shows considerable variability and is likely to be influenced by a number of factors. These are summarized next (*see* Table 2).

Season of the Year

Home blood pressure tends to be up to 5 mmHg higher in the winter than in the summer in temperate climates *(18,19)*.

Time of Day

In studies where morning and evening measurements were taken, the evening readings tended to be higher for systolic pressure (by about 3 mmHg), but there were no consistent differences for diastolic pressure *(20,21)*. These differences may be more pronounced in hypertensive patients: in one study of untreated hypertensives *(22)*, the average home blood pressure was 147/86 mmHg at 8 AM, 145/82 mmHg at 1 PM, and 152/86 mmHg at 10 PM. The differences between morning and evening pressures may be higher in men and in smokers *(21)*.

The pattern of blood pressure change over the day may vary considerably from one patient to another, depending on daily routine. Antihypertensive treatment may also have a major influence *(21)*. For this reason, it is generally recommended that patients should take readings in both the early morning and at night.

Table 2
Environmental Factors That Affect Home Blood Pressure (BP)

Factors that increase BP	*Factors that decrease BP*
Winter	Summer
Caffeine	Exercise
Cigarettes	
Stress	
Talking	

Day of the Week

There is relatively little information as to whether pressures recorded on nonwork days are the same as on workdays. In a study using ambulatory monitoring of blood pressure, we found that the pressures at home in the evening were consistently higher if the patient had gone to work earlier in the day *(23)*.

Meals

In younger subjects there is typically an increase in heart rate, a decrease in diastolic pressure, and little change of systolic pressure for up to 3 h after a meal *(24)*. In older subjects there may be a pronounced fall of both systolic and diastolic pressure after food. Thus, one study compared the effects of a breakfast of two eggs, two slices of toast, and orange juice in healthy elderly subjects (mean age 82 yr) and controls aged 35 yr *(25)*. The average fall of blood pressure between 30 and 60 min after the meal was 16/10 mmHg in the elderly but only 4/3 mmHg (not significant) in the young.

Alcohol

In people who drink alcohol regularly, it has been reported that evening blood pressure is lowered by 7/6 mmHg and that there is also a smaller increase in morning blood pressure (5/2 mmHg) that is only seen after a delay of 2 wk *(26)*.

Caffeine

Drinking coffee increases blood pressure, but not heart rate. The increase in blood pressure begins within 15 min of drinking coffee, is maximal in about 1 h, and may last for as much as 3 h. Typical increases

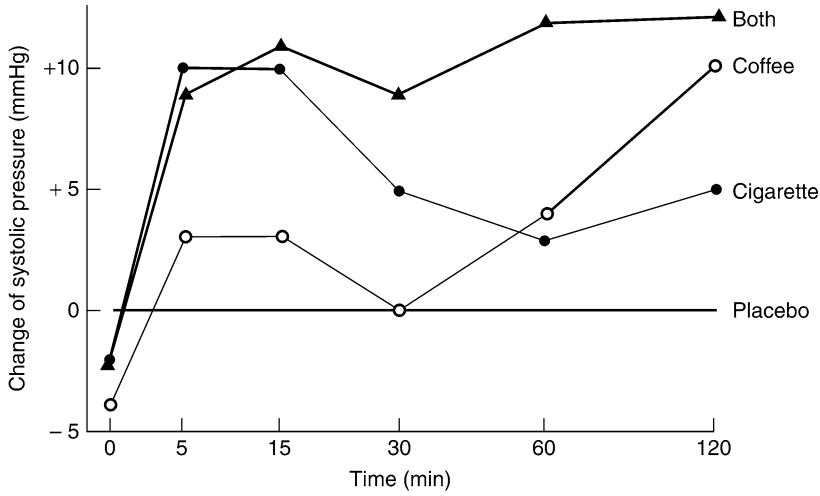

Fig. 3. Changes of systolic pressure occurring after drinking coffee and smoking cigarettes, alone and in combination. (Adapted with permission from ref. *32*.)

are between 5/9 and 14/10 mmHg *(27,28)*. Drinking decaffeinated coffee produces little or no change *(27)*. These changes are dependent on the level of habitual caffeine intake: in people who do not use it regularly they are much larger than in habitual users (12/10 vs 4/2 mmHg, respectively). Older subjects show bigger increases in pressure than younger ones *(29)*. Caffeine also has an additive effect on the blood pressure response to mental stress: higher absolute levels of pressure are achieved after caffeine, but the rise of pressure during the stressor is not affected *(30)*.

Smoking

Smoking a cigarette raises both heart rate and blood pressure. In patients who were studied smoking in their natural environment during intraarterial ambulatory blood pressure monitoring, it was found that the blood pressure increased by about 11/5 mmHg *(31)*, sometimes preceded by a transient fall of pressure; changes were quantitatively similar in normotensives and hypertensives. The effect on blood pressure is seen within a few minutes and lasts about 15 min. Coffee and cigarettes are often taken together, and a study by Freestone and Ramsay showed that they may have an interactive effect *(32)*, which may raise blood pressure for as long as 2 h (Fig. 3). Home blood pressures are usually lower than clinic blood pressures, but this difference is less in smokers *(33)*, presumably because they are likely to have smoked before taking the home readings.

Talking

Talking is a potent pressor stimulus that has both physical and psychological components. Reading aloud produces an immediate increase of both systolic and diastolic pressure (by about 10/7 mmHg in normotensive individuals) and of heart rate, with an immediate return to baseline levels once silence is resumed *(34)*. Reading silently, however, does not affect the pressure. Speaking fast produces a bigger increase than speaking slowly *(35)*. Although this is unlikely to be a factor in patients using a stethoscope to record their blood pressure, it could be relevant when a spouse is taking the readings.

Stress

Emotional stress can produce marked elevations of blood pressure, which can outlast the stimulus. In a study in which people were asked to recall a situation that made them angry, we found that the blood pressure could increase by more than 20 mmHg and was still elevated by more than 10 mmHg 15 min later *(36)*. In a survey of hypertensives who were monitoring their blood pressure at the time of the Hanshin-Awaji earthquake in Japan in 1995, it was found those who lived within 50 km of the epicenter showed an increase in blood pressure of 11/6 mmHg on the day following the quake, which took 1 wk to wear off, whereas those living further away showed no change *(37)*. After the terrorist attacks on the World Trade Towers in New York on 9/11/2001, we observed a 30 mmHg increase in home systolic pressure in a patient whose office was immediately opposite one of the towers, which persisted for several days *(38)*. And in a larger series of subjects who were monitoring their pressure using a teletransmission device in the months before and after 9/11/2001 in four sites in the United States, we observed a 2-mmHg increase in systolic pressure *(39)*. This was not a seasonal effect, because comparable data were available for the same time during the previous year.

Exercise

Although blood pressure rises markedly during physical exercise, it rapidly returns to its baseline level when the exercise is completed, and there may be a period of several hours after a bout of heavy exercise when the pressure may remain below the preexercise level, a phenomenon described as postexercise hypotension *(40)*.

COMPARISON OF HOME AND CLINIC PRESSURES

The original observation of Ayman and Goldshine *(3)* that home pressures are usually much lower than clinic pressures has been

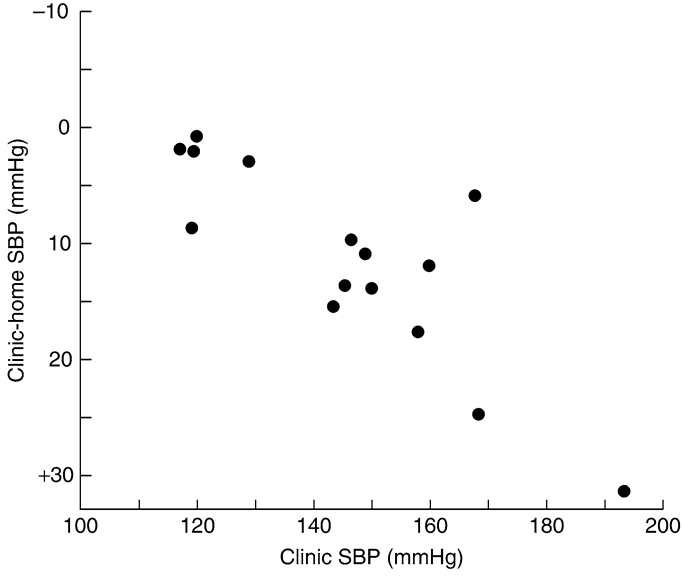

Fig. 4. Differences between systolic pressure between clinic and home in several studies; each point represents average value for one group of subjects.

confirmed in a number of studies *(5,41)*, including the population surveys previously described, in which the vast majority of subjects were normotensive. In the Didima study of 562 normotensive subjects, home and clinic blood pressures were very similar (using the second of two clinic visits) (clinic systolic blood pressure [SBP] was 1 mm lower and diastolic blood pressure [DBP] 1 mm higher) *(20)*. Home blood pressure was higher on day 1 of monitoring than on subsequent days. These differences may be more marked in older subjects *(42)*. The correlations between the clinic and home blood pressure readings in the population studies were quite close, ranging from 0.73/0.64 (for systolic and diastolic pressures, respectively) in the PAMELA study *(43)* to 0.84/0.77 in PURAS *(42)*.

In hypertensive subjects, the differences between clinic and home pressures are greater than in normotensive subjects, as shown in Fig. 4. A notable exception to this was the HOT study, which included a substudy of 926 treated hypertensives who had their blood pressure evaluated by both clinic and home measurements, using a semiautomatic device in both cases *(44)*. There were no differences between the two (the average blood pressures were 137/83 mmHg in the clinic and 137/83 mmHg at home). The probable explanation for this is that the readings were mostly within the normal range, where differences are slight.

In patients with severe hypertension clinic pressures may be 20/10 mmHg higher than home readings, and these clinic readings are also higher than readings taken in hospital by a nurse *(45)*. The Ohasama study found that the correlations between home and clinic blood pressure were stronger in untreated ($r = 0.57$ and 0.54 for SBP and DBP, respectively) than in treated hypertensive subjects ($r = 0.30$ and 0.38) *(21)*.

In some cases, home pressures may show a progressive decline with repeated measurement *(46)*, but this is by no means always seen *(5,47)*. Kenny et al. measured blood pressure by four different techniques on three occasions separated by intervals of 2 wk in 19 patients with borderline hypertension *(47)*. The techniques included conventional clinic measurement, basal blood pressure (measured after lying for 30 min in a quiet room), daytime ambulatory pressure, and self-recorded home pressure. None of the four measures showed any consistent change over the three study days, although there was an insignificant downward trend in all of them. For all 3 d, the clinic pressures were consistently higher than any of the other measures, but there were no significant differences between any of the other three measures. The average difference between clinic and home pressures was 9/4 mmHg.

That the clinic–home difference is a result of the setting rather than the technique of blood pressure measurement can be demonstrated by having patients take readings both at home and in the clinic. In the clinic it may be found that the patients' and the physicians' readings are very similar and in both cases higher than the home readings. In 30 treated hypertensives who were evaluated using both clinic and home blood pressure, clinic blood pressures were taken by either the physician or the patient using an electronic device, and the blood pressures were the same *(48)*.

The discrepancy between home and clinic pressures raises the question: Which is closer to the true pressure? As shown in Fig. 5, the home pressures are closer to the 24-h average than the clinic pressures *(5)*. Figure 5 also demonstrates the phenomenon seen in Fig. 10, namely that there is a progressively greater discrepancy between the clinic and the true pressure at higher levels of blood pressure. Other studies have also found that the correlation between home and ambulatory pressure is closer than for either of them with clinic pressure *(49)*.

REPRODUCIBILITY OF HOME READINGS

Relatively little has been published on this issue, but it is important. In a study that we performed some years ago comparing the reproducibility of home, clinic, and ambulatory readings, all measured twice separated by an interval of 2 wk, we found that in hypertensive patients

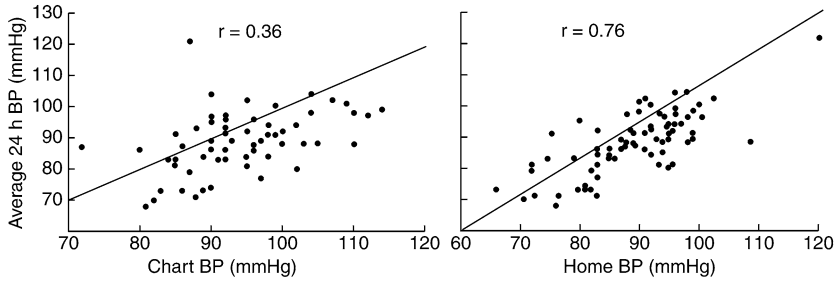

Fig. 5. Comparisons of clinic (chart), home, and 24-h average pressures in 93 patients. Lines of identity are shown. (Reproduced with permission from ref. *5*.)

there was a significant decline of systolic pressure in the clinic over this period, but the home and ambulatory pressures showed no significant change *(50)*. In normotensive subjects there was no consistent change in any of the three measures of blood pressure. In another study, Jyothinagaram et al. measured clinic and home pressures three times over a 4-wk interval in 17 hypertensive patients *(51)*. The clinic pressure fell from 181/97 to 162/93 mmHg, whereas the home pressure showed no change (153/89 to 154/89 mmHg) (Fig. 6). The superior reproducibility of home and ambulatory measurements may be partly explained by the greater number of readings. These findings support the notion that the fall of clinic pressure on successive visits is primarily because of habituation to the clinic setting or regression to the mean.

A commonly used measure of the stability of a measure is the standard deviation of the difference (SDD) between successive readings. When a measure is reproducible, this number is low. In our study, the SDD for the home readings was 5.6/4.6 mmHg, which was similar to the SDD for ambulatory readings (5.3/5.4), and lower than for clinic reading (9.7/6.7) *(50)*. The correlation coefficients for all three sets of measurements were very close (0.96/0.94 for home systolic and diastolic pressures, 0.93/0.87 for ambulatory, and 0.94/0.87 for clinic readings). Another study of 133 hypertensive subjects found that home blood pressure gave the lowest SDD for systolic and diastolic pressures (6.9/4.7 mmHg), compared with 8.3/5/6 for ambulatory blood pressure and 11.0/6.6 for clinic blood pressure *(52)*.

The studies previously described investigated the reproducibility of home blood pressures over a period of weeks, and it might be expected that over longer periods of time the reproducibility would be lower. This is not necessarily the case, however. In the Ohasama study, 136 untreated subjects measured home blood pressure for 3 d on two occasions 1 yr

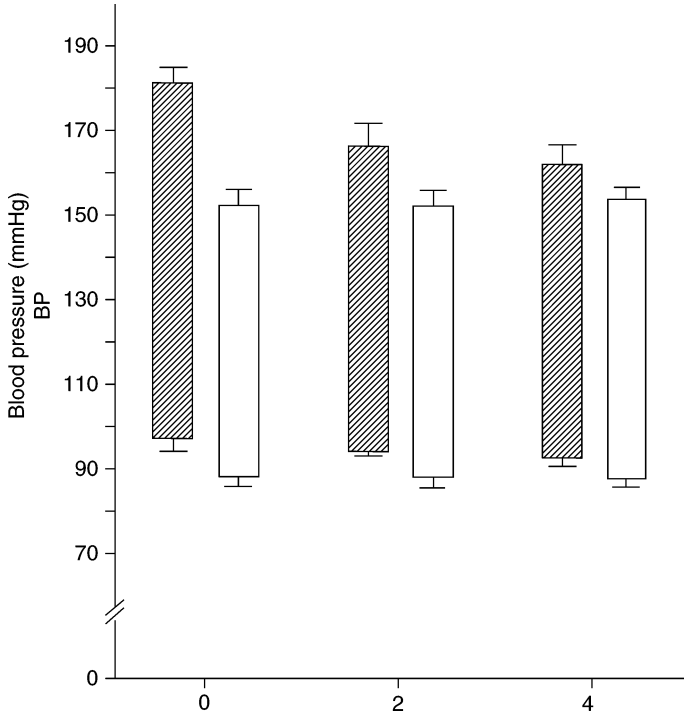

Fig. 6. Effect of repeated measurement on clinic (hatched bars) and home (open bars) blood pressure, each measured on three occasions over a 4-wk period. Despite a progressive decrease in clinic pressure, home pressure remains unchanged. (Reproduced with permission from ref. *51*.)

apart *(53)*. The correlations between the two were high (r = 0.84 and 0.83 for SBP and DBP), and there were no consistent change over the year. In contrast, the clinic blood pressures declined 4/3 mmHg over the same period and were less closely correlated (r = 0.69 for SBP and 0.57 for DBP). Thus, home blood pressure appears to be relatively stable.

HOME BLOOD PRESSURE IN NORMAL SUBJECTS

As with ambulatory pressure, there is no universally agreed-upon upper limit of normal home blood pressure, but several studies have compared home and office levels of pressure, and others have described average levels in normal populations. There have been six large epidemiological studies of home blood pressure, which have attempted to define the normal ranges: the Tecumseh Study *(54)*, the Dubendorf Study *(55)*, the Ohasama Study *(17)*, the Limbourg Study *(56)*, the Didima

study *(20)*, and the PURAS study *(42)*. All six studies found that home pressures were higher in men than in women (as has been shown for ambulatory pressures), and five of the six found that they increased with age (the Tecumseh Study could not evaluate this). The average values for home blood pressure for four of the studies are shown in Table 3.

What Is the Upper Limit of Normal Home Pressure?

The distribution of blood pressure in the population is in the form of a skewed Gaussian or bell-shaped curve, which tails off at the higher end. Any division into "normal" and "high" blood pressure is thus arbitrary, and this applies whichever measure of blood pressure is used. In practice, the need for such a dividing line is that it can be used as a treatment threshold. One common technique used to define the upper limit of a variable such as blood pressure, which is continuously distributed in the population, is to take the 95th percentile, which defines the upper 5% as being "abnormal." A variation of this method is to use the mean plus 2 SD, which is very similar to the 95th percentile. An obvious problem with this is that hypertension affects more than 5% of the population; another is that hypertensive individuals are often excluded from population surveys. Thus, if in the population studies previously described, the upper limit of normal home pressure was defined as the 95th percentile, the values would range from 137/86 to 152/99 mmHg, which are clearly too high. In a meta-analysis of 17 studies of home blood pressures in normotensive subjects, Thijs et al. *(57)* used a number of techniques to define the upper limit of normal. One was to use the 95th percentile, which gave a level of 135/86 mmHg; the mean plus 2 SD gave 137/89 mmHg.

An alternative method of defining the upper limit of normal home pressure is to estimate the home pressure equivalent to a clinic pressure of 140/90 mmHg, as has also been done for ambulatory pressure. In the Thijs meta-analysis, two techniques were used to derive the home blood pressure equivalent to 140/90 mmHg *(57)*. The first was to compute the linear regression between clinic and home readings, which gave a value for the home pressure of 125/79 mmHg. The second was the percentile method, which calculated the percentile in the distribution of clinic blood pressures that corresponded to 140/90 mmHg, and used the same percentile for the distribution of the home BP; this gave a value of 129/84 mmHg. In the PAMELA study, the home blood pressure equivalent to a clinic BP of 140/90 was 133/82 mmHg calculated by the linear regression method *(58)*. The values for some of the population studies are shown in Table 3.

Table 3
Average Values and Proposed Upper Limits of Normal Home Blood Pressure (BP) From Population Studies

		Average values		*Home BP equivalent to 140/90 in clinic*	
Study	*N*	*Clinic BP*	*Home BP*	*Percentile*	*Regression*
PAMELA	1438	127/82	119/74	–	132/81
Didima	562	118/73	120/72	140/86	137/83
Dubendorf	503	130/82	123/77	133/86	–
PURAS	989	126/76	118/71	134/84	131/82

The American Society of Hypertension recommended that an appropriate level for the upper limit of normal home blood pressure should be 135/85 mmHg *(4)*. This was based on the fact that home pressures tend to be somewhat lower than clinic pressures and is in accord with the findings of several studies, as previously described. It is also consistent with the prospective findings of the Ohasama study, where home pressures higher than 138/83 mmHg were found to be associated with increased mortality *(59)*. The same value has been adopted by the JNC seven recommendations *(60)* and the American Heart Association *(61)*. As with office blood pressure, a lower home blood pressure goal is advisable for certain patients, including diabetics, pregnant women, and patients with renal failure. No specific limits have been set for these patients, however.

SELF-MONITORING FOR THE DIAGNOSIS OF HYPERTENSION

The goal of blood pressure measurement in the initial evaluation of hypertensive patients is to obtain an estimate of the true blood pressure, or the average over prolonged periods of time, for which any of the three measures available for clinical use (clinic, home, and ambulatory monitoring) are a surrogate measure. It is generally accepted that the best measure is the 24-h level, on the grounds that several prospective studies have found that it is the best predictor of risk. As described next, there are also three studies showing that home pressure predicts outcomes as good or better than clinic pressures. Because many of the readings taken during ambulatory monitoring are taken in the setting of the home, it is to be expected that there should be reasonably close agreement, although the self-monitored home readings tend to be taken during periods of relative inactivity. The potential advantages of home readings over clinic readings for evaluating the true pressure are twofold: first, the home readings largely eliminate the white coat effect, and, second, more readings can be taken. It has been demonstrated that a better estimate of the true blood pressure can be obtained by taking a few readings on several different occasions than by taking a larger number on a single occasion *(62)*.

A limitation of home pressures is that they usually represent the level of pressure at the lower end of the waking range, when the patient is relatively relaxed. Thus, they do not necessarily provide a good guide to what happens to the patient's pressure when undergoing the stresses of daily life, such as those occurring during work. The blood pressure at

work tends to be higher than the pressure at home and is similar to the clinic pressure, although the latter is not necessarily a good guide to the level of pressure at work *(63)*. In patients with mild hypertension, we found only a moderate correlation between home and work blood pressures ($r = 0.55$ for systolic and 0.65 for diastolic pressure) *(5)*. Although the majority of subjects do show a higher pressure at work than at home, we have encountered others whose pressure is the same or even higher at home. This is particularly true of women with children.

A potential concern with the use of self-monitoring of blood pressure is that it will increase the patient's anxiety about his or her condition. In practice, this has been found usually not to be the case: one study 70% of patients reported that they found the technique to be reassuring *(64)*. Nevertheless, there are some patients who become so obsessed with their blood pressure readings that self-monitoring becomes counterproductive.

Interpretation of Readings

Almost all patients who start to use self-monitoring are surprised at the large variations between individual readings, which may be as much as 40 mmHg. Thus, the minimum number of readings that can be interpreted with any confidence is about 10 or more. At the present time, there are no data to indicate that the variability of home blood pressure readings has any independent prognostic significance, so the average level is the preferred measure for making clinical decisions. It should be recognized that in some patients the first few days of self-monitoring may result in higher readings than subsequent ones. Two aspects of the average home blood pressure level are helpful: first, the absolute level, and, second, the difference between the clinic readings and the home readings. In the newly diagnosed patient in whom the decision is whether or not drug treatment should be started, the finding of a normal home blood pressure (<135/85 mmHg) in the presence of an elevated clinic blood pressure (>140/90 mmHg) suggests that the patient has white coat hypertension, in which case drug treatment may not be needed. This finding raises the issue of whether or not other means should be performed to establish the diagnosis, because home blood pressure is not generally thought to be adequate on its own. This decision will depend on the cost and availability of ambulatory monitoring. Another factor might be the magnitude of the difference between the home and clinic blood pressure. If this is very large (say, >30 mmHg), the case for performing ambulatory monitoring is strengthened. Another

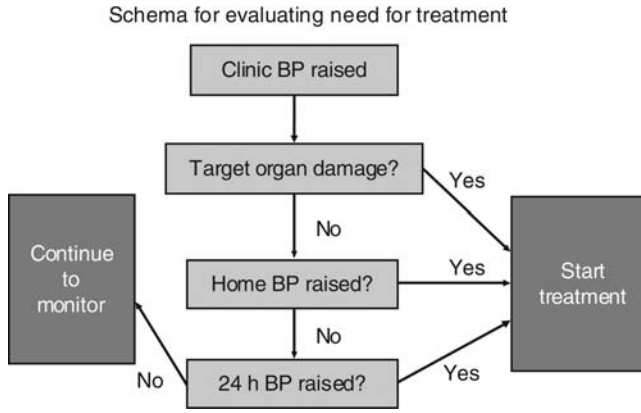

Fig. 7. Schema for diagnosing white coat hypertension based on home and ambulatory monitoring.

consideration is the difference between morning and evening readings. This is of particular relevance in patients who are taking antihypertensive drugs, because it helps to ensure that blood pressure control is sustained throughout the 24-h day. If patients take their medications in the morning, the early morning home readings may be taken as the trough blood pressure.

Diagnosis of White Coat Hypertension

In the newly diagnosed patient with hypertension in the clinic setting, the first issue is whether the patient has sustained or white coat hypertension, because antihypertensive mediation is more likely to be prescribed in the former case. White coat hypertension is conventionally diagnosed by comparing the clinic and ambulatory (typically daytime) pressures. Whether or not self-monitored home pressures can be used as substitutes is unresolved. Larkin et al. found that 79% of patients would be classified the same way using either ambulatory or home readings, whereas the remaining 21% would not *(65)*. Two other studies have found that home blood pressures are not reliable for diagnosing white coat hypertension *(66,67)*.

Some years ago, we proposed an algorithm for the detection of patients with white coat hypertension (*see* Fig. 7), whereby patients with persistently elevated clinic pressure and no target organ damage would undergo self-monitoring; if this showed high readings (>135/85), the patient would be diagnosed as having sustained hypertension, but if it was below this level, 24–h blood pressure monitoring

would be recommended to establish which patients had white coat hypertension. This algorithm was evaluated in 133 previously untreated hypertensives, all of whom had elevated clinic blood pressures on two visits *(68)*, and their home blood pressure was monitored for 6 d. All underwent ambulatory blood pressure monitoring, which identified 38 (28%) with white coat hypertension. However, nearly half of these (39%) were not diagnosed by the algorithm, because they had high home blood pressures. The main finding from this study was that a high home blood pressure does not exclude the possibility of white coat hypertension. However, these data did support the idea that if the home blood pressure was normal, white coat hypertension was likely. A somewhat similar study was performed by Mansoor and White *(69)* in 48 untreated patients with at least two elevated clinic blood pressure readings, who were evaluated with home blood pressure (three readings in the morning and evening for 7 d) and ABP. They looked to see how well a home blood pressure of 135 mmHg or higher predicted ambulatory hypertension (defined as a daytime SBP > 135 or DBP > 85). The sensitivity was 41% and the specificity 86%. The low sensitivity is perhaps not surprising, because, as previously discussed, home readings may underestimate the daytime blood pressure. They found that the sensitivity for detecting ambulatory blood pressure could be increased by lowering the threshold level for home blood pressure to 125/76 mmHg, but this of course would result in a larger number of false-positives.

Because the correlations between home and ambulatory blood pressures are in the region of 0.7, it would be unreasonable to expect that there would be a precise correspondence between any level of home pressure and the establishment or exclusion of ambulatory hypertension.

How Often Should Readings Be Taken?

A wide variety of schedules has been used to evaluate the home blood pressure levels in published studies, ranging from two readings taken on a single day *(43)* to six readings a day for a week or more *(18)*. The frequency of blood pressure readings can be varied according to the stage of the patient's evaluation. In the initial diagnostic period, frequent readings are desirable, but when the blood pressure is stable and well controlled, the frequency can decrease. The first reading is typically higher than subsequent readings *(20)*; therefore, multiple readings (two or three at each session) are routinely recommended. For estimating the true blood pressure, at least 30 readings are advisable. This number can be justified in two ways. First, the maximum reduction in

the SDD of home readings is obtained when there are at least 30 measurements (3 per day for 10 d) *(70)*. Second, the Ohasama study *(71)*, which was the first to establish the prognostic value of home readings, found that the prediction of the risk of stroke became stronger with more home readings, up to a maximum of 25 measurements; there was no evidence of a threshold number of readings.

It is desirable to obtain readings both in the morning and in the evening to detect diurnal variations in blood pressure in the untreated state and to assess the adequacy of treatment in patients who are taking medications. Readings taken in the morning before or just after taking the medication can be used as a rough measure of the "trough" effect of treatment, and those taken in the evening as a measure of the "peak" effect *(72)*.

In the newly diagnosed patient, a typical recommendation would be to take three consecutive readings in the morning and three in the evening 3 d a week for at least 2 wk (a total of at least 36 readings). This represents a reasonable compromise between obtaining the maximal number of readings and not overburdening the patient. It is also helpful to get some readings on weekend days in patients who work during the week, because they are often lower than readings taken on weekdays. It is often convenient to provide the patient with a form on which to enter the readings.

Another situation in which frequent readings are needed is when a new medication is being prescribed or a change made in the dose of an existing one. The frequency of readings can be much lower in patients who are stable.

HOME BLOOD PRESSURES, TARGET ORGAN DAMAGE, AND PROGNOSIS

One of the factors that has limited the acceptance of home blood pressure for clinical decision making has been the lack of prognostic data, but there are increasing numbers of studies showing that self-measured blood pressure predicts target organ damage and clinical outcomes better than traditional clinic blood pressure. These are reviewed next.

HOME BLOOD PRESSURE AND TARGET ORGAN DAMAGE

In one of the first studies using home monitoring it was reported that regression of left ventricular hypertrophy (LVH) evaluated by electrocardiogram (ECG) correlated more closely with changes of

Table 4
Correlations Between Measures of Target Organ Damage and Blood Pressure Measured at Home or in the Clinic

Author (ref.)	*n*	*Measure of TOD*	*Clinic SBP*	*Home SBP*
Kleinert *(5)*	45	LV mass	0.22	0.45
Verdecchia *(74)*	34	LV mass	0.30	0.41
Kok *(22)*	84	LV mass	0.32	0.31
Cuspidi *(76)*	72	LV mass	NS	0.35
Mule *(75)*	38	LV mass	NS	0.43
		Albuminuria	NS	0.40
		Combined[a]	0.41	0.60
Tachibana *(77)*	101	Carotid IMT	0.21	0.42

TOD, target organ damage; SBP, systolic blood pressure; LV, left ventricular; IMT, intima-media thickness.

[a]LV mass, albuminuria, and fundoscopic changes.

home blood pressure than with clinic blood pressure following the initiation of antihypertensive treatment *(73)*. Several other studies have indicated that the correlation between echocardiographically determined LVH and blood pressure is better for home than for clinic readings *(5,74,75)*, as shown in Table 4. However, in one study of 84 previously untreated hypertensive patients, home blood pressure and clinic blood pressure gave similar correlations with LVH ($r = 0.31$ and 0.32, respectively), but not as good as the correlation between ABP and LVH ($r = 0.51$) *(22)*. In a study of treated hypertensives home blood pressure correlated with LVH, but clinic blood pressure did not *(76)*.

Home blood pressure has also been related to other measures of target organ damage. It has been reported to correlate more closely than clinic blood pressure with microalbuminuria *(75)* and carotid artery interomedial thickness *(77)*.

HOME BLOOD PRESSURE AND PROGNOSIS

Three studies have compared the predictive value of clinic and home measurements, and all have shown that home measurements are potentially superior. In the first, which was conducted as a population survey in the town of Ohasama, Japan, 1789 people were evaluated with home, clinic, and 24-h blood pressure measurements *(78)*. Over a 5-yr follow-up it was found that the home pressure predicted risk better than the clinic readings. For each measure of blood pressure, the subjects were

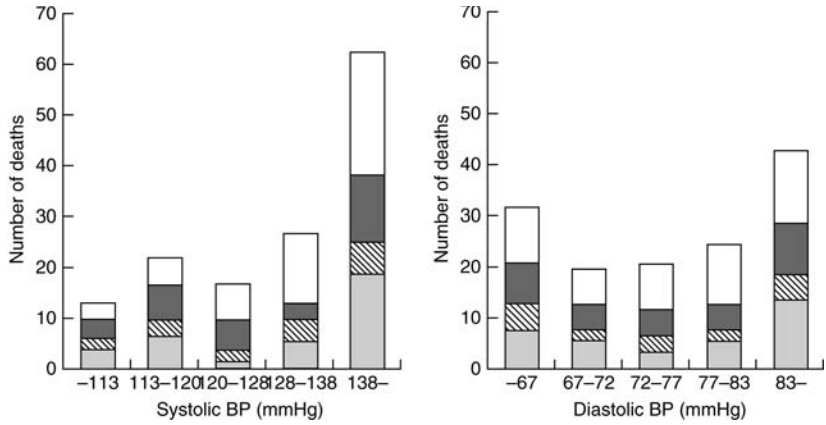

Fig. 8. Death rate according to home blood pressure (BP) level from the Ohasama study. Shaded bars, cerebrovascular disease; striped bars, heart disease; solid bars, cancer; open bars, other causes. (Reproduced with permission from ref. *79*.)

divided into quintiles. As shown in Fig. 8, the survival rate was significantly lower for people whose initial home pressure was greater than 138 mmHg systolic and 83 mmHg diastolic pressure *(79)*. As also shown in the figure, the consequences of a high clinic pressure were less clear. There was some suggestion from these data of a J-shaped curve, which is a paradoxical increase of mortality at low home blood pressures; the actual numbers were too small to be sure of this, however, and it was not observed for the screening blood pressures. A subsequent analysis over 10 yr *(71)* found that the prediction of risk became stronger with more home readings, up to a maximum of 25 measurements; there was no evidence of a threshold number. The second study was conducted in France; it recruited 4939 elderly hypertensives who were currently on treatment and found that morbid events observed over a 3.2-yr follow-up period were predicted by the home blood pressure at baseline, but not by the clinic pressure *(80)*. One particularly interesting aspect of this study was that patients who had normal clinic pressures but high home pressures were at increased risk, a phenomenon known as masked hypertension. It is not known if the variability of home blood pressure readings is an independent predictor of events, although there is some evidence that the variability of daytime readings measured with ABP monitors may be *(81)*. The third study was an Italian population-based study *(82)* of 2051 subjects who had one set of three clinic blood pressure readings and two home blood pressure readings (one in the morning and one in the evening) who

were followed for 11 yr. Adding the data from a second clinic visit on the following day did not improve the prediction of cardiovascular events, whereas adding the home readings did.

A not uncommon finding is isolated diastolic hypertension, in which the systolic pressure is normal and the diastolic pressure raised. There has been some controversy as to its prognosis, but the only report using home monitoring (the Ohasama study) concluded that it is benign *(83)*. The threshold values for defining it were a home systolic pressure <138 mmHg and a diastolic pressure >85 mmHg. In contrast, patients with isolated systolic hypertension were at increased risk.

There is also some evidence that self-monitored blood pressure may predict the change of blood pressure over time and the decline of renal function in diabetics. In the Tecumseh study of 735 healthy young adults (mean age 32), home blood pressure predicted future blood pressure over 3 yr better than clinic blood pressure *(66)*. A prospective study of 77 hypertensive diabetic patients whose clinical course was followed over a 6-yr period using both clinic and home monitoring found that home blood pressure predicted the loss of renal function (decrease in glomerular flitration rate) better than the clinic blood pressure *(84)*.

SELF-MONITORING FOR THE EVALUATION OF ANTIHYPERTENSIVE TREATMENT

When patients are having their antihypertensive medication initiated or changed, it is necessary to measure their blood pressure on repeated occasions. Self-monitoring is ideal for this purpose, because it can obviate the need for many clinic visits. It has the additional advantage of avoiding the biases inherent in clinic pressure measurements.

The validity of using home readings for monitoring the effects of treatment on blood pressure has been well established in a number of studies that have compared the response to treatment evaluated by clinic, home, and ambulatory pressures. Despite the general parallelism between clinic and home blood pressure during treatment, there may be considerable discrepancy between the two in individual patients. Thus, in a study of 393 patients treated with trandolapril *(85)*, the correlation coefficient between the clinic and home pressure response, while highly significant, was only 0.36. The slope of the line was also rather shallow, indicating that a decrease of 20 mmHg in clinic pressure is on average associated with a decrease in home pressure of only 10 mmHg. Other studies have shown that drug treatment lowers clinic blood pressure more than home blood pressure; in a study of 760 hypertensives

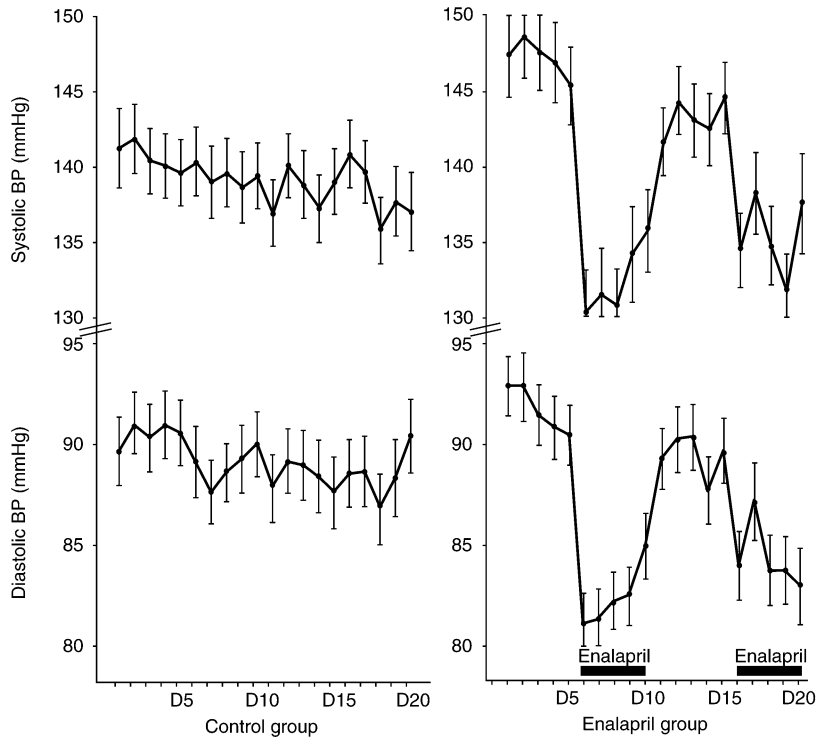

Fig. 9. (Left panel) Home blood pressure in a control group of patients with no intervention. (Right panel) Response to enalapril in one patient who took drug twice a day for 4 d. (Reproduced with permission from ref. *70*.)

treated with diltiazem 300 mg the clinic blood pressure fell by 20/13 mmHg and the home blood pressure by 11/8 mmHg *(86)*. In another study *(87)* losartan lowered clinic blood pressure by 17/13 mmHg and home blood pressure by 7/5; trandolapril lowered clinic blood pressure by 17/13 and home blood pressure by 7/5; changes of ABP were closer to the changes of home blood pressure. It is well recognized that drug treatment also lowers ambulatory blood pressure less than clinic blood pressure *(88)*. One study has looked at the effects of exercise training on clinic and home blood pressure. Clinic blood pressure fell by 13/8 mmHg in the experimental group and 6/1 mmHg in the controls, whereas home blood pressures fell by 6/3 and 1/–1, respectively *(89)*.

Home monitoring is also ideal for evaluating the time course of the treatment response. As shown in Fig. 9, for a drug with a relatively rapid onset of action like enalapril, the maximal fall of blood pressure

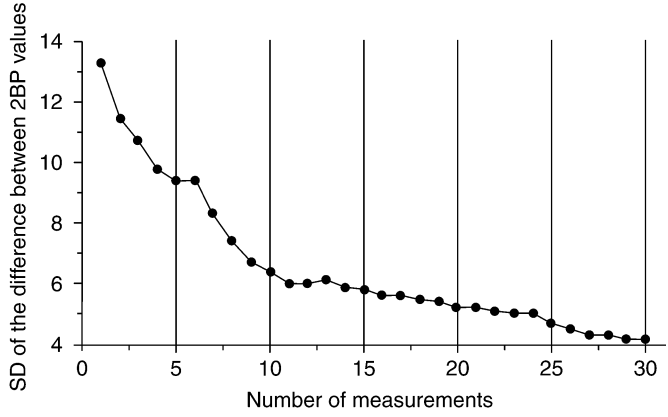

Fig. 10. Reduction of the standard deviation (SD) of the difference between two mean levels of home blood pressure as a result of increasing the number of readings used to define each level. (Reproduced with permission from ref. *70*.)

is seen within 1 d of starting the drug, and the pressure also returns to the pretreatment level quite promptly *(70)*.

How Many Readings Are Needed to Establish the Efficacy of Treatment?

It is helpful to know what the minimum number of home readings should be to establish a stable level when assessing the response to antihypertensive treatment, whether it be using medications or nonpharmacological treatment. To determine the influence of the number of readings used to define the difference between two average blood pressure levels (which might be before and after treatment) Chatellier et al. instructed patients to take three readings in the morning and three in the evening over a period of 3 wk *(70)*. They then calculated the standard deviation (SD) of the difference between two means derived from increasing numbers of individual readings over two 10-d periods. As shown in Fig. 10, the SD of the difference between the two means decreased progressively as larger numbers of individual readings were used to define each of the two means. About 80% of this reduction was obtained when 15 readings were used to define a mean, and including a larger number of readings brought little additional precision. The authors concluded that three readings taken over 5 d (preferably at the same time of day) should be sufficient to detect a drug-induced decrease of blood pressure.

N-*of-1 Trials for Identifying Optimal Treatment*

The increasing number of drugs available for the treatment of hypertension has done relatively little to improve the success of controlling hypertension in the population. In part this may be because people vary widely in the degree to which they respond to any one drug, and there is no good way of predicting which drug is best for which patient. It is thus largely a matter of trial and error, which will require a large number of clinic visits. One potential way of improving this situation is using home monitoring for "*N*-of-1" trials, in which each tries a number of different medications given in sequence *(70)*. Because individual drugs vary in the time needed to achieve their full effect on blood pressure, it is likely that a minimum of 3 wk would be needed to test each drug, although blood pressure readings need only be taken for the last few days of each period.

Use in Clinical Trials

One of the advantages of using home monitoring rather than traditional clinic measurements in trials of antihypertensive drugs is that fewer patients should be needed to show an effect. The greater statistical power inherent in the use of home recordings rather than clinic recordings for the evaluation of antihypertensive medications was well illustrated in a study by Menard et al. *(90)*. It was estimated that in order to detect a treatment effect of 5 mmHg, 27 patients would be needed if clinic blood pressures were used for the evaluation, but only 20 patients if home pressures were used. Home monitoring can be a useful way of estimating the trough:peak (T:P) ratio. Morning readings are taken just before the dose (trough), and evening readings (or midday) approximate the peak effects for many long-acting drugs. Menard et al. used this procedure to evaluate the effects of enalapril and found a T:P ratio of 77%, which is similar to estimates made using ambulatory monitoring *(91)*.

EFFECTS ON COMPLIANCE

There is substantial evidence that self-monitoring can improve blood pressure control; a recent meta-analysis of 18 randomized trials comparing self-monitoring with usual care found that blood pressure control was improved by about 4/2 mmHg in the self-monitoring groups *(92)*. One study randomized hypertensive African Americans to usual care, self-monitoring, or "community-based monitoring," which involved having blood pressure checked three times a week in a community health center. At 3 mo the blood pressure had decreased the

most in the self-monitoring group, with smaller changes in the community monitored group and no change in the controls *(93)*. Another study compared self-monitoring against usual care and found a significant reduction of 24-h blood pressure in the former and again no change in the control group *(94)*. The changes were most pronounced in African Americans, in whom mean arterial pressure decreased by 9.6 mmHg in the monitored group and increased by 5.2 mmHg in the usual care group. In the SVATCH study of 622 hypertensives, who were treated with losartan, there was a modest increase in control rate as a result of adding self-monitoring (66 vs 60% achieving target), which was more pronounced in women than men *(95)*.

COST-EFFECTIVENESS OF HOME MONITORING

There is some evidence that self-monitoring may be cost-effective. In a randomized study conducted by the Kaiser Permanente Medical Care Program in San Francisco *(96)*, 430 patients with mild hypertension, most of whom were taking antihypertensive medications, were randomized either to a usual care group or to use self-monitoring. Their technique was checked by clinic staff, and they were asked to measure their blood pressure twice weekly and to send in a record of their readings every month. At the end of 1 yr the costs of care (which included physician visits, telephone calls, and laboratory tests) were 29% lower and blood pressure control slightly better in the self-monitoring group. The vast majority of both patients and their physicians considered that the self-monitoring procedure was worthwhile. The authors estimated that the annual cost of self-monitoring was $28 per year (in 1992 dollars), which assumed a depreciation of a $50 monitor over 5 yr, $10 for training (also depreciated), $1 for blood pressure reporting, and $6 for follow-up to enhance compliance. Combining this estimate with their study results led to an estimated cost saving per patient of $20 per year. Projecting these numbers on a national level, they estimated that about 15 million hypertensive patients in the United States are candidates for self-monitoring and that 20 of the 69 million annual hypertension-related physician visits could be saved, with a cost saving of $300 million per year. These numbers seem very optimistic, but they clearly establish the potential for cost saving.

CONCLUSIONS AND FUTURE TRENDS

It is likely that the use of self-monitoring using electronic devices for the evaluation of hypertensive patients will continue to grow in the

foreseeable future and become a standard component of the clinical routine. This will be spurred by further developments in the processing of the readings, such as the storage of larger numbers of readings and calculating average values, variability of readings, and trends over time Because the readings are available in electronic form, there is in principle no reason why the patient should have to write them down. In addition, the use of telemonitoring, whereby patients can automatically transmit their readings to the health care provider by telephone or the Internet, will greatly facilitate the communication between physicians and their patients and form a "virtual hypertension clinic."

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2 Evaluation of Journals, Diaries, and Indexes of Work-Site and Environmental Stress

Gary D. James, PhD

CONTENTS

INTRODUCTION

Noninvasive ambulatory blood pressure monitors are increasingly used in the clinical evaluation of hypertension. With this technology, blood pressures are measured at fixed time intervals over the course of a single day (up to 24 h) while the patient goes about his or her typical

From: *Clinical Hypertension and Vascular Disease: Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics*
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daily activities, including sleep. There is substantial intraindividual variation in ambulatory blood pressure measurements that is not cyclical or repetitive. It occurs as a consequence of homeostatic and allostatic circulatory processes that act to maintain adequate blood flow to body tissues when changes in the internal physiological and external environmental conditions occur *(1,2)*. Thus, cardiovascular adjustments are continuously made every second of every day as people change their behavior to adapt to recurrent and sometimes patterned stressors that pervade and define their lifestyles. There are many behavioral and lifestyle factors that will increase the level of ambulatory blood pressure measurements *(1,3–6)*. If circumstances that raise blood pressure are experienced or sampled with high frequency during ambulatory monitoring in a patient with normal blood pressure, it is possible that they may be incorrectly diagnosed with hypertension *(2)*.

In clinically evaluating ambulatory blood pressures, it is critical to have appropriate and sufficient information about the conditions of measurement in order to differentiate adaptive physiological responses from true cardiovascular pathology. Much of this information is collected from diaries and questionnaires that are filled out at the time of the monitoring. The primary objective of this brief overview is to describe and evaluate the reported relationships between ambulatory blood pressure measurements and the psychological, behavioral, and environmental data collected in diaries and questionnaires during the course of ambulatory monitoring. How behavioral and environmental information can be usefully employed in evaluating ambulatory blood pressure measurements in the diagnosis and treatment of hypertension will also be briefly discussed.

DETERMINING THE CONDITIONS OF AMBULATORY MEASUREMENTS

There are two ways to determine what the environmental conditions are during noninvasive ambulatory blood pressure monitoring. The first is through direct observation. Specifically, a person other than the monitored patient continuously watches and records in a journal the ambient conditions of each individual blood pressure measurement. This approach is necessary when small children or demented elderly subjects are being evaluated *(7)*, but it is really only practical when the patients are institutionalized. A drawback of this method of environmental assessment is that data concerning personal factors such as the patient's physiological or psychological state cannot be collected.

The second method involves having the patient self-report the conditions in a diary. In this scenario, the patient writes down or inputs into a handheld computer the various parameters that are manifest when the blood pressure cuff inflates, including both personal and environmental factors. Several diary formats have been devised for patients to report the circumstances when their pressures are being taken (*see*, for example, refs. *1,3,4,8–11*).

For clinical (and analytic) purposes, the best diaries are those that are simple and straightforward and easy for a patient to complete *(1)*. Every time the monitor takes a pressure, the patient is either writing something down or inputting information into a handheld computer. If too much information is required or the form is overly complex, the information gathered is likely to be spotty, incomplete, or may even affect the measurements themselves, in that completing a complicated diary may itself be a stressor. The most common information collected in the diary includes posture during and place of measurement, activity just prior to measurement, and perhaps mood of the patient. A diary that was successfully used clinically at the Hypertension Center of the Weill College of Medicine of Cornell University is shown in Fig. 1.

Thorough patient instruction is also important in the use of diaries as a means for assessing the conditions of blood pressure measurements because insufficient or superfluous overreporting of the circumstances will affect the ability to properly analyze the blood pressure measurements. Pickering *(1)* has discussed several additional issues with ambulatory blood pressure diary design and use that are relevant to the evaluation of the data collected with them. These include the content and form of the diary, the validity and reliability of self-reported behavior, and the influence of self-reporting behavior on actual behavior. However, if adequate instruction is provided to the patient before the monitoring, the information collected in diaries should reasonably describe the approximate conditions of each ambulatory blood pressure measurement and should be useful in analyzing and interpreting the total data.

Finally, from the standpoint of the data collection, how important is it that the diary entries occur at the exact time of the blood pressure measurement? Might filling in the diary after the fact affect accuracy of reporting? Stone et al. *(12)*, in a study of pain reporting, found that 94% of patients were compliant in writing down pain assessment at the appropriate time when there was a signal to do so. With blood pressure monitoring, the monitor signals 5 s before the measurement; hence it is likely that the patient will record something in his or her diary at the time of measurement. If missing, conditions of interest, such as posture, place of

NAME _____

Location codes
H = Home
W = Work
M = Miscellaneous

Position codes
S = Sitting
U = Upright/standing
R = Reclining

Mood codes
Place a number from 1 (low) to 10 (high) in the appropriate box (skip if mood is neutral)

Time	Location	Position	Mood				Activities
			Happy	Sad	Angry	Anxious	

Fig. 1. A useful ambulatory blood pressure diary for clinical practice.

measurement, and activity, can probably be added at a debriefing when the patient returns the monitor without sacrificing too much accuracy about those conditions at each measurement. However, mood and mood intensity reports will likely be less accurate if filled in later *(12)*.

AMBULATORY BLOOD PRESSURE VARIATION AND PATHOLOGY DETERMINATION

Hypertension (high blood pressure) is defined from an arbitrary cut-off point in the distribution of seated blood pressure measurements

(13,14). Although the definition has expanded to include severity *(14,15)*, its diagnosis is still confirmed from standardized seated blood pressure measurements that persistently exceed the threshold of 140/90 mmHg.

The variation in blood pressure measurements that occurs among patients as they go about their daily activities, even when sampled intermittently, can be viewed as an estimate of the cardiovascular adaptation to environmental challenges that are extant when the measurements are taken *(6)*. In evaluating the pathology in these ambulatory blood pressures, the question that should be asked is whether the magnitude of the measurements is appropriate for the circumstances, not whether or how often they transgress the arbitrary "hypertension Rubicon" (140/90 mmHg).

It is also not entirely appropriate to simply examine the average of all the measurements taken to see if it is excessive. As previously noted, in outpatients allowed to follow their daily routines, the average may be calculated from measurements taken under circumstances that tend to raise pressure; thus, the value on which a hypertension diagnosis would be based may actually be normal for the circumstances and not pathological. Interestingly, despite this fact, it is becoming increasingly clear that the cutoff of 135/85 mmHg is being accepted as the normalcy–pathology dividing line with regard to awake ambulatory blood pressure averages *(15–20)*.

DETERMINING AMBULATORY BLOOD PRESSURE RESPONSES

Over the past 20 yr, many factors that form a part of daily life have been found to affect the diurnal variation of ambulatory blood pressure. Before presenting data on the effects of diary-reported circumstances on ambulatory blood pressure measurements, a brief discussion of methodological issues concerning how the blood pressure measurements are analyzed is needed. In a study sample (or, more generally, a population of subjects), every individual will have a different experience and mix of diary-reported factors (locations, postures, moods, and activities). Thus, in order to analyze these uneven data, certain statistical assumptions must be made *(3,4,21)*. Although nearly every study that has examined diary data for the purpose of estimating the effects of reported conditions has found similar results (remarkably), the exact estimates vary. This variation either occurs as a consequence of differences in the statistical assumptions about the data or, more likely, occurs because of differences in the populations studied *(3)*. The most

problematic and contentious statistical issue in analyzing individual ambulatory blood pressure measurements is accounting for the between-person variance when estimating the effects of within-person parameters such as posture, location, and mood *(4,10,11,22,23)*. Person effects also need to be considered when evaluating the influence of risk factors such as gender and body mass index, which are characteristics of the person, not each individual blood pressure measurement *(4,10,24)*. A protracted detailed discussion of the merits of various statistical approaches is beyond the scope of this brief review, but it should be realized that every approach has its limitations. However, it is probably true that as long as reasonable assumptions concerning the partitioning of daily blood pressure variance are made and not violated, the estimates of the calculated factor effects will be valid.

A final consideration in evaluating the magnitude of the effects of various environmental, ecological, or psychological factors on any given blood pressure measurement is knowing the referent value from which the effect is calculated; that is, when one states that being at work elevates blood pressure by some amount, that amount will depend on the "standard value" with which it is being compared. Values that have been used include the average sleep blood pressure *(25)*, the average 24-h ambulatory pressure of the individual *(22)*, the average blood pressure of the entire population studied *(4,10,11)*, and the average seated blood pressure while at home *(24)*. Values presented in this discussion will be relative to the individual's average 24-h ambulatory pressure and will be calculated using the method of James et al. *(22)*, assuming a daily standard deviation of 10.

DIARY FACTORS ASSOCIATED WITH AMBULATORY BLOOD PRESSURE VARIATION

Virtually all of the studies that have examined the effects of diary-reported factors on blood pressure have been conducted on sample groups from Western societies *(3)*. Most of the investigations that have examined the effects of work on ambulatory blood pressures (i.e., refs. *8,23,26–31*) found that the average pressure at the place of employment is higher than the average pressure in all other daily venues. The work-related elevation in blood pressure is also independent of time of day, as the average pressure at the place of employment is elevated even in night-shift workers *(32–35)*.

Reported posture has also been found to have a substantial effect on ambulatory blood pressures. Standing is associated with the highest

Table 1
Average[a] Effects of Activity on Ambulatory Blood Pressures[b]

Activity	*Systolic*	*Diastolic*
Talking	5.1	5.9
Writing	3.3	6.7
Physical activity	8.6	7.4
Eating	6.3	7.0
Relaxing	–2.0	–3.6
Dressing	7.5	9.7
Traveling	6.5	5.5

[a]Assumes a 24-h standard deviation of 10.
[b]mmHg from 24-h mean.
Modified from ref. *37*.

pressures and reclining (while awake) with the lowest pressure during the day *(4,22,24,25,28)*. Postural effects, however, co-vary with activity, because many activities occur in a single posture. Research examining the effects of reported activity on ambulatory pressure show that physical activities such as doing household chores tend to elevate pressures the most, whereas activities such as reading or writing, which require mental effort, or other activities such as eating, watching TV, or talking have less effect *(8,23,36–38)*. Table 1 presents estimates of the effects of several activities on blood pressure levels.

Personality may further interact with activity in affecting blood pressure such that individuals whose behavior is characterized as Type A *(39)* (manifested as impatience, chronic time urgency, enhanced competitiveness, aggressive drive, and an inclination toward hostility) may 0uals during activities such as driving a car, talking, walking, desk work, and attending business meetings. Finally, in one study, physical activity was estimated from motion-sensing monitors instead of diary reports *(41)*. The results showed that constant change in motion during the day accounted for about one-third of the variance among intermittently sampled ambulatory pressure measurements *(41)*. More recent studies confirm this finding *(42)*.

Blood pressure during the day is also influenced by the emotional state, with most emotions elevating both systolic and diastolic pressures to some extent *(4,22,25,43–49)*. Happiness, however, may elevate pressure less than anger and anxiety *(4,22)*. An important finding reported by Schwartz et al. *(4)* was the relative rarity of experienced anger. In their study, diary reports of anger during an ambulatory monitoring,

when pressures were taken every 15 min while awake, occurred less than 1% of the time. Because this emotional state has been thought to play an important role in the development of coronary disease and hypertension, the fact that it is rarely experienced suggests that it may contribute to these conditions more through its effect on the variability of blood pressure rather than on elevating the overall average daily pressure *(68)*. Finally, the location where emotions are experienced may further modify how high blood pressures rise *(25,37,45,50)*. For example, anxiety may have a greater effect when it occurs at work or some place other than home *(22)*.

The influence of location (i.e., work, home, sleep), posture, activity, and emotional state has been found to differ by gender *(22)*, by month of the year (winter or summer months) *(51)*, and, among men, by occupational classification *(37)*. In a study *(50)* comparing the effects of posture (standing, sitting, reclining), location (work, home, elsewhere), and emotional state (happy, angry, anxious) on the ambulatory blood pressures of 137 hypertensive men and 67 hypertensive women, the cumulative effects of location, posture, and reported emotions on the blood pressures of the women were found to be greater than those of the men. There were also gender differences in the way the emotions and situations affected blood pressure. Estimates of these effects are shown in Table 2.

The effects of posture, location, and emotional state (classified in the same way as in the previous gender study) were also found to differ among hypertensive patients measured in winter months (November–March) ($N = 101$) and summer months (May–September) ($N = 56$) in New York City *(51)*. Specifically, several effects were found to be more accentuated in the winter months. Estimates of these effects are shown in Table 3.

Emotional state may also affect the blood pressures of men in professional occupations (i.e., lawyers, physicians, scientists) differently than men employed in nonprofessional occupations (technicians and union laborers) *(37)*. Specifically, happiness and anxiety were found to have differing effects by occupational classification on blood pressures measured in locations such as bars and restaurants such that professional men had higher pressures when they were anxious, whereas nonprofessional men had higher pressures when they were happy. Estimates of these effects are shown in Table 4.

Finally, increased salt in the diet has also been found to increase the mean daily ambulatory blood pressure *(52–54)*, an effect that may be more accentuated in men than women *(54,55)*. However, the amount of

Table 2
Comparisons of the Average[a] Effects of Posture, Situation of Measurement, and Emotion on Systolic and Diastolic Pressure Between Men and Women[b]

		Women			*Men*		
Posture	*Situation*	*Happiness*	*Anger*	*Anxiety*	*Happiness*	*Anger*	*Anxiety*
Sitting work	Systolic	4.1	3.3	5.8	2.9	10.9	6.6
	Diastolic	5.2	2.1	7.1	5.0	13.2	8.7
Home	Systolic	0.3	6.4	5.2	0.8	5.0	1.4
	Diastolic	2.3	5.5	5.5	–0.1	8.4	3.0
Elsewhere	Systolic	5.2	3.6	6.6	3.6	10.8	6.7
	Diastolic	2.5	0.8	7.4	3.8	10.6	6.4
Standing work	Systolic	11.7	18.2	16.6	3.4	10.6	7.1
	Diastolic	5.7	12.7	13.8	2.4	6.7	10.3
Home	Systolic	6.2	5.3	7.0	4.2	4.3	3.9
	Diastolic	5.7	9.3	7.2	7.7	9.8	5.3
Elsewhere	Systolic	11.9	9.2	7.9	5.3	6.9	12.9
	Diastolic	5.1	9.8	8.3	3.1	16.6	9.5

[a]Assumes a 24-h standard deviation of 10.
[b]mmHg from 24-h mean.
Modified from ref. *50*.

dietary salt may also affect how blood pressure varies during the day with activity. In a study comparing ambulatory blood pressure variation in 19 hypertensive patients who consumed a low-salt (18 meq/day) and high-salt (327 meq/day) diet for a month each, the daily pressure variation associated with changing diary activities after a month on the low-salt diet tended to be higher than the variation after a month on the high-salt diet. Estimates of the posture, location, and activity effects on blood pressure measured on each diet are presented in Table 5 *(56)*.

In examining the estimated blood pressure changes associated with diary data in Tables 1–5, it is obvious that pressure is elevated (sometimes substantially) under specific circumstances during an ambulatory monitoring. A closer examination of the effects of posture (activity), location, and emotional state on blood pressure show that the influence of these factors is more or less additive. Thus, being angry while standing at work will increase pressure substantially more than either the experience of being angry or standing singularly. The effects of these factors are, to some extent, more accentuated (larger) in men than

Table 3
Average[a] Effects of Emotions, Posture, and Situation of Measurement on Systolic and Diastolic Pressure in Winter and Summer Months[b]

	Winter		*Summer*	
	Systolic pressure	*Diastolic pressure*	*Systolic pressure*	*Diastolic pressure*
Emotions				
Happiness	3.4	4.4	2.3	2.3
Anger	8.4	9.0	5.1	7.0
Anxiety	6.9	7.8	3.9	5.8
Posture				
Sitting	4.2	5.6	2.3	3.7
Standing	7.2	7.2	6.0	5.6
Situation				
Work	7.8	8.7	3.5	5.6
Home	3.3	4.8	1.2	3.1
Elsewhere	6.8	6.1	8.0	6.0

[a]Assumes a 24-h standard deviation of 10.
[b]mmHg from 24-h mean.
Modified from ref. *51*.

women, more so when measurements are taken in winter (cold) months than in summer (warm) months, and also possibly elevated when the patient is on a low-salt diet. Indicators of social class such as occupation may also affect the magnitude of effects, particularly emotional states. Thus, factors such as gender, time of year, diet, and social class need to be considered when evaluating ambulatory blood pressure measurements for pathology.

JOB STRAIN AND AMBULATORY BLOOD PRESSURE

Studies of employment-related stress and blood pressure have mostly focused on the concept of "job strain." These investigations have relied on the Job Content Survey, from which a measure of job strain has been developed *(57)*. The presence of job strain is determined from elevated scores on two orthogonal subscales of the questionnaire: "psychological job demands," which measures the psychological workload of the job, and "decision latitude," which describes the degree of control that subjects perceive they have over their jobs *(58,59)*. Schnall et al. *(60)* estimated that in men, current job strain tended to elevate

Table 4
Average[a] Effects of Place of Measurement and Emotional State on Systolic and Diastolic Pressures in Two Occupational Groups[b]

Place	*Emotion*	*Professional*	*Nonprofessional*
Systolic pressure			
Work	Happy	2.0	2.9
	Angry	11.2	15.4
	Anxious	7.1	6.5
Home	Happy	–1.0	0.4
	Angry	5.7	2.4
	Anxious	1.6	–0.7
Elsewhere	Happy	0.6	10.5
	Angry	11.5[c]	
	Anxious	10.9	6.8
Diastolic pressure			
Work	Happy	3.1	5.4
	Angry	13.7	7.0
	Anxious	8.0	10.9
Home	Happy	–4.8	2.8
	Angry	7.4	9.8
	Anxious	1.8	–1.3
Elsewhere	Happy	–0.1	4.8
	Angry	10.1	–5.7
	Anxious	9.4	4.9

[a]Assumes a 24-h standard deviation of 10.
[b]mmHg from 24-h mean.
[c]Not estimable.
Modified from ref. *37*.

work systolic pressure by 7 mmHg and diastolic pressure by 3 mmHg. More recent work by Landisbergis and colleagues *(61)* suggests that longer term, the systolic blood pressure of men employed for 25 or more years who were exposed to job strain for at least half of their work life was about 5 mmHg higher at work and 8 mmHg higher at home than that of men with no past exposure to job strain. In contrast to men, the effects of job strain in women appear to be variable and are apparently affected by both ethnicity and socioeconomic factors *(62)*.

It should be noted that some investigations show no effect of job strain on ambulatory blood pressure *(63)*. It has been suggested that studies may reach different results because researchers use different formulations in the index of job strain *(63)*. The variation in results may also be affected by other independent factors that can influence whether

Table 5
Average[a] Effects of Activities, Postures, and Situations on Systolic and Diastolic Pressures of Subjects on High- and Low-Sodium Diets[b]

	High sodium		*Low sodium*	
	Systolic pressure	*Diastolic pressure*	*Systolic pressure*	*Diastolic pressure*
Activity				
Telephone/talking	6.7	3.3	2.6	5.0
Writing	5.6	4.6	4.5	8.5
Walking	6.2	3.3	7.1	4.8
Reading	0.8	0.4	1.8	1.3
Eating	3.7	5.9	1.1	4.1
Relaxing	2.1	0.7	–0.2	–2.2
TV	0.2	–2.1	–2.0	–4.2
Transportation	7.1	5.3	5.8	9.4
Distress	7.1	8.6	17.5	12.2
Dressing/washing	2.2	6.4	0.6	–0.5
Posture				
Standing	6.4	4.9	5.5	3.9
Sitting	3.5	1.7	2.4	4.9
Reclining	–1.5	–1.2	–1.2	–4.5
Situation				
Work	6.2	4.6	5.1	8.1
Home	1.4	0.0	–0.4	–0.3
Elsewhere	7.3	5.2	6.3	3.6

[a]Assumes a 24-h standard deviation of 10.
[b]mmHg from 24-h mean.
Modified from ref. *56*.

or how job strain is perceived. A comparison of two studies in which job strain was indexed similarly illustrates this possibility. In the first, Van Egeren *(40)* studied 37 employees at Michigan State University (20 women and 17 men) and found that the women with high job strain had higher systolic blood pressure while at work than those with low job strain. The second study, conducted in North Carolina, included 34 white and 30 black women who worked for several different employers *(29)*. There were no effects of job strain on the blood pressures of the women.

Why were the results of these two studies at variance? One possibility is that the number of subjects in each study was small and nonrandomly selected; thus, the differences could be the result of sampling error. However, it is also possible that specific work-site factors were

involved; that is, there is a fundamental difference in the nature of the work sites sampled in the two studies. The Michigan study consisted of women from the same workplace, whereas the North Carolina study includes women from a cross-section of occupations in several work settings. As Schlussel et al. *(64)* have shown, the actual workplace has a marked effect on work blood pressures. Specifically, they showed that people with the same occupational title (job) but who work in different companies had significantly different blood pressures. Because all the women in the Michigan study were from the same work site, the place of employment had an equal effect on all the study subjects and, thus, was unlikely to affect the job strain effect. However, the North Carolina study sample was selected from several workplaces. Therefore, it is possible that differing environments in the different workplaces could dilute the job strain effects examined in the overall study. Finally, a third possibility is that the results vary because of local cultural, climatic, and demographic differences between the states of Michigan and North Carolina *(59)*. These factors may affect how people view the stressfulness of their jobs. This possibility is supported by the fact that many intrapopulational studies show that climate and subtle cultural variation among population subgroups are associated with differences in blood pressure (e.g., refs. *65–67*).

Finally, in examining the impact of job strain and other psychosocial or psychological constructs on blood pressures in differing venues, it is difficult to know whether they directly affect blood pressure or they reflect the increasing effects of emotional state, posture, activity, and their interactions; that is, it is possible that the perception of job experience is dictated by how often intense emotional arousal or long periods of standing or doing errands occur. This issue is an important one from a clinical standpoint in that the clinician needs to know whether diary data alone are sufficient to interpret the blood pressure variation properly during the day or whether a battery of psychometric questionnaires that measure complex behavioral constructs are needed as well. Anecdotally, one would expect that for most patients, the diary data will be sufficient.

HOME STRESS AND AMBULATORY BLOOD PRESSURE

In further studies of women employed in wage jobs outside the home, stress in the home environment has been found to influence blood pressure as much or more during the day than stress experienced at work *(30,68–72)*. Specifically, if the home environment experience

is as stressful or more stressful than the work environment, ambulatory blood pressures measured at home may be as high or higher than those measured at work *(30,70–73)*. The home stress effects found among women have been related to factors associated with the family, such as marital status or the number of children (*30*,*69,72,73*). In fact, it was estimated that women with children experience a 3-mmHg increase in both systolic and diastolic pressures at home for each child they have. Thus, for women, it may be important to know whether they have dependent children at home, as they could tend to experience pressure increase during a time when one might clinically expect it to fall. However, it is probably also true that this information will likely be reflected in diary-reported data as well.

ETHNICITY AND BLOOD PRESSURE VARIATION

The literature examining ethnicity and blood pressure variation during the day is sparse, meaning that few studies have examined whether diary-reported conditions influence blood pressure differently in different ethnic groups. Gerber et al. *(24)* evaluated whether ethnic groups (white, African American, Hispanic) were different with regard to the effects of posture and location on blood pressure and found no differences. More recent studies by Kamarck and colleagues *(11,49)* have also found that there were no differences in diurnal blood variation associated with any diary reported factors between whites and African Americans. However, in a study examining factors affecting the daily variation of blood pressure in Filipino-American and white women employed as nurses in Hawaii, Brown et al. *(74)* found that the Filipino-American women reported negative moods more frequently, had a greater proportion of readings taken while standing at work, and had different blood pressure responses than white women to specific activities, such as household chores. They suggested that blood pressure variation in daily life may be significantly influenced by the cultural background of the individual. Finally, a recent study of Nigerians found that there was an association between nocturnal dipping in blood pressure and the magnitude of daily variation associated with posture, location, activity, and mood *(75)*.

From a clinical standpoint, the question is: Should the ethnic background of the patient be considered as a factor when evaluating how diary-reported data influence daily blood pressures? The current evidence is too sparse to make a definitive judgment. Because there are so few

studies, this inquiry cannot be adequately answered. Further research is needed to make this assessment.

WHAT DOES IT ALL MEAN?

Realistically, when evaluating ambulatory blood pressure measurements for the purpose of treatment, the individual values of patients with low averages over 24 h (i.e., less than 120/80 mmHg) do not need to be scrutinized because whatever they are doing is not excessively raising their pressure. Likewise, patients whose average ambulatory pressures are very high (i.e., greater than 170/110 mmHg) do not require a close evaluation of every pressure either, in that even after adjusting their pressures for their activities and situations, their averages would still probably exceed 150/100 mmHg. The evaluation of what people are doing is most useful in the "borderline" patients. As previously reported *(2)*, a patient with an ambulatory average of 145/92 mmHg may be perfectly normal if the mix and duration of behaviors were such that they tended to raise pressure. The same values may also indicate the need for treatment if the reported behaviors were ones that had a minimal effect on pressure or tended to lower it.

In summary, because behavior can strongly influence blood pressure, it probably needs to be considered when assessing ambulatory blood pressures for the determination of treatment for hypertension. Thus, clinicians should examine the diary data that are collected during an ambulatory monitoring and compare it to the measurements collected, particularly among patients whose pressures are "borderline." Ignoring behavior in the evaluation of ambulatory blood pressures might be considered as clinically incorrect as confirming a diagnosis of hypertension based on a single blood pressure measurement of 140/90 mmHg at a single office visit.

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3 Electronic Activity Recording in Cardiovascular Disease

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CONTENTS

INTRODUCTION

Electronic activity recording is a noninvasive technique to monitor human movements without direct input from the subject or the need for an observer. One of its main advantages is the ability to monitor persons for long periods of time and in the free-living state. Actigraphy, the main form of activity monitoring, is in commercial use. Actigraphs are small technologically mature devices that perform well in everyday use. Actigraphy is extensively used in psychology and sleep research

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(1) and is increasingly used in cardiovascular disease research. Although there exist guidelines for its use in sleep research *(2–4)*, there are no standards for its use in cardiovascular-related diseases. The main uses for actigraphy at this time are to estimate the duration and quality of sleep, to determine the extent of daytime activity, and to study circadian cycles of humans.

EQUIPMENT, MODES OF OPERATION, AND LIMITATIONS

Several types of actigraphs are manufactured worldwide. All have a built-in sensor that generates a tiny voltage after a directional movement exceeding a certain threshold. This voltage is then sent through an analog circuit, filtered, amplified, and compared to a reference. This comparison is performed and kept in temporary memory for the duration of time called an epoch (e.g., 1 min) set by the user. Many devices have additional features including an event marker that can be activated to define a particular event such as arising out of bed or removal or reattachment of the actigraph. Most recent actigraphs have incorporated ambient light detection and/or temperature monitoring.

The units of activity are arbitrary and instrument specific. They reflect our limited understanding of the optimal methods to define and measure complex human motion *(1)*. Because the units of activity vary from manufacturer to manufacturer, it is necessary for researchers to be familiar with the way each unit works and the differing modes of data collection. Commercial devices can collect data for up to 30 d, and the user can modify the instruments' sensitivity and sampling frequency. In general, it is best to stick to one type of device and to be aware of its operational characteristics for varying types of studies.

Significant limitations exist with current actigraph devices. Data generated by actigraphic devices from different manufacturers are not interchangeable or readily comparable. This is illustrated in a study *(5)* of two widely activity recorders in which important differences in performance and sensitivity were reported. The Mini-Motionlogger Actigraph (Model 20000, Ambulatory Monitoring, Inc.) and the Activity Monitor (Model Z80-32K V1, Gaehwiler Electronics) were compared in five subjects after a total of eight separate recordings of 7–92 h. The authors also compared two devices from the same manufacturer. The devices were worn one above the other and the positions reversed in the middle of the recording. Within-actigraph-type comparisons indicated excellent

correlations ($r > 0.98$). When the two types of recorders were compared, interesting similarities and differences were discovered. Both actigraphs detected circadian activity patterns of day and night adequately, as inferred from the activity recordings. The Gaehwiler actigraph, however, frequently recorded zeros when the Mini-Motionlogger recorded movement, indicating a lower sensitivity of the former instrument *(5)*. However, the Motionlogger also had limited sensitivity during certain activities as judged by relatively frequent zero readings. Therefore, the two instruments were comparable to globally assess circadian activity but were not comparable when the objective was low-level activity or sleep data analysis. In another study *(6)*, 20 healthy adults were studied with the Actiwatch L (Mini-Mitter Co., Inc., Bend, OR) and the Basic Mini-Motionlogger for two nights. The Motionlogger reported more total sleep time, less wake after sleep onset, and greater sleep efficiency than did the Actiwatch (set at high sensitivity). When sensitivity was set to medium level on the Actiwatch, the results were comparable to the Motionlogger.

There are also important differences in the data generated when different modes of operation are used in the same actigraph. A direct comparison of the Zero Crossing Mode (ZCM) and the Time after Threshold (TAT) modes of the Motionlogger was performed by Leidy in 20 healthy volunteers of mean age 36 yr *(7)*. The volunteers wore a dual-mode actigraph twice on the nondominant wrist and performed specified common tasks representing three graded levels of activity: light (1–2 metabolic equivalents, or METs), moderate (3–4 METs), and heavy (4–6 METs). These three levels of activity were designed to include tasks commonly performed by subjects in their home environment. Both modes successfully distinguished between light and moderate and light and heavy activities. However, neither mode was able to distinguish between moderate and heavy level activities, indicating the possibility of a saturation effect of moderate exercise on the instruments scoring of activity. Reproducibility correlations across activity levels were 0.80 and 0.66 for ZCM and TAT modes, respectively. Interestingly, the authors also found that average movement duration, calculated as the TAT divided by the ZCM, was less useful in distinguishing the activity level and was only able to distinguish light and heavy activity levels. It is likely that each mode of data collection may be particularly suited to certain types of activity monitoring, and the two modes should be further studied in various types of activity.

An additional limitation of current actigraph use is the lack of a consensus regarding the optimal body site for attachment during research studies *(2)*. It is not difficult to conceive of certain movements during which the upper limbs or the trunk are moved more than the lower limbs and vice versa. Nevertheless, most research studies have attached the actigraph to the nondominant or dominant wrist. In cardiovascular disease research, where ambulatory blood pressure or heart rate monitoring equipment is already attached to the patient's nondominant arm, logistical issues arise about the preferable attachment site. In our experience, most patients can comfortably wear the actigraphs on either wrist without problems, and both sites provide similar data. In studies of the relationship between physical activity and peripheral arterial disease, actigraphs have been placed on the hip *(8)*. However, consistent site placement is needed in methodological studies to assess the performance of these devices in clinical settings.

The relative advantages of uniaxial or multiaxial accelerometers have not been well studied. Uniaxil sensors are sensitive to motion in the vertical plane and may be limited in examining certain types of motion. The multiaxial sensors are more sensitive to smaller multidirectional movements and hence interference by vibration and tremor. Most studies today use multiaxial sensors to assess physical motion. A typical actigraphic tracing is shown in Fig. 1.

RELATIONSHIP BETWEEN PHYSICAL ACTIVITY, BLOOD PRESSURE, AND HEART RATE

Before we discuss how electronic activity monitoring is used in understanding the effects of activity on blood pressure, we will briefly review normal blood pressure variation. The normal blood pressure and heart rate pattern is one of relatively higher blood pressure and blood pressure variation during the day, with lower readings during sleep and then a sharp rise in the early morning on awakening (Fig. 2). The decline in blood pressure and heart rate during sleep has been ascribed to both an endogenous rhythm and the relative effects of physical inactivity during sleep. Irrespective of the cause, there are several pathophysiological implications of blood pressure variability. A small but significant group of subjects does not have the expected decline of blood pressure during sleep. These so-called "nondipper" hypertensive patients are generally older, and have a higher prevalence of secondary hypertension. This "nondipping" pattern may not be an academic curiosity because it has been shown to be a contributing factor in

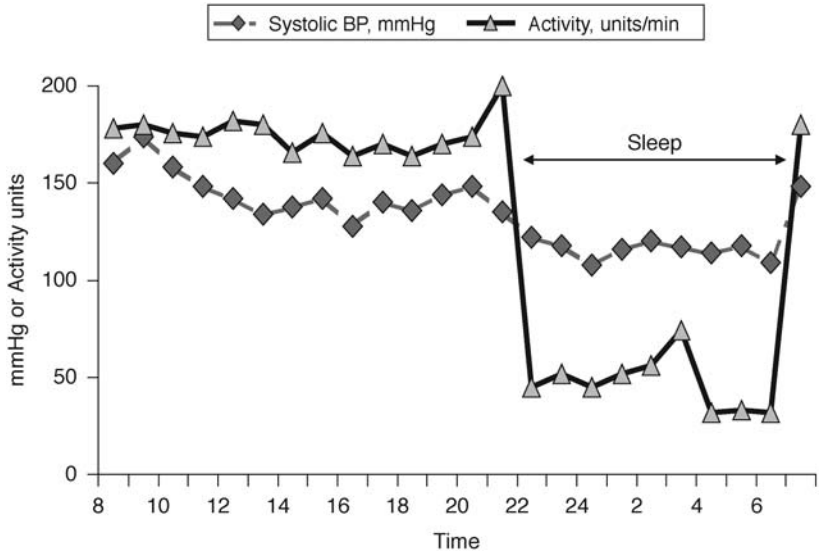

Fig. 1. Typical 2-d actigraphic tracing showing daytime high activity and reduced nighttime activity. The actigraph was worn on the dominant wrist, and epochs of 1 min were used. Scored sleep is shown in the shaded area. Event markers are shown with small triangles.

increasing left ventricular mass *(9)*, ischemic cerebro-vascular damage *(10)*, and cardiovascular events *(11)*.

One of the first areas in cardiovascular medicine in which electronic activity monitoring has been used is the study of the relationship between daily physical activity, blood pressure, and heart rate. There is undoubtedly some relationship between short-term physical activity and blood pressure variability, as illustrated in Fig. 3. Van Egeren *(12)* pioneered the study of actigraphic wrist motion and ambulatory blood pressure by studying 82 healthy normotensive employed subjects. Most of his study subjects were found to have a moderate correlation (averaged $r = 0.50$) of blood pressure with activity (counts taken for 10 min before each blood pressure reading). This positive linear relationship of physical activity to blood pressure was not significantly influenced by any other clinical factors. Similarly, Gretler et al. *(13)* performed a study with 10 healthy young (mean age, 32 yr) normotensive volunteers. Interestingly, in this study each subject wore four activity monitors—on wrists, waist, and left ankle. The authors then calculated the activity level 30 s and 2, 5, 10, 15, and 30 min prior to each valid blood pressure

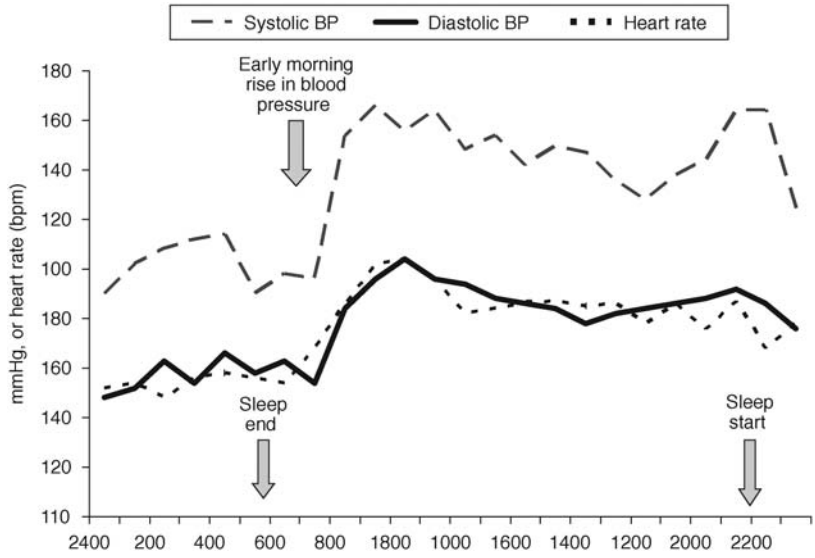

Fig. 2. Graph illustrating the concordance between activity data and blood pressure data. As nocturnal activity decreases, so does nighttime blood pressure.

reading and correlated it with blood pressure. Activity data correlated significantly with both blood pressure and heart rate in every subject, although there was a wide range of correlation coefficients. The authors also determined that the dominant wrist site provided the best correlation with activity measured 2–10 min just prior to a reading. Actigraphic physical activity accounted for 18–69% of the systolic blood pressure variability, and it was suggested that ambulatory blood pressure data should be interpreted in association with concomitant physical activity measures. Stewart et al. *(14)* reported similar findings in a group of 30 middle-aged patients (mean age 52 yr) and were able to ascribe 20% of systolic blood pressure variation to actigraphically measured activity. Our own work *(15)* in untreated essential hypertensive subjects reveals that there is considerable interperson variability in the effects of activity on ambulatory blood pressure and heart rate. We studied 39 untreated hypertensive subjects of average age 57 yr using actigraphy and ambulatory blood pressure monitoring. Our analyses included both average activity for 5 min and peak activity during that time prior to each valid blood pressure and heart rate reading. We found substantial variability in the correlation of 5-min activity with blood pressure and heart rate. Indeed, in some patients there was no correlation. We also found a trend

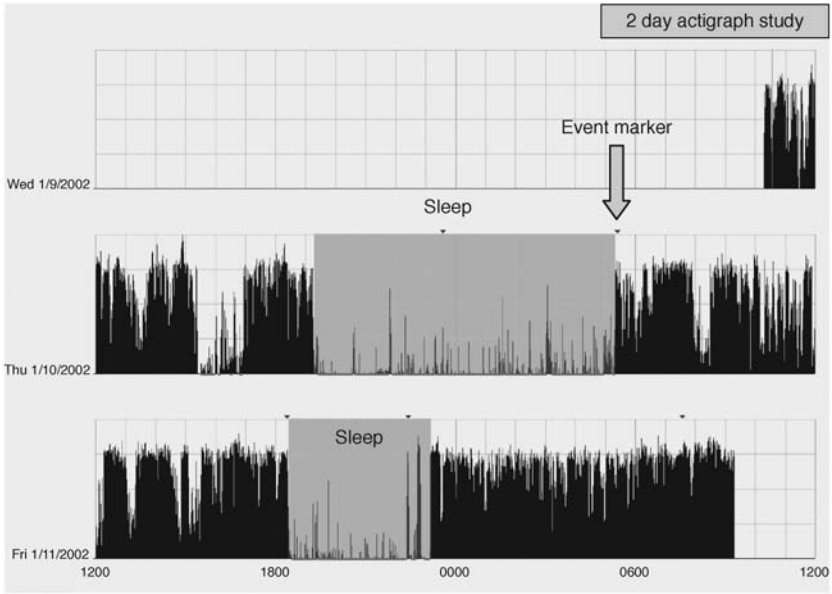

Fig. 3. Graph showing the typical hourly blood pressure and heart rate during a 24-h period. The fairly low-sleep blood pressure is followed by an abrupt rise in blood pressure and heart rate upon awakening.

toward the strength of the positive correlation being higher in younger subjects. Furthermore, the best correlate of average and peak 5-min activity was the heart rate–blood pressure product.

Others have found weak or only moderate relationships between activity and ambulatory blood pressure. For example, Shapiro et al. *(16)* found little or no relationship between activity and ambulatory blood pressure and heart rate in 119 older healthy subjects (mean age 67 yr, 68% were retired) *(16)*. They concluded that activity monitoring was not likely to improve the ambulatory blood pressure data reproducibility. Certainly in individuals, a modest relationship has generally been observed.

It seems that considerable disagreement remains about whether ambulatory blood pressure data need to be adjusted for activity levels. Additional work in hypertensive subjects is needed to study the effects of average physical activity on blood pressure and heart rate.

Another important area of research is whether activity during the daytime and/or nighttime influences the circadian blood pressure changes. Kario et al. *(17)* studied 160 adults with both ambulatory blood pressure

monitoring and actigraphy. They found that those who had a nondipping blood pressure profile had higher sleep activity measured actigraphically. This finding was extended by Leary et al. *(18)*, who showed that both daytime and nighttime activity were independently predictive of the nocturnal dip in blood pressure. Mansoor et al. *(19)*, in a group of patients not on pharmacological treatment for hypertension, demonstrated that nocturnal activity was higher in those with a nondipping blood pressure profile. Contradictory findings were reported by Hermida et al. *(20)*. In their study of 306 hypertensive patients, some of whom were medicated, no discernible differences were seen in nocturnal physical activity between dippers and nondippers. In summary, most studies but not all have found that daytime and nighttime activity may influence the circadian blood pressure profile.

These findings are consistent with the reports that a relatively flat blood pressure profile is seen if patients are kept in bed or hospitalized, indicating that a major determinant of blood pressure and the circadian profile is to the result of variations in daily physical activity *(21)*.

ACTIGRAPHY, SLEEP, AND AWAKENING

Actigraphy can also play a role in defining sleep and wake times as well as examine the effects of activity early morning blood pressure and heart rate.

Systematic study *(22,23)* has revealed that there is a definite excess of cardiovascular events in the early to mid-morning period—the time of the largest increase in blood pressure and heart rate. Several large studies have shown that acute myocardial infarction, sudden death, arrhythmias, and stroke (both ischemic and hemorrhagic) all have excessive rates in the morning period *(22–24)*. These findings have led to the hypothesis that both hemodynamic (sharp rise in blood pressure and heart rate) and other changes in blood hemostatic and neurohumoral mechanisms may be responsible for these excess events. Researchers are, therefore, very interested in understanding the factors responsible for the sleep blood pressure decline and the factors contributing to the excess cardiovascular events in the early morning.

Electronic activity monitoring, by its ability to monitor activity and the sleep–wake cycle continuously, complements chronotherapeutics research. Actigraphy has been used to identify sleep and awake periods, the time of awakening, and sleep quality accurately. Automated scoring of sleep quantity and quality as well as the presence of a circadian character to sleep is

possible from the actigraphic data. Such algorithms have been validated prospectively against polysomnography *(25,26)*. It should be noted, however, that most validation studies have been performed on relatively healthy cohorts and not persons with sleep disorders. The method correctly distinguished sleep from wakefulness with more than 88% accuracy. However, actigraphy tends to overestimate sleep time in general, and other parameters vary depending on the specific algorithm used to define sleep *(27)*. Furthermore, actigraphy cannot provide any information on sleep stages such as can be obtained from polysomnography.

A widespread application of actigraphy appears to be in the noninvasive determination of sleep times during ambulatory blood pressure monitoring. It is generally accepted that daytime or awake averages should be separated from nighttime or sleep periods for the calculation of average blood pressure and blood pressure loads. Traditionally, several different methods of defining these two periods have been used; the more common one divides the 24-h period using a fixed arbitrary time for sleep (e.g., 10 PM to 6 AM) or uses a patient-kept diary. Although the difference in blood pressure when calculated by these two methods is small, moderate differences have been observed in some subjects especially during sleep *(28)*. Furthermore, the definition of the sleep-associated decline in blood pressure implies accurate sleep time recognition. Several groups of researchers have reported that the diary method of defining sleep is superior to the arbitrary fixed-time methods in which an arbitrary sleep time is imposed on all subjects *(29–33)*. It appears that based on current data, the best methods for dividing ambulatory blood pressure data for research purposes is by the use of diary times and/or actigraphically determined sleep times.

Several problems remain in the use of actigraphy as a tool to identify sleep times during ambulatory blood pressure monitoring. No consensus has been reached on the best actigraphic criteria or scoring algorithm to identify sleep onset or awakening. Patients will provide a diary, including time on going to bed and arising time in the morning, as well as any times the actigraph was removed. For the time in bed, sleep is scored and sleep parameters calculated. Several different methods could theoretically be used, including built-in sleep algorithms or arbitrary manual scoring criteria. Furthermore, it is not clear what should be done about blood pressure readings taken during periods when the patient is in bed but movement is detected by the actigraph.

Actigraphy may also be useful to define better for researchers the early morning period after awakening *(34)*. Recent studies *(35)* have examined the hemodynamic and neurohormonal changes of the early morning

period, and a novel form of antihypertensive drug therapy has been developed targeting this time period *(35)*. Therefore, accurate determination of wake-up time is essential. Khoury *(35)*, by monitoring blood pressure and actual wake-up times, found that the act of physically getting out of bed was the main reason for the steep rise in blood pressure and heart rate.

ACTIGRAPHY IN ASSESSING SLEEP QUALITY AND OVERALL PHYSICAL ACTIVITY

Sleep quality has been assessed in a number of studies related to cardiac disease. For example, the effects of coronary artery bypass surgery on actigraphically determined sleep, both in the short term (1 wk) and the long term (6 mo), have been reported *(36,37)*. The authors described significant sleep fragmentation in the first week after coronary artery bypass grafting, which improved over long-term follow-up. Furthermore, an increase in overall physical activity and restoration of a circadian sleep rhythm was seen over the study period. Actigraphy has also been used to examine overall physical activity levels in women 2 yr postcardiac transplant *(38)*. A low level of physical activity was seen overall, especially in older women. This type of information regarding sleep and physical activity may allow intelligent therapeutic intervention to improve sleep hygiene or to objectively monitor activity levels in the postoperative and rehabilitative phases of recovery after cardiac surgery.

VALIDATION OF AMBULATORY BLOOD PRESSURE MONITORS

Traditionally, validation of ambulatory blood pressure monitors is done according to one of several national and international protocols *(39,40)*. It has been reported that physical activity increases errors during ambulatory blood pressure monitoring *(41)*. Therefore, if very sedentary individuals are included in the validation protocol, real-life performance of the monitor is not being tested. In one validation study of an ambulatory blood pressure monitor *(42)*, a significantly higher reading rejection rate was noted in the highest tertile of physical activity compared to the lowest tertile of activity. Clinically the groups were similar, and no other clinical factor could explain the differences seen. The authors suggested that electronic activity monitoring be incorporated into validation protocols of ambulatory blood pressure monitoring equipment to ensure that subjects participating in validation of monitors maintain an average level of physical activity.

ACTIGRAPHY AND SLEEP APNEA SYNDROME

An important opportunity for actigraphy is its possible use in the diagnosis and monitoring of obstructive sleep apnea. Sleep apnea is commonly found in association with hypertension and coronary artery disease *(43)*. It has also been observed that treatment of sleep apnea can improve blood pressure levels *(44)*. It is possible that the frequent waking episodes resulting from hypoxemia may be detectable by actigraphy, and the technique may be incorporated into a simple screening tool for the disorder. Aubert-Tulkens et al. *(45)* tried to determine if any actigraphically determined sleep indices could distinguish sleep apnea patients. They compared a movement index (a percentage of time with movement divided by total sleep time) and fragmentation index (ratio of the number of phases of 1-min immobility to the total number of immobility phases of all duration expressed as a percentage) between 18 subjects with sleep apnea and 22 control subjects. Sleep apnea was diagnosed in the study subjects with polysomnography. Half of these subjects were hypertensive. The sleep apnea patients had significantly higher movement index and fragmentation index than controls. Similarly, Sadeh et al. *(46)*, using activity measures, reported that sleep apnea patients were distinguishable from controls. However, Middelkoop et al. *(47)* did not confirm these data in a study of 116 community-based subjects suspected of sleep apnea (snoring and daytime sleepiness). Using an ambulatory monitor of respiration (oronasal flow thermistry) and an activity wrist recorder, they evaluated the use of actigraphic activity indices during sleep to determine the presence of sleep apnea syndrome. More recently, researchers have combined actigraphy with oxygen saturations, chest wall sensors, arterial tonometry, and/or airflow sensors to try to establish simpler methods to diagnose sleep apnea. Such an approach appears to have great promise. Pittman et al. *(48)* studied 30 patients with obstructive sleep apnea using actigraphy, arterial tonometry, and pulse oximetry as well as standard polysomnography. Arterial tonometry is said to detect airway obstruction by detecting vasoconstriction in the finger. They reported in this population a good agreement with in-house polysomnography. Other researchers have reported similar results *(49)*. It is likely that actigraphy in combination with flow sensors and oxygen saturation may provide a useful way to screen patients for sleep apnea. Nevertheless, the clinical standard for the diagnosis of obstructive sleep apnea remains polysomnography in the sleep laboratory.

CONCLUSION

Actigraphy is a widely used tool for the study of overall physical activity, and sleep assessment. Its main attraction is its nonintrusiveness and its ability to measure activity and sleep over prolonged periods of time. However, much work is needed in standardization of equipment, sites of attachment, criteria, and consistency of sleep determination. Examples of current uses in cardiovascular research show that it is used either to assess sleep quantity and quality or in the assessment of overall physical activity. There will undoubtedly be more use in the future of actigraphy in the diagnosis and treatment of a variety of cardiovascular disorders.

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4 Ambulatory Monitoring of Blood Pressure

Devices, Analysis, and Clinical Utility

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CONTENTS

INTRODUCTION

Ambulatory blood pressure monitoring (ABPM) has been available for more than 40 yr, but its use has been primarily restricted to research trials. Ambulatory blood pressure (ABP) monitors are becoming increasingly popular in clinical medicine. The numerous benefits include the avoidance of potential blood pressure measurement errors such as observer bias and terminal digit preference and provision of more comprehensive information on blood pressure behavior than is possible with office or home blood pressure measurement *(1)*.

Blood pressure varies reproducibly over a 24-h cycle with a number of well-recognized patterns. Most patients are "dippers:" these individuals are characterized by at least a 10% decline in nocturnal blood

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pressure compared to their awake blood pressure *(2)*. Some patients may have an exaggerated drop in nocturnal pressures of >20% and have been referred to as "extreme" dippers. Kario et al. conducted a study that demonstrated that extreme dippers were more likely to have ischemic lesions on magnetic resonance imaging compared to dippers *(3)*. Approximately 10–30% of patients are "nondippers," in whom the blood pressure decline is blunted or absent during sleep *(4,5)*. This may be the result of various types of autonomic dysfunction or certain causes of secondary hypertension *(6)*. Multiple studies, in hypertensives as well as normotensives (NTs), have consistently shown that target organ damage is more likely in nondippers than dippers *(7)*. A small proportion of patients exhibit an "inverse" dipping pattern *(8)*. Here, the nocturnal blood pressures do not fall during sleep and, in some cases, may actually be higher than the daytime readings. Other 24-h blood pressure patterns that have been observed resulting from the advent of ABP include "white coat" hypertension (WCH) or the "white coat" effect *(9)*. In these patients, office blood pressures are substantially higher than ambulatory awake blood pressure averages. There are also some individuals who may present with a "masked hypertension," where ABP is elevated but office blood pressure is normal ("white coat" normotensive pattern). This phenomenon may, in part, be the result of factors not present in the physician's office (e.g., smoking cigarettes, mental stress, or excessive physical activity). Liu et al. reported that white coat NTs are as likely to have left ventricular hypertrophy (LVH) and carotid artery intimal-medial thickening as those patients with definite hypertension *(10)*. More recently, a 10-yr follow-up of the Ohasama study showed that the cardiovascular mortality and stroke rates were significantly higher in masked hypertensives as compared with NTs (relative hazard ratio 2:13) *(11)*.

Most research has shown that isolated clinical blood pressure readings do not accurately estimate a patient's overall hypertension burden because they represent only one point in time on a patient's 24-h blood pressure profile. ABP monitors overcome this problem by obtaining multiple readings over the 24-h period and capturing the blood pressure variability. Numerous studies have also shown that clinical blood pressures are inferior in predicting hypertensive target end-organ damage, as well as long-term cardiovascular outcomes, compared with 24-h blood pressure averages or loads. This chapter will focus on the various types of ABPM devices and their validation and discuss their clinical application in managing patients with hypertension.

ABPM DEVICES: AUSCULTATORY AND OSCILLOMETRIC

ABP monitors are automated and programmable devices that detect blood pressure either by the auscultatory method or the oscillometric route. Some devices have the option of using both techniques. Each method has its own advantages and limitations. The auscultatory devices employ the use of a microphone to detect Korotkoff sounds. Unfortunately, these devices are also sensitive to external artifactual noise, which may limit their accuracy. They may also be less precise in the obese upper extremity. In some devices, these limitations are overcome by synchronizing the Korotkoff sounds with the R-wave of the electrocardiogram (electrocardiographic gating) *(12)*. The oscillometric technique, which is utilized in most present-day monitors, detects the initial and maximal arterial vibrations or the mean arterial blood pressure and is less affected by external artifacts. The systolic and diastolic blood pressure values used in this technique are actually computed via set algorithms. Hence, the more sensitive the algorithm, the more accurate the device. Extreme blood pressure values increase the likelihood of error with the oscillometric devices *(13)*. Modern ABP recorders are compact, lightweight monitors that can be programmed to take blood pressure readings at various intervals (e.g., every 15 min during the day and every 30 min at night). In most devices the bleed rates of deflation of the cuff and maximal inflation pressures can be programmed; some devices also have a patient-initiated event button (to monitor symptoms). Most devices have algorithms to screen out erroneous readings (to a certain extent) and will perform a repeat of the blood pressure measurement within 1–2 min. Prior to initiation and again at the termination of a 24-h monitoring study, the ABP device should be calibrated against a mercury-column sphygmomanometer to verify that the systolic blood pressure and diastolic blood pressure agree within about 5 mmHg. Patients should be educated regarding the use of the ABPM at device hookup. For example, the patient needs to be aware that when the actual readings are being measured, the arm should be held motionless to avoid artifact and repetitive readings *(14)*. Excessive heavy physical activity during measurements should be discouraged, as it usually interferes with the accuracy of the measurements. A diary that records wake-up and sleep times, time of medication administration, meals, and any occurrence of symptoms—the ability to manually initiate an additional reading out of sequence must be stressed at ABP hookup—should be maintained. The ABPM study should be

Table 1
Advantages and Disadvantages of Ambulatory Blood Pressure Monitoring Compared to Clinic Blood Pressures

Advantages	*Disadvantages*
Elimination of observer bias/error	Cost
Elimination of the white coat effect	Time commitment on behalf of patient
More comprehensive assessment of antihypertensive therapy	Disturbed sleep
Superior prognostic indicator	Cuff discomfort
Calculation of blood pressure loads	Inaccurate in atrial fibrillation
Evaluation of dipping/nondipping status	
Ability to better assess blood pressure variability	
More reproducible over time	

performed on a regular working day rather than a nonworking day or on the weekend to obtain the most representative blood pressure values. A study conducted by Devereux et al. demonstrated that daytime (work) blood pressures were a more sensitive determinant of left ventricular mass index compared to daytime values taken at home *(15)*. The clinical advantages of ABPM studies are many and the disadvantages are few (Table 1). ABP monitoring eliminates observer error as well as the white coat effect, and it allows for a more comprehensive assessment of antihypertensive therapy. In addition, ABP is a superior prognostic indicator for hypertensive target end-organ damage as compared to clinical blood pressures. The potential limitations of ABP devices include poor technical results in patients with atrial fibrillation or frequent ectopic beats or in those patients with an obese or muscular upper extremity that exceeds a mid-bicep circumference of 40 cm. Imprecise data may also be recorded in patients with weak pulses or an auscultatory gap. The devices are usually well tolerated by patients, although occasionally there may be bruising or petechiae at the upper or distal arm. Some subjects may experience a lack of sleep at night or poor sleep quality because of the repeated cuff inflations.

VALIDATION OF ABP MONITORS

The Association for the Advancement of Medical Instrumentation (AAMI) has long recognized the importance of the accuracy of ABP monitors. A protocol was first developed in 1987 for the assessment of

device accuracy and reliability *(16)*. The AAMI protocol was followed by a more complex method of independent validation from the British Hypertension Society (BHS) in 1990 *(17)*. Although the protocols differed, their aim was to establish minimum accuracy standards for these devices in order for them to be considered reliable clinical tools. Since then, both protocols have been revised *(18,19)*. In addition to clinical testing, the protocols include recommendations such as labeling information, details for environmental performance, as well as stability and safety requirements.

In an updated version in 1992, the AAMI *(18)* advised that blood pressure should be measured at the onset and conclusion of the validation study in three positions (supine, seated, and standing) and the difference between the ABPM vs the reference standard should not be more than 5 mmHg with a standard deviation of 8 mmHg. Additionally, the disparity between the ABPM and the reference sphygmomanometer should be assessed in 20 subjects at the beginning and at the end of a 24-h blood pressure study. This difference should not exceed 5 mmHg in at least 75% of the readings. For reliability testing, three different instruments should be assessed in a minimum of 10 subjects for a total of 30 24-h ABP studies. It is recommended that a minimum of 75 readings in each of the 24-h studies be obtained, with 15-min intervals during the awake period and 30-min intervals during sleep. The number of satisfactory readings (i.e., no error codes) should exceed 80% of the total number of readings programmed for the day.

The BHS protocol is a more complex validation protocol that has the grading system outlined in Table 2. The BHS protocol calls for five phases of validation: (1) before use device validation, (2) in-use (field) assessment, (3) after-use device calibration, (4) static device calibration where the device is rechecked after 1 mo of usage, and (5) report of evaluation. Each phase has its passing criteria *(19)*.

In 2002, the Working Group on Blood Pressure Monitoring of the European Society of Hypertension approved a new protocol—the international protocol for validation of blood pressure measuring devices *(20)*. The main purpose of this protocol was to simplify the previous protocols without compromising their integrity. Briefly, this protocol consists of the following steps:

1. Observer training and assessment.
2. Familiarization session.
3. Validation measurements (done in two phases, with 15 patients required in the first phase and 33 in the second).
4. Analysis after each phase.
5. Reporting of results.

Table 2
British Hypertension Society Grading Criteria

Absolute difference between standard and test device (mmHg)			
Grade	*≤5*	*≤10*	*≤15*
A	60%	85%	95%
B	50%	75%	90%
C	40%	65%	85%
D		Worse than C	

Grades are derived from percentages of readings within 5, 10, and 15 mmHg. To achieve a grade, all three percentages must be equal to or greater than the tabulated values.

From ref. *19*.

This protocol uses "pass" or "fail" for grading the devices as opposed to the A–D classification of the BHS protocol. One of the changes from the BHS protocol is the exclusion of the prevalidation phases (phases 1–3 in the previous list), thereby considerably reducing time and labor. Also, the specifications regarding observer training reduces errors in the actual measurement of blood pressures and resolves major differences between individual observers. A reduced sample size, a refinement in the range of test blood pressure, and a two-phase system of evaluation will decrease the time and cost required for validation by using fewer total subjects and eliminating extremely inaccurate devices in an initial phase of testing. The international protocol has also been criticized for certain differences from prior protocols *(21)*. First, the protocol does not specify a range of arm circumference over which the device must be tested. Arm circumference is known to affect the accuracy of blood pressure measurement. Second, the protocol does not specify the maximum number of subjects that can be excluded. Some experts have brought up concerns that this might give the manufacturers excessive control over data reporting.

A list of all currently available ABP monitors (up to 2006) is shown in Table 3.

ANALYSIS OF ABPM DATA

Upon completion of the 24-h ABP recording, the data are downloaded and analyzed statistically to calculate blood pressure averages (i.e., 24-h, awake or daytime, and sleep or nighttime) as well as blood

Table 3
Validated Ambulatory Blood Pressure Monitors

Device	*Mode*	*AAMI*	*BHS grade*	*ESH*
A&D TM-2430	Osc	Pass	A/A	
BP Lab	Osc			Pass
IEM Mobil O Graph	Osc	Pass	B/A	
Meditech ABPM-04	Osc	Pass	B/B	
Nissei DS-250	Aus			Pass
Seinex SE-25M	Osc	Pass	A/B	
Spacelabs 90207	Osc	Pass	B/B	
Spacelabs 90217	Osc	Pass	A/A	
Suntech AGILIS	Osc			Pass
Suntech Medical Oscar-2	Osc			Pass
Tensioday	Osc	Pass	A/A	
Tonoport	Osc			Pass

For fulfillment of BHS protocol, the device must achieve at least grade B/B (where A indicates best agreement with mercury standard sphygmomanometer; D, worst agreement). For fulfillment of AAMI standard, mean difference ≤5 ± 8 mmHg. European Society of Hypertension (International Protocol) uses Pass/Fail.

From DABL Educational Trust.

pressure loads. Approximately 75–80 valid readings should be obtained. The American Society of Hypertension has proposed limits of normal blood pressure and blood pressure loads as depicted in Table 4 *(22)*.

Descriptive Blood Pressure Data From ABPM

Data are reported separately for the 24-h, daytime, and nighttime periods. These averages should be accompanied by the standard deviations as a simple indicator of blood pressure variability. Some studies have indicated that there is a significant relationship between blood pressure variability and target end-organ damage *(23)*, especially with beat-to-beat intraarterial data. Frattola et al. conducted a study on 73 essential hypertensives who underwent intraarterial blood pressure monitoring at the initiation of the study *(24)*. Subsequently, echocardiography was performed to assess left ventricular mass on subjects at the onset and at the conclusion of the study 7 yr later. The standard deviations were obtained, and the average blood pressure variability for the group was calculated as 10.8 mmHg. The authors observed that end-organ damage was significantly higher in patients who had a greater than average blood pressure variability (for the group as a whole) given

Table 4
Suggested Upper Limits of Normal of Average Ambulatory Blood Pressure and Load

Blood pressure measure	*Probably normal*	*Borderline*	*Probably abnormal*
Systolic average			
Awake	<135	135–140	>140
Asleep	<120	120–125	>125
24-h	<130	130–135	>135
Diastolic average			
Awake	<85	85–90	>90
Asleep	<75	75–80	>80
24-h	<80	80–85	>85
Systolic load (%)			
Awake	<15	15–30	>30
Asleep	<15	15–30	>30
Diastolic load (%)			
Awake	<15	15–30	>30
Asleep	<15	15–30	>30

From ref. *22*.

that the 24-h mean arterial pressure was similar in both groups. Unfortunately, 24-h blood pressure monitoring was not conducted at the end of the study to confirm if the same level of blood pressure variability persisted.

Blood Pressure Loads

The blood pressure load is calculated as the proportion of blood pressures >135/85 mmHg during the awake period and >120/75 mmHg during the sleep hours. White et al. were one of the first groups to introduce the concept of blood pressure loads *(25)*. They conducted a study in 30 previously untreated hypertensives and observed that the blood pressure load was a sensitive predictor of indices of hypertensive cardiac involvement. The results demonstrated that when the systolic or diastolic blood pressure loads were less than 30%, the likelihood of LVH was negligible. However, with a systolic blood pressure load exceeding 50%, the incidence of LVH approx 90%, and with the diastolic blood pressure load more than 40%, LVH occurred in 70% of the subjects (Fig. 1) *(26)*. Similar results were obtained when Mule et al.

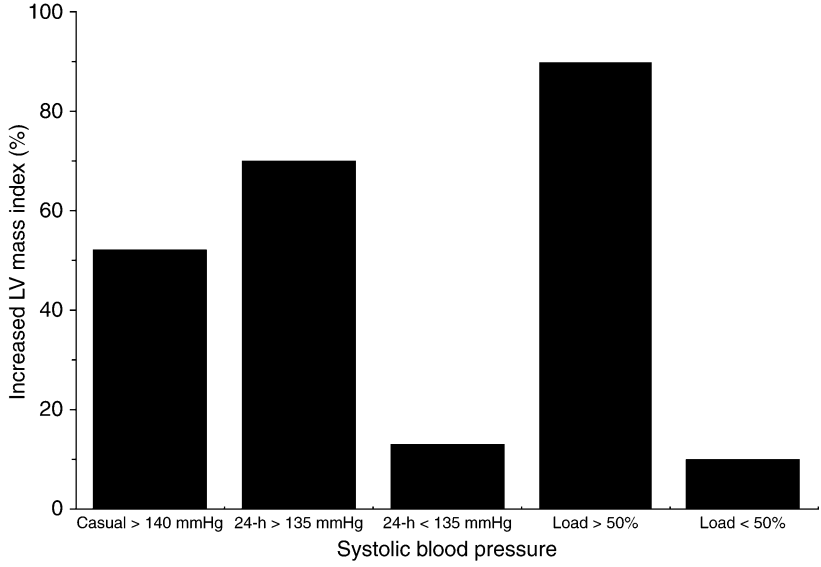

Fig. 1. Bars show percentage of increased left ventricular (LV) mass in subjects with elevated systolic clood pressures (both clinical and ambulatory) and systolic blood pressure loads. (From ref. *34*.)

studied 130 patients with mild to moderate hypertension *(27)*. Subjects with a higher systolic blood pressure load, adjusted to average 24-h SBP, were found to have increased relative myocardial wall thickness and total peripheral vascular resistance as well as increased prevalence of hypertensive retinopathy. These studies suggest that blood pressure load is an independent predictor of hypertensive target organ damage and adverse cardiovascular risk profile.

WCH and the White Coat Effect

WCH is diagnosed when the patient's 24-h blood pressure is within normal limits, but blood pressure in the clinic is persistently elevated (Fig. 2). In contrast, the white coat effect is defined as that additional pressor response in the established hypertensive subject causing an overestimation of the real blood pressure (Fig. 3).

Masked Hypertension

Masked hypertension ("white coat normotension" or "reverse white coat hypertension") is an entity that has been closely studied during the past 3–4 yr. This condition is defined by a normal office blood

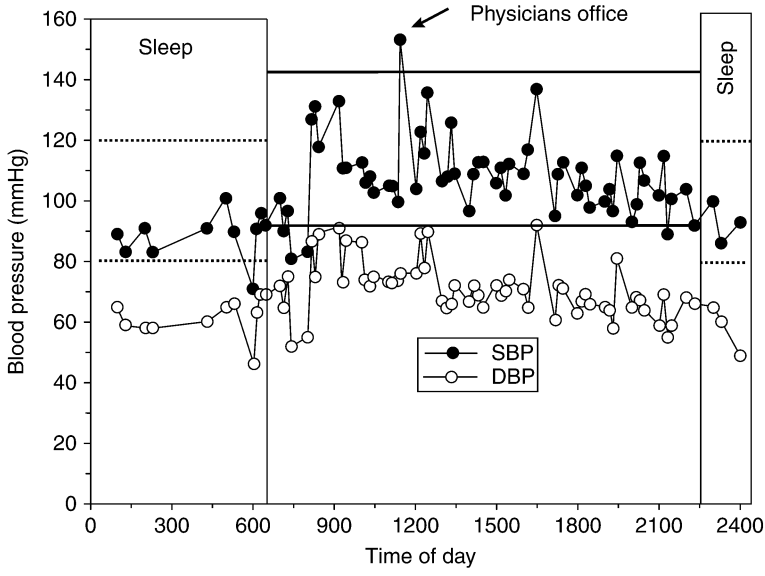

Fig. 2. Plot showing 24-h pressure curve depicting white coat hypertension (WCH) and dipping status. The patient's blood pressure in the physician's office is 153/76 mmHg. The daytime ambulatory average is normal at 108/71 ± 13/9 mmHg. The subject has WCH with a 45/5-mmHg rise in blood pressure in the physician's office. The patient also has a normal drop in nocturnal pressures, with a nightime average of 90/60 ± 7/6 mmHg.

pressure and an elevated ABP. Masked hypertension is associated with an increased risk of target organ damage as well as cardiovascular mortality *(10)*.

Dipping/Nondipping

Blood pressure normally has a circadian pattern in which blood pressure drops during sleep and is higher during the awake hours of the day. This pattern is referred to as "dipping" (Fig. 2). The dipping status can be determined by evaluating awake and asleep blood pressures and calculating differences between the two averages. The percentage "dip" is then determined by dividing this difference by the awake average. The degree of decline in blood pressure varies from person to person, but a general, arbitrary consensus is that 10–20% drop in blood pressure during sleep is "normal" *(28)*. The patient who has *less* than a 10% drop in blood pressure at night is referred to as a "nondipper" (Fig. 3).

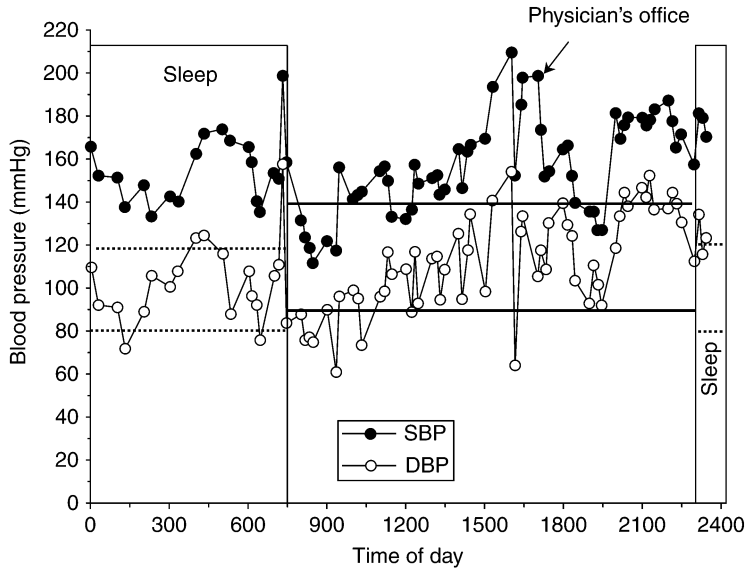

Fig. 3. Plot showing 24-h blood pressure curve depicting white coat effect and nondipper status. The patient is hypertensive with a daytime average of 158/110 ± 21/23 mmHg. The nighttime blood pressure does not drop significantly (157/105 ± 15/16 mmHg). The patient, in addition to his hypertension, has a significant white coat effect in which the blood pressure is 216/98 mmHg in the physician's office.

Reporting of ABP Data

Using all of the above-referenced values, an informative report can be generated indicating the status of the patient's blood pressure. The reports should include demographics, all medications taken during the study, the number of accurate readings obtained, the sleep times, and any symptoms that were experienced. The clinical report could also graphically depict blood pressures and heart rates over the 24 h, as shown in Figs. 1–3.

REPRODUCIBILITY OF ABPM

The majority of clinical trials conducted to evaluate ABP reproducibility confirm both superior short-term (<1 yr) *(29,30)* and long-term (>1 yr) *(31–33)* reproducibility of ABPM as compared to clinical blood pressure measurement. One substudy from the Systolic Hypertension in Europe (SYST-EUR) trial evaluated 112 patients who were randomized to receive placebo *(31)*. Clinical and ABPM readings

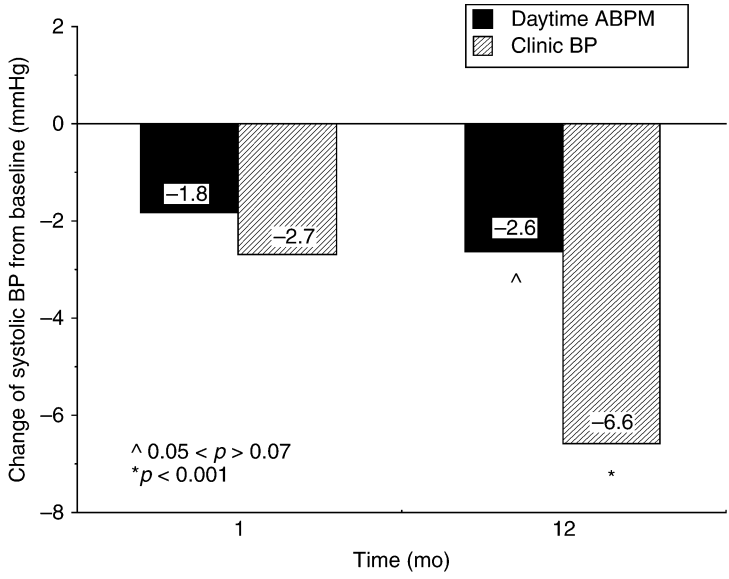

Fig. 4. Bars show the superior reproducibility of ambulatory blood pressure (ABP) vs clinic/office blood pressure from the SYST-EUR trial (n = 112). Blood pressures were measured 1 and 12 mo after baseline measurements. (From ref. *31*.)

done at baseline were repeated after 1 mo in 51 subjects and a full year in 112 subjects. The results indicated that differences in 24-h ambulatory systolic blood pressure (2.4 ± 10.7 mmHg [$p < 0.05$]) were far less than for clinical systolic blood pressure (6.6 ± 15.9 mmHg [$p < 0.001$]) taken at 1 yr (Fig. 4). Another large-scale trial that also observed better reproducibility for ABP monitoring than clinical blood pressure was the Hypertension and Ambulatory Recording Study (HARVEST), in which 508 subjects were evaluated *(32)*. ABP monitors were conducted at baseline and 3 mo later in the untreated state. A very modest difference in the two sequential ABPMs for the group as a whole was observed (0.4/0.7 mmHg).

Studies evaluating the reproducibility of the circadian rhythm have not had such promising results. For example, in a study by Mochizuki et al., they found that there was limited reproducibility of the circadian rhythm *(34)*. In that study, 253 untreated essential hypertensives were monitored for 48 h. In these 2 d, 16% of dippers "converted" into nondippers and 13% of nondippers "converted" into dippers (Fig. 5). The authors suggested that 48-h ABP monitors be performed to assess the circadian blood pressure profile of an individual *(35)*. Although

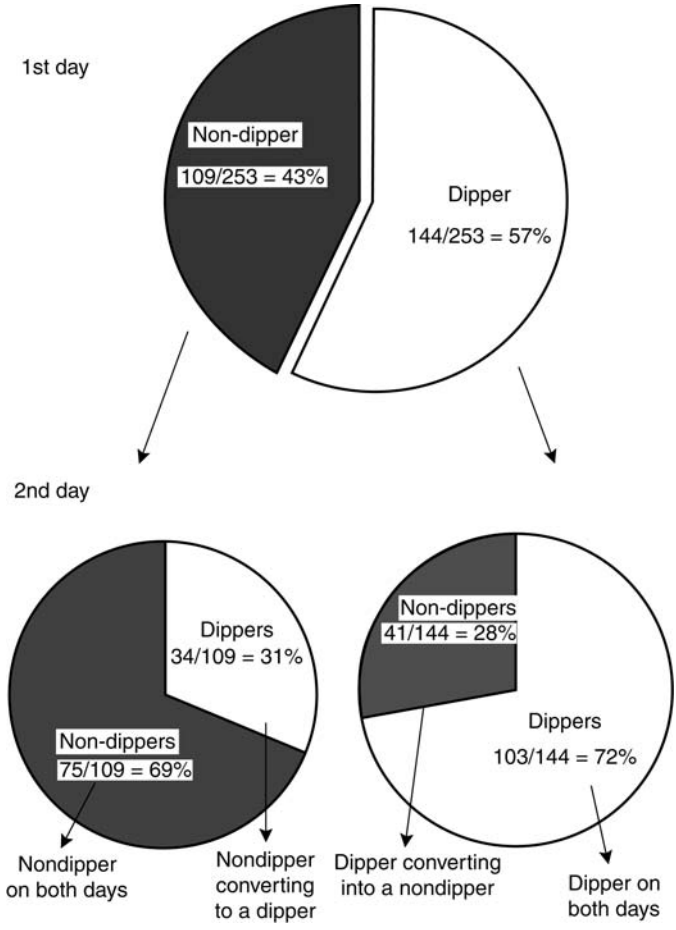

Fig. 5. Illustration of the limited reproducibility of the circadian rhythm (i.e., the dipping/nondipping status) with ambulatory blood pressure monitoring studies conducted over 48 h in 253 subjects. (From ref. *34*.)

this will not solve the problem entirely, it should decrease the likelihood of error.

INDICATIONS FOR ABPM

ABPM has been recognized as an important clinical tool by a number of expert medical groups and societies. The Joint National Committee (JNC VII) recommended ABP monitoring for a number of clinical situations (Table 5) *(28)*. There is definite benefit to be gained

Table 5
Primary Indications for Ambulatory Blood Pressure Monitoring

Suspected white coat hypertension
Apparent drug resistance
Hypotensive symptoms with antihypertensive medications
Episodic hypertension
Autonomic dysfunction

from ABP if the study is used judiciously. The next section briefly discusses the various indications for this test.

WCH

WCH, a well recognized clinical entity since 1983 *(9)*, is a result of the pressor response that patients experience when entering a medical environment. The patients have normal blood pressure outside of the doctor's office during activities of regular daily life. The prevalence has been estimated to be approx 20% in untreated borderline hypertensives *(36)*. The prognostic significance of this diagnosis has been the subject of considerable debate. Multiple prospective as well as cross-sectional studies have been done looking at this issue, a large majority of which have shown no significant difference in long-term cardiovascular outcomes in the WCH group when compared to NTs. In one of the initial long-term studies, Verdecchia et al. prospectively followed 1187 subjects from the PIUMA registry for up to 7.5 yr *(37)*. In their study, WCH was defined as an ambulatory daytime blood pressure of <131/86 mmHg for women and <136/87 mmHg for men, and the clinic blood pressure was >140/90 mmHg. No difference was initially observed between the WCH and NT groups, although follow-up of this database was later conducted with the use of a larger number (n = 1500) of patients *(38)*. The WCH patients were stratified into two subgroups. The first subgroup had a more restrictive and conservative definition of WCH (daytime ABP <130/80 mmHg), whereas the second group had more liberal limits for ABP (daytime ABP <131/86 mmHg for women and <136/87 mmHg for men). Cardiovascular morbid events in the first group were similar to the NT controls, but event rates in the more liberally defined group were significantly higher than the NT population. In the HARVEST trial, 722 hypertensive patients were evaluated using a more restrictive threshold to define WCH *(39)*. There was a significantly higher left ventricular mass index in the population with WCH

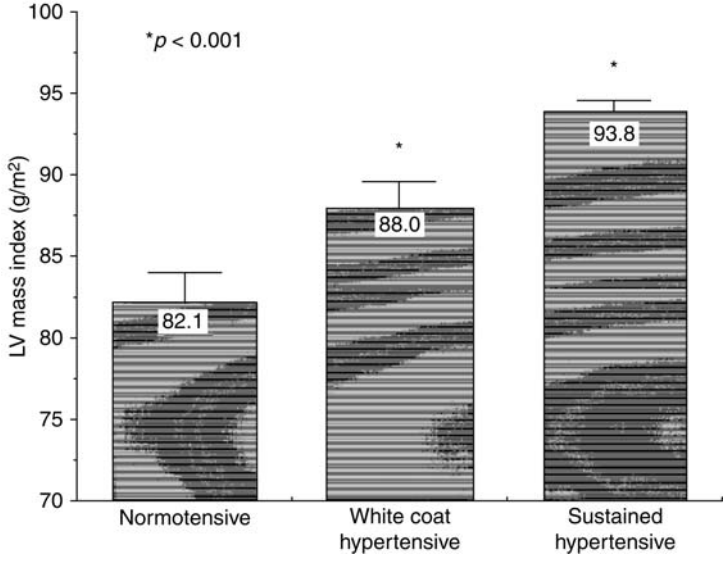

Fig. 6. Bars show the left ventricular mass in three categories of patients ($n = 722$): normotensives, those with white coat hypertension (threshold <130/80 mmHg), and sustained hypertensives (HARVEST trial). (From ref. *39*.)

(threshold <130/80 mmHg) when compared with the NT population (Fig. 6). The PAMELA study also showed that patients with WCH have cardiac morphological and functional indices that seem to be intermediate between NTs and sustained hypertensives *(40)*. Given the results of these rather large trials, WCH might be considered a prehypertensive state in some patients. Thus, close monitoring and follow-up is required, and at some point the institution of therapy may be needed. We believe that follow-up is necessary even in the 6–8% of true WCH patients with daytime ABP <130/80 mmHg.

Therapeutic Interventions

Accurate blood pressure measurement is the key step in formulating an effective treatment plan for hypertensive patients. ABPM can be used to assess the need for and effectiveness of both initial and additional antihypertensive therapy. To illustrate this benefit, Staessen et al. conducted a randomized controlled trial evaluating 419 untreated hypertensive patients over a course of approx 6 mo *(41)*. The Ambulatory Blood Pressure Monitoring and Treatment of Hypertension (APTH) trial randomized patients to an ABP arm vs a clinical blood pressure arm.

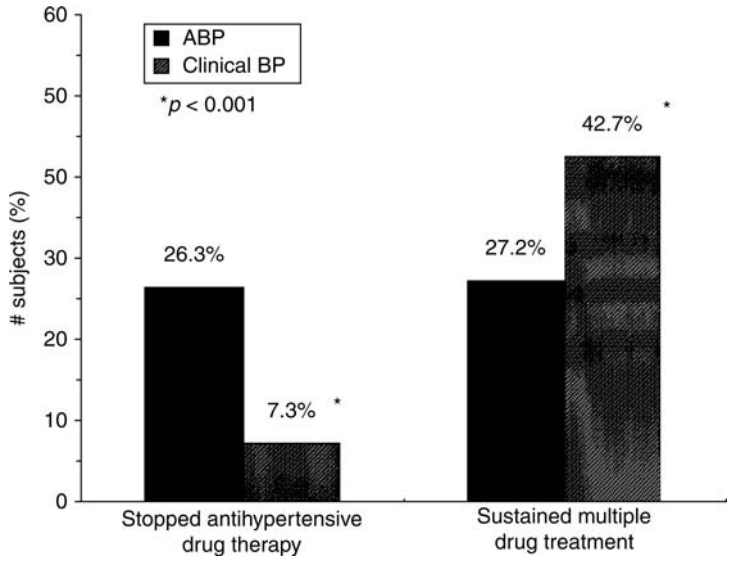

Fig. 7. Bars depict the percentage of subjects ($n = 419$) who stopped antihypertensive therapy and those who sustained multiple-drug therapy with the medication regimen being controlled either by ambulatory blood pressure monitoring results or by clinical measurements (APTH trial). (From ref. *41*.)

Drug treatment was adjusted in a stepwise fashion based on daytime ABP readings vs the average of three clinical measurements. At the end of the study it was shown that more subjects in the ABP group discontinued antihypertensive drug therapy. Furthermore, fewer subjects in the ABP group had progressed to receive multiple antihypertensive drugs (Fig. 7). There were no significant differences in the final blood pressure, left ventricular mass, or reported symptoms between groups. Therefore, ABP monitors can complement conventional approaches in determining optimal medication dosage and frequency of dosing.

Resistant Hypertension

Resistant hypertension has been defined as the failure to achieve goal blood pressure despite strict adherence to near-maximal doses of an appropriate triple drug therapy that includes a diuretic *(28)*. ABP monitors are useful in the evaluation of those patients who do not appear to be responding to therapy or for those on complicated medication regimens. With data derived from an ABPM, one can ascertain if and at what time additional therapy is needed or if it is needed at all.

Mezzetti et al. evaluated 27 subjects with resistant hypertension by ABPM *(42)*. They observed that more than 50% of the subjects showed a large white coat effect and were actually NT (<135/85 mmHg) on their current medication regimens. Later, Muxfeldt et al. conducted a cross-sectional study in 286 resistant hypertensives and divided them based on their ABP into a true resistant group (56.3%) and a white coat resistant group (43.7%) *(43)*. The former group was found to have a significantly increased prevalence of both LVH and nephropathy. In a 5-yr follow-up study, Pierdomenico et al. found that the cardiovascular event rate was much lower in false-resistant patients than true-resistant hypertensives (1.2 vs 4.1 events per 100 patient per year) *(44)*. Finally, Redon et al. conducted a study in 86 refractory hypertensives over 49 mo *(45)*. These patients were divided into tertiles of average diastolic blood pressure from the ABPM. The office blood pressures were not different among the three groups. It was found that subjects in the highest tertile group (diastolic blood pressure > 97 mmHg) had greater progression of hypertensive end-organ damage compared to the lower two tertile groups. Thus, ABPM was capable of identifying high-, medium-, and low-risk patients with refractory hypertension that was not apparent by office blood pressure measurements alone.

Type of Therapy/Chronotherapuetics

It has been well documented that a majority of cardiovascular events occur in the morning hours because of a number of inciting hemodynamic, hormonal, and hematological factors. Gosse et al. established in 181 patients that the arising blood pressure correlated with left ventricular mass better than did the office blood pressures *(46)*. Hence, the higher the early morning blood pressure, the greater the left ventricular mass. The rise in postawakening morning blood pressure can be obtained best by a 24-h ABP monitoring study. More recently, a prospective study performed in older hypertensives showed a higher incidence of stroke (relative risk = 2.7; $p = 0.04$) in subjects with a morning blood pressure surge after matching for age and 24-h blood pressures *(47)*. These studies stress the importance of identifying vulnerable subjects and targeting antihypertensive therapy to avoid morning surges of blood pressure.

Orthostatic Hypotension/Autonomic Dysfunction

Individuals with autonomic dysfunction (e.g., diabetics) or orthostatic hypotension tend to lose the normal circadian variation in blood pressure and may even demonstrate an inverse dipping phenomenon (Fig. 8).

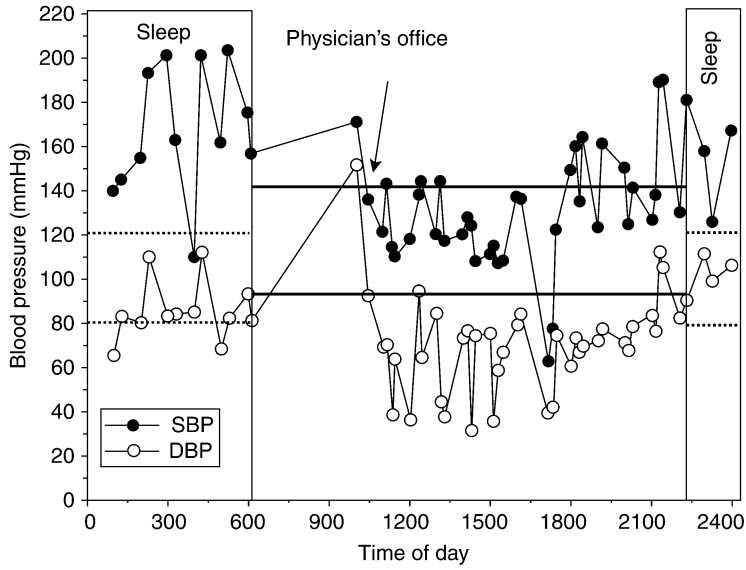

Fig. 8. Plot showing a 24-h blood pressure curve depicting autonomic dysfunction and inverse dipping. There is significant variability of blood pressure, as seen by the standard deviation. The awake blood pressure average is 132/71 ± 26/23 mmHg, and the sleep average is 164/89 ± 28/15 mmHg. The sleep averages are higher than awake averages, indicating an inverse dipping pattern.

The Ohasama, Japan, study clearly demonstrated in 1542 subjects that patients with inverse dipping had a significantly worse cardiovascular outcome as compared to the other patient groups (Fig. 9) *(8)*. Generally, there is also considerable variability of blood pressure noted in the inverse-dipping patient population. Patients with inverse dipping may benefit from short-acting medications that can be taken at bedtime to reduce the nighttime blood pressure average. In addition, some complicated patients with idiopathic orthostatic hypotension may be severely hypertensive in the supine position and markedly hypotensive in the upright position. Medication regimens can be tailored individually for these patients by using the detailed blood pressure information obtained via a 24-h ABPM.

Other indications for an ABPM study, as outlined by the JNC VII committee, include evaluation of symptoms and episodic hypertension. With the help of a patient-initiated event button, the physician can determine if the symptoms correlate with either a hypertensive (in the case of pheochromocytoma) or hypotensive period (in the case of excessive medication).

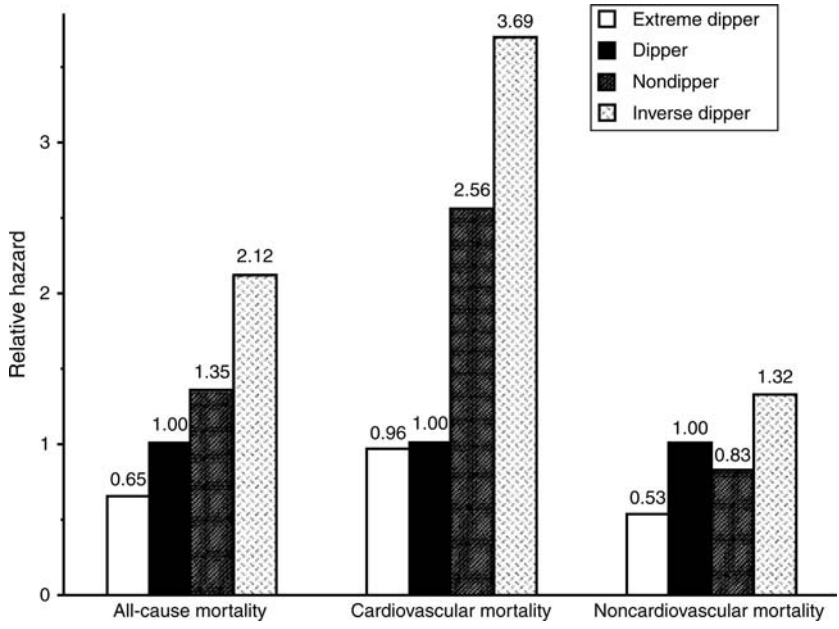

Fig. 9. Bars show the relative hazard of all-cause mortality, cardiovascular mortality, and noncardiovascular mortality in four subsets of patients (n = 1542): the extreme dipper, the dipper, the nondipper, and the inverse dipper. (From ref. *8*.)

COST-EFFECTIVENESS OF ABPM

ABPM studies generally cost $100–$350 in the United States. In 2002, a national insurance policy was created by the Centers for Medicare and Medicaid Services to cover 24-h ABPM for "suspected white coat hypertension." The ICD-9 code for this diagnosis is somewhat elusive, because it is under a different category than the hypertension codes (transient increases in blood pressure, hypertension nonconfirmed, 796.2). Many private insurance carriers have followed the lead of Medicare and also cover part or all of the cost of a 24-h blood pressure test.

However, there has been some controversy regarding the cost-effectiveness of ABPM. Moser has argued that if 24-h ABPM were to be performed on 3–5 million of the hypertensives in the United States, it would add an additional $600 million to $1.75 billion per year to the cost of treatment *(48)*. However, the APTH trial *(41)* performed a cost–benefit analysis of ABPM vs clinical blood pressure monitoring. They observed that the cost of medication was less for the ABP arm

compared to patients who were solely evaluated by office blood pressures ($4188 vs $3390 per 100 patients treated for 1 mo). Additionally, the ABP arm required fewer office visits for close blood pressure monitoring, thereby reducing physician fees. The authors concluded that the potential saving in the ABP group was offset by the cost of the study, rendering it equally cost-effective but therapeutically more beneficial. In 1994, Yarows et al. also conducted a cost-effective study in clinical practice *(49)*. They followed two sets of patients: the treatment group that had documented hypertension on an ABPM and was given appropriate antihypertensive therapy (n = 192) and a diagnostic group that was documented to be hypertensive in the physician's office and was off antihypertensive therapy (n = 131). The diagnostic group had a 24-h ABPM conducted, and the prevalence of WCH in this group was determined to be 34% (using a 24-h mean diastolic pressure of 85 mmHg) *(50)*. The authors ascertained the average yearly cost of antihypertensive medications for the 192 hypertensive subjects to be $578.40 (range $94.90 to $4361.75). They concluded that in the diagnostic group, the fee for the ABPM ($188) would be offset by the savings for 1 yr of antihypertensive therapy (if no medications were used for the WCH patients). In a recent cost-effectiveness analysis, Krakoff used the most up-to-date information on the prevalence of WCH, probability of WCH transitioning to a sustained hypertension, and the costs of medical care and testing *(51)*. His analysis predicted savings of 3–14% in health care costs for hypertension when ABP monitoring was routinely used as a diagnostic tool. The annual cost savings calculated for secondary screening using ABPM was also less than 10% of treatment costs, based on the current reimbursement rates. Hopefully, these types of important analyses will convince the payers as well as clinicians that ambulatory blood pressure monitoring has matured into a useful tool for both the diagnosis and management of patients with hypertension.

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5 Validation and Reliability of Blood Pressure Monitors

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CONTENTS

INTRODUCTION

With the increasing marketing of automated and semiautomated devices for the measurement of blood pressure, there is a need for potential purchasers to be able to satisfy themselves that such devices have been evaluated according to agreed-upon criteria *(1)*. With this need in mind, the Association for the Advancement of Medical Instrumentation (AAMI) published a standard for electronic or aneroid sphygmomanometers in 1987 *(2)*, which included a protocol for the evaluation of the accuracy of devices; this was followed in 1990 by the protocol of the British Hypertension Society (BHS) *(3)*. Both protocols

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were revised in 1993 *(4,5)*. These protocols, which differed in detail, had a common objective, namely the standardization of validation procedures to establish minimum standards of accuracy and performance and to facilitate comparison of one device with another *(6)*.

Since their introduction, a large number of blood pressure measuring devices have been evaluated according to one or both protocols (*see* www.dableducational.org). However, experience soon demonstrated that the conditions demanded by these protocols were extremely difficult to fulfill because of the large number of subjects that needed to be recruited and the ranges of blood pressure required. The time required to complete a validation study according to the BHS protocols had become such that it proved increasingly difficult to recruit trained staff for the duration of a study. These factors made validation studies difficult to perform and very costly, with the result that fewer centers were prepared to undertake them.

When the BHS dissolved its Working Party on Blood Pressure Measurement, the Working Group on Blood Pressure Monitoring of the European Society of Hypertension (ESH) undertook to produce an updated protocol, named the International Protocol, which was published in 2002 *(7)*. In setting about its objective, the ESH Working Group has recognized the urgent imperative to provide a simplified protocol that does not sacrifice the integrity of the earlier protocols. When the AAMI and BHS protocols were published *(2–5)*, the relevant committees did not have evidence from previous studies on which to base their recommendations. The ESH Working Group had the advantage of being able to examine and analyze the data from 19 validation studies performed according to the AAMI and BHS protocols at the Blood Pressure Unit in Dublin *(8–24)*. Critical assessment of this database of evidence permitted rationalization and simplification of validation procedures without losing the merits of the much more complicated earlier protocols.

The International Protocol was drafted so as to be applicable to the majority of blood pressure measuring devices on the market. The validation procedure was confined, therefore, to adults over the age of 30 yr (as these constitute the majority of subjects with hypertension), and it did not make recommendations for special groups, such as children, pregnant women, and the elderly, or for special circumstances, such as exercise. The protocol did not preclude manufacturers of devices from subjecting their products to more rigorous assessment and validation.

INTERNATIONAL PROTOCOL VALIDATION PROCEDURE

The validation team should consist of four persons experienced in blood pressure measurement: two observers and a supervisor (generally nurses) and an "expert" (a doctor overseeing the entire procedure). If the doctor can be present throughout the entire validation procedure, he or she can take over the role of supervisor, thereby reducing the number of personnel to three. The validation procedure consists of the following steps:

1. Observer training and assessment: Two observers are trained in accurate blood pressure measurement.
2. Familiarization session: The validation team becomes familiar with the workings of the device and accompanying software.
3. Validation measurements: Observer and device measurements are recorded on subjects in two phases. In the first phase, 15 subjects are recruited; devices passing this primary phase proceed to the secondary phase, in which a further 18 subjects are recruited.
4. Analysis: Analysis of the recorded measurements is carried out after each phase.
5. Reporting: The results are presented in tabular and graphical forms.

OBSERVER TRAINING AND ASSESSMENT

Consideration must first be given to the technique of blood pressure measurement, which should be as follows throughout the validation procedure.

Blood Pressure Measurement Technique

A standard mercury sphygmomanometer, the components of which have been checked carefully before the study, is used as a reference standard. It is appreciated that terminal digit preference is a problem with conventional mercury sphygmomanometry, and care should be taken to reduce this in the observer training session. The Hawksley random-zero sphygmomanometer only disguises digit preference, and its accuracy has been questioned *(8,25)*; therefore, its use is not recommended in validation studies. All blood pressures should be recorded to the nearest 2 mmHg.

Blood pressure should be measured with the arm, supported at heart level *(26)*; the manometer level does not affect the accuracy of measurement, but it should be at eye level and within 1 m of the observer.

The quality of the stethoscope is also crucial to performing the evaluation procedure. Stethoscopes with badly fitting earpieces and poor-quality diaphragms preclude precise auscultation of Korotkoff sounds. A well-maintained quality stethoscope is recommended.

Observer Training

The first prerequisite for this validation test is to ensure that the observers have adequate auditory and visual acuity and that they have achieved the required accuracy, as laid out next. However, it is possible that observers who fulfill these criteria at the outset of the study will not do so at the end of the study, and if this happens the observers must be reassessed for accuracy. To avoid this occurrence, analysis should be performed as the study proceeds to detect any drift in agreement between the observers.

Observers may be trained in the following ways:

1. By fulfilling the test requirements of the CD-ROMs produced by the British Hypertension Society (http://www.abdn.ac.uk/medical/bhs/).
2. By formal training and assessment *(27,28)*.

Alternatively, an audiovisual device, such as the Sphygmocorder *(29,30)*, can be used for validation.

FAMILIARIZATION SESSION

Because automated devices for blood pressure measurement may be complex, it is important that the personnel performing a validation study be fully conversant with the equipment. The observers, having satisfied the training criteria, should next be instructed in the use of the device to be validated and any accompanying computer software. For uncomplicated devices designed to provide a straightforward blood pressure measurement, the familiarization session should consist of performing a series of practice measurements on volunteers. However, a more formal session should be applied to complex devices, such as systems for measuring 24-h blood pressure. This session has two functions: (1) it serves as a familiarization period for the personnel performing the validation study and (2) any technical peculiarities of the device being tested, which might influence the validation procedure, may be identified.

VALIDATION MEASUREMENTS

General Considerations

Device validation should be performed at room temperature without disturbing influences, such as telephones and bleeps.

Some automated devices have more than one method of measuring blood pressure. For example, it may be claimed for a particular device that electrocardiogram gating may be used when more accurate measurement is required. In these circumstances, validation must be performed with and without electrocardiogram gating. Similarly, some Korotkoff sound-detecting devices provide an oscillometric backup when sound detection fails. When both systems generate simultaneous readings, only one comparative validation is required with analysis of both methods, but when the oscillometric method is a backup to the auscultatory method and provides a separate measurement, both systems of measurement must undergo individual validation.

Arm Circumference and Bladder Dimensions

The circumference of the arms should be measured to ensure that the bladder being used is adequate for the subject. Measurements made with the test device should use the appropriate bladder according to the manufacturer's instructions. The standard mercury manometer measurements must be taken with a bladder of sufficient length to encircle 80% of the arm circumference *(31)*. Where a test device recommends different cuff sizes, the appropriate cuff/bladder should be used, but no other part of the apparatus should be changed. It is important to ensure that, when assessing auscultatory devices, the same microphones be used throughout the validation test.

Devices for Measuring Blood Pressure at the Wrist

The International Protocol may be used to validate devices that measure blood pressure at the wrist by comparing the wrist-recorded measurements against auscultatory blood pressure measured at the arm. (Devices that measure blood pressure at the finger for self-measurement are not recommended because vasoconstriction of the digital arteries can introduce substantial errors.)

There is little literature regarding the accuracy of devices for wrist measurement, and most studies have shown these devices to be inaccurate *(1)*. Generally, measurements of blood pressures at the wrist with oscillometric devices overestimate blood pressure compared to conventional sphygmomanometry on the upper arm, and the differences can be substantial *(32,33)*.

It must, however, be emphasized that although a device designed for measuring blood pressure at the wrist may be accurate when tested according to the International Protocol, it may be inaccurate for

Table 1
Blood Pressure Ranges for BPA (Entry Blood Pressure)

	SBP	*DBP*
Low	90–129	40–79
Medium	130–160	80–100
High	161–180	101–130

For the primary phase, 5 of the 15 subjects should have systolic blood pressures (SBP) in each of the ranges. Similarly 5 of the 15 subjects should have diastolic blood pressures (DBP) in each of the ranges. For the secondary phase, 11 of the 33 subjects (including the first 15 subjects) should have SBP and DBP in each of the ranges. It is recommended that recruitment should commence by targeting subjects likely to have pressures in the low systolic and high diastolic ranges, then progress to complete the high systolic and low diastolic ranges so that it will be easy to complete the recruitment with the remaining medium ranges.

self-measurement of blood pressure if the instructions to have the wrist at heart level during measurement are not strictly followed.

Subject Selection

In selecting 33 subjects (15 for phase 1 and 18 for phase 2) with a wide range of blood pressure, it is likely that there will be a representative range of arm circumference, and subjects should not be selected on the basis of arm circumference. Subjects may be on antihypertensive medication but must not present in atrial fibrillation or any sustained arrhythmia.

Numbers:
Phase 1: 15 subjects
Phase 2: 18 subjects

Sex:
Phase 1: at least 5 male and 5 female
Phase 2: at least 10 male and 10 female
Age range: all subjects should be at least 30 yr
Arm circumference: distribution by chance
Blood pressure range: *see* Table 1

There are three ranges for systolic blood pressure (SBP) and three for diastolic blood pressure (DBP), with 11 subjects in each range, to provide 99 pairs of measurements. To optimize on recruitment, it is recommended that subjects for the high diastolic and low systolic groups should be recruited first. Then the emphasis should be placed on filling the remaining high systolic and low diastolic groups. Finally, the remaining gaps in

the middle groups should be filled. The blood pressure used in this categorization is the entry blood pressure at the time of the validation procedure (BPA), and not any earlier measurement that might have triggered an invitation to the subject to participate in the study.

Observer Measurement

Measurements can be either assessed live using two observers or recorded and later reassessed using the Sphygmocorder *(29,30)*. Measurements made simultaneously by two observers must be checked by the validation supervisor. If the systolic and diastolic measurements are both no more than 4 mmHg apart, the mean value of the two observer measurements for both SBPs and DBPs is used. Otherwise the measurement must be taken again. Where the Sphygmocorder is used, two observers should assess the recording separately. Where they differ they should reassess it together until agreement is reached. Further references to "observer measurement" refer to either the mean of two observer measurements or the agreed measurement using the Sphygmocorder. At least 30 s should be allowed between each measurement to avoid venous congestion, but not more than 60 s so as to minimize variability.

Procedure

1. The subject is introduced to the observers and the procedure is explained. Arm circumference, sex, date of birth, and current date are noted. The subject is then asked to relax for 10–15 min. (This is to minimize anxiety and any white-coat effect, which will increase variability.)
2. Nine sequential same-arm measurements between the test instrument and a standard mercury sphygmomanometer are recorded as follows:
   BPA: entry blood pressure—observers 1 and 2 each with mercury standard. The mean values are used to categorize the subject as low, medium, or high ranges separately for SBP and DBP (*see* Table 1).
   BPB: device detection blood pressure—supervisor. This blood pressure is determined to permit the test instrument to determine the blood pressure characteristics of the subject; more than one attempt may be needed with some devices; this measurement is not included in the analysis. If the device fails to record a measurement after three attempts, the subject is excused and the reason noted.
   BP1: observers 1 and 2 with mercury standard.
   BP2: supervisor with test instrument.
   BP3: observers 1 and 2 with mercury standard.
   BP4: supervisor with test instrument.

BP5: observers 1 and 2 with mercury standard.
BP6: supervisor with test instrument.
BP7: observers 1 and 2 with mercury standard.

Documentation must be provided for data omitted for legitimate technical reasons; once a subject is included, the data for that subject should not be excluded from the study if blood pressure values are obtainable; if blood pressure measurements from either the reference method or the test instrument are unavailable, data entry for that individual may be excluded with an accompanying explanation. Additional individuals must then enter into the study to ensure a sample size of 33.

ANALYSIS

Accuracy Criteria

The BHS protocol introduced the concept of classifying the differences between test and control measurements according to whether these were within 5, 10, 15, or greater than 15 mmHg. Final grading was based on the number of differences falling into these categories. This protocol seeks to keep this concept but expand its flexibility.

Differences are always calculated by subtracting the observer measurement from the device measurement. When comparing and categorizing differences, their absolute values are used. A difference is categorized into one of four bands according to its rounded absolute value for SBP and DBP:

0–5 mmHg	These represent measurements considered very accurate (no error of clinical relevance).
6–10 mmHg	These represent measurements considered to be slightly inaccurate.
11–15 mmHg	These represent measurements considered to be moderately inaccurate.
>15 mmHg	These represent measurements considered to be very inaccurate.

The analysis is based on how values in these bands fall cumulatively into three zones:

Within 5 mmHg	This zone represents all values falling in the 0- to 5-mmHg band.
Within 10 mmHg	This zone represents all values falling in the 0- to 5- and 6- to 10-mmHg bands.
Within 15 mmHg	This zone represents all values falling in the 0- to 5-, 6- to 10-, and 11- to 15-mmHg bands.

Subject Measurements

For accuracy assessment, only the measurements BP1–BP7 are used. The mean of each pair of observer measurements is calculated. This is denoted as observer measurement BP1, BP3, BP5, or BP7. Each device measurement is flanked by two of these observer measurements, and one of these must be selected as the comparative measurement.

From these, further measurements are derived as follows:

1. The differences BP2-BP1, BP2-BP3, BP4-BP3, BP4-BP5, BP6-BP5, and BP6-BP7 are calculated.
2. The absolute values of the differences are calculated (i.e., the signs are ignored).
3. These are paired according to the device reading.
4. Where the values in a pair are unequal, the observer measurement corresponding to the smaller difference is used.
5. Where the values in a pair are equal, the first of the two observer measurements is used.

For each subject there are three device readings for SBP and three for DBP. Each of these six readings has a single corresponding observer measurement, a difference between the two, and a band for that difference as previously described.

Experience with existing protocols has demonstrated that the overall outcome of a device can be apparent from a very early stage. This is particularly so with poor devices and is in accordance with statistical expectancy: the larger the error, the smaller the sample size required to prove it. To persist with validation of a device that is clearly going to fail is an unnecessary waste of time and money and is an inconvenience to participating subjects. Therefore, a mechanism for eliminating poor devices at an appropriate stage is introduced by dividing the validation process into two phases. In a primary phase, three pairs of measurements are performed in 15 subjects in the pressure ranges in Table 1, and a device failing this phase (Table 2A) is eliminated from further testing. One passing it proceeds to a secondary phase, in which a further 18 subjects (total 33) are recruited (Table 2B).

Assessment of Phase 1

Once there are five subjects in the six blood pressure ranges (Table 1), recruitment should be stopped and an assessment is performed. Data from the first five subjects in each range only are used. (In filling these ranges, some ranges may be oversubscribed as a result of subjects

Table 2A
Requirements to Pass Phase 1

Measurements	*Within 5 mmHg*	*Within 10 mmHg*	*Within 15 mmHg*
At least one of	25	35	40

After completing 15 subjects, the data (45 comparisons) should be analyzed to determine the number of comparisons falling within the 5, 10, and 15 mmHg error bands. At least 25 comparisons must be within 5 mmHg or at least 35 comparisons must be within 10 mmHg or at least 40 comparisons within 15 mmHg. If none of these counts reaches the criteria in the table, the device is deemed to have failed.

Table 2B
Requirements to Pass Phase 2.1

Measurements	*Within 5 mmHg*	*Within 10 mmHg*	*Within 15 mmHg*
Two of	65	80	95
All of	60	75	90

After completing all 33 subjects, the data (99 comparisons) should be analyzed to determine the number of comparisons falling within the 5, 10, and 15 mmHg error bands. For the device to pass, there must be a minimum of 60, 75, and 90 comparisons within 5, 10, and 15 mmHg, respectively. Furthermore, there must be a minimum of either 65 comparisons within 5 mmHg and 80 comparisons within 10 mmHg or 65 comparisons within 5 mmHg and 95 comparisons within 15 mmHg or 80 comparisons within 10 mmHg and 95 comparisons within 15 mmHg.

Table 2C
Requirements to Pass Phase 2.2

Subjects	*2/3 within 5 mmHg*	*0/3 within 5 mmHg*
At least	22	
At most		3

The data should now be analyzed per subject to determine the number of comparisons per subject within 5 mmHg. At least 22 of the 33 subjects must have at least two of their three comparisons within 5 mmHg. (These include those who have all three comparisons within 5 mmHg.) At most 3 of the 33 subjects can have all three of their comparisons more than 5 mmHg.

having different SBP and DBP ranges.) This will yield 45 sets of measurements for both SBP and DBP.

1. The number of differences in each zone is calculated using the difference bands as previously described.
2. A Continue/Fail grade is determined according to Table 2A (*see also* Table 3).

Table 3
Example of Device Validation Table[a]

Phase 1		*≤5 mmHg*	*≤10 mmHg*	*≤15 mmHg*	*Grade*
Required	One of	25	35	40	
Achieved	SBP	**22**	**35**	**43**	**Continue**
	DBP	**35**	**42**	**44**	**Continue**

Phase 2.1		*≤5 mmHg*	*≤10 mmHg*	*≤15 mmHg*	*Grade*	*Mean*	*SD*
Required	Two of	65	80	95			
	All of	60	75	90			
Achieved	SBP	**52**	**79**	**90**	**Fail**	3.4 mmHg	8.4 mmHg
	DBP	**77**	**90**	**94**	**Pass**	–0.6 mmHg	6.9 mmHg

Phase 2.2		*2/3 ≤5 mmHg*	*0/3 ≤5 mmHg*	*Grade*
Required		≥22	≤3	
Achieved	SBP	**17**	**4**	**Fail**
	DBP	**28**	**2**	**Pass**

[a]The device passes for diastolic blood pressure but fails for systolic blood pressure, thereby failing overall.

If the device fails, the validation is complete; if it passes, it proceeds to phase 2.1.

Assessment of Phase 2

This phase determines how accurate the device will be for individual measurements and for individual subjects by determining the number of differences within 5, 10, and 15 mmHg and then determining the number of subjects with at least two device measurements with differences of less than 5 mmHg. After all ranges have been filled, there will be 99 sets of measurements for both SBP and DBP.

1. The number of comparisons per subject within 5, 10, and 15 mmHg is calculated.
2. A Pass/Fail grade for phase 2.1 is determined according to Table 2B.
3. For each of the 33 subjects, the number of measurements within 5 mmHg is determined.
4. For the 33 subjects, each of whom has three comparative measurements, in at least 22 subjects, at least two comparative differences must be within 5 mmHg, and only 3 subjects can have all three comparative differences more than 5 mmHg (Table 2C).
5. If the device passes both phase 2.1 and phase 2.2, it passes the validation and can be recommended for clinical use. Otherwise it fails and is not recommended for clinical use.

REPORTING

Statistical Report

The report should be prefaced with subject data so as to describe the key characteristics of the subjects in the study. An example of a device validation is shown in Table 3.

Sex distribution: the number of males and females.

Age distribution: the mean, standard deviation, and range of the subjects' ages.

Arm circumference distribution: the mean, standard deviation, and range of the subjects' arm circumferences and, where different cuff sizes are used, the number of subjects on which each size was used.

Blood pressure: the mean, standard deviation, and range of the subjects' entry SBP and DBP (BPA).

The report should then give the results of the validation.

PHASE 1

The number of differences falling within 5 mmHg, 10 mmHg, and 15 mmHg zones (Table 2) together with the requirements should be

reported in text and tabular form as in Table 3. The mean and standard deviation of the observer and device measurements and the differences should be stated. The basis on which the decision to continue or stop at this stage should be stated.

Phase 2

The number of differences falling within 5 mmHg, 10 mmHg, and 15 mmHg zones together with the requirements should be reported in text and tabular form as in Table 3. The number of subjects with at least two differences and no differences within 5 mmHg should be reported in text and tabular form as in Table 3. The mean and standard deviation of the observer and device measurements and the differences should be stated. The basis on which the decision is made to pass or fail the device should be stated.

Graphical Representation

Difference against mean plots should be presented for the data at the phase at which the study ceased. Phase 1 data should be plotted for devices failing at that stage, and phase 2 data for those passing. The *x*-axis of these plots represents blood pressures in the systolic range 80–190 mmHg and the diastolic range 30–140 mmHg and the *y*-axis values from –30 to +30 mmHg. Horizontal reference lines are drawn at 5-mmHg intervals from +15 to –15 mmHg. Vertical reference lines are drawn at the range changeover points, which are at 130 and 160 mmHg for SBP and at 80 and 100 mmHg for DBP. The mean of each device pressure and its corresponding observer pressure is plotted against their difference with a point. Differences greater than 30 mmHg are plotted at 30 mmHg. Differences less than –30 mmHg are plotted at –30 mmHg. The same scales should be used for both SBP and DBP plots. An example is shown in Fig. 1 *(34)*.

Problems

Any problems encountered during the validation procedure, the date of their occurrence, date of any repairs to the device, the effect of these on the validation procedure should be recorded.

Operational Report

The following information should be provided with blood pressure measuring devices, and the final report should acknowledge that such information is available. Although this need not be presented in detail, any deficiencies should be listed in the report.

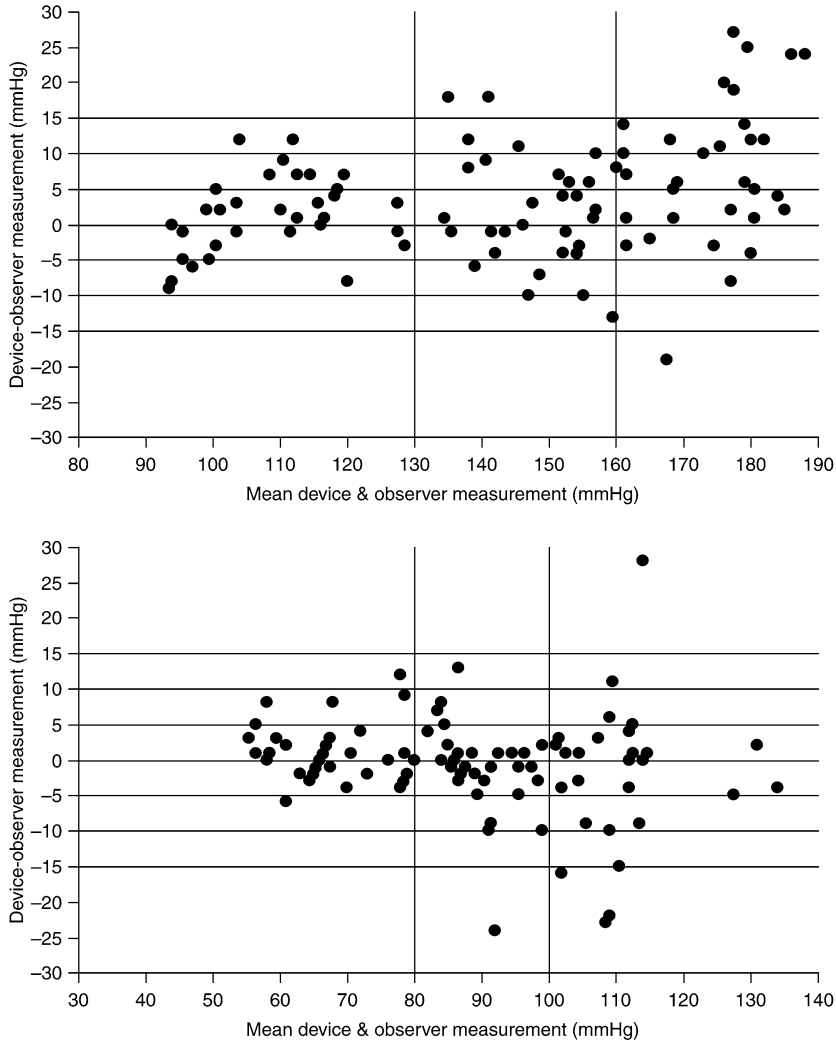

Fig. 1. Devices passing and failing phase 2.1. The *x*-axis represents the mean of the device and observer measurements. Both systolic blood pressure (SBP; upper plot) and diastolic blood pressure (DBP; lower plot) ranges should be plotted on the same scale. Recruitment limits are indicated by the vertical hatched lines. The *y*-axis represents the difference between the device and observer measurements. The 5-mmHg bands from +15 to –15 mmHg are indicated by the horizontal hatched lines. The 99 comparisons are presented in a difference-against-mean scatterplot. In this example, the SBP plot depicts a poor device, whereas the DBP plot depicts an accurate device.

Basic Information

The information provided in operational manuals is often deficient. Without appropriate specifications and operational instructions, it is difficult to obtain optimal performance.

List of Components

All major components of the system should be listed. The dimensions of the bladders supplied and those of the range of bladders available should be indicated.

Method of Blood Pressure Measurement

The basic method of pressure detection (e.g., auscultatory or oscillometric) should be stated, and if more than one method is used the indications for changing methods and the means of denoting this on the recording should be stated. With Korotkoff sound-detecting devices it must be disclosed whether phase IV or V is being used for the diastolic endpoint. If data are derived from recorded measurements, such as mean pressure, the method of calculation must be stated.

Factors Affecting Accuracy

Many factors may affect the accuracy of automated recordings, such as arm movement, exercise, arm position, and cuff or cloth friction. All such factors should be listed by the manufacturer.

Operator Training Requirements

Some automated systems require considerable expertise on the part of the operator if accurate measurements are to be obtained, whereas other systems require relatively little instruction. These requirements should be stated.

Computer Analysis

Some automated systems are compatible with personal computer systems. The exact requirements for linking with computer systems and their approximate cost should be stated. If the automated system is dependent on its own computer for plotting and analysis, this should be made clear and the cost of the computer facility, if it is an optional extra, should be stated. Clear instructions should be provided for setting recording conditions (e.g., frequency of recordings during defined periods and on–off condition of digital display); retrieving recordings and saving data to disk; retrieving data from disk, displaying numerical data and graphics; exporting data to statistical/graphic/spreadsheet software programs; and printing results (partial or complete). Where data

cannot be exported, information on how it is stored should be available to facilitate external analysis of several monitoring events. The manufacturer should list compatible computers (PC or other) and printers together with memory requirements, operating systems, compatible graphic adaptors, and additional software or hardware requirements (including interfaces and cables if these are not supplied).

EXPERIENCE WITH THE INTERNATIONAL PROTOCOL

The International Protocol was published in 2002 *(7)*, and to date (December 2006) 26 validation studies on 23 devices have been performed using this protocol *(35–56)*. It is timely to review the use of the protocol and to identify its shortcomings so that these can be rectified in the next revision and to examine how well the protocol is being used.

Reporting of Basic Characteristics

The protocol states clearly that the mean, standard deviation, and range of the subjects' ages, arm circumferences, and entry blood pressures should be stated along with the number of males and females recruited; only 16 of the 26 studies provided all this information (Table 4). The protocol stipulates that if different cuff sizes are used, the number of subjects on which each size was used should be given. Seven studies involved wrist monitors *(41,43,48,49,54,56)*. In two studies it was stated that only one cuff was available *(36,47)*. A choice of available cuffs was described in 10 studies *(37,40,45,46,50,52,54,55)*, but their use was only described in five of these *(40,46,50,54)*. The remaining seven studies made no references to cuffs.

Subject Recruitment

Most of the studies stated simply that 15 subjects were recruited for phase 1 and a further 18 subjects for phase 2. However, the reality is that studies do not go so smoothly, and it is important that problems with recruitment should be reported. The protocol requires that "documentation must be provided for data omitted for legitimate technical reasons." In particular, the total number of subjects recruited, the numbers rejected and the reasons for rejection, and the number of subjects used for both systolic and diastolic assessments should be stated. Experience with the International Protocol has shown that there are three common reasons for subjects to be excluded: (1) the ranges have been filled and the subjects are no longer needed; (2) the presence of an arrhythmia; (3) the presence of poor quality Korotkoff sounds. It is

Table 4
Recruitment Demographic Details

				Age		*Sex*	*Arm circumference*		*Recruitment BP*	
Device	*Ref.*	*BP*	*Recruited*[a]	*Mean (SD)*	*Range*	*M:F*	*Mean (SD)*	*Range*	*Mean (SD)*	*Range*
A&D UA-631	*35*	SBP	66						142 (31)	84–206
		DBP		49 (16)	18–76		29 (3)	22–32	85 (18)	54–118
A&D UA-787	*36*	SBP	33						142 (23)	94–180
		DBP		52 (18)		20:13	29 (3)	24–35	84 (11)	64–104
Omron M5-I	*37*	SBP	33							
		DBP		52 (14)		17:16				
Omron 705IT	*37*	SBP	33							
		DBP		54 (13)		18:15				
Rossmax	*38*	SBP	37 (29)	54 (11)	30–81	19:14	30 (3)	22–37	144 (24)	104–180
		DBP		56 (11)	30–81	19:14	30 (3)	22–37	88 (17)	54–144
Tonoport V	*39*	SBP	42 (24)	45 (16)	30–77	16:17	30 (3)	22–37	144 (26)	92–180
		DBP		45 (16)	30–74	19:14	30 (3)	22–37	91 (19)	50–122
Tonoport V	*44*	SBP	35 (31)	54 (11)	30–83	20:13	28 (3)	23–36	147 (24)	12–210
		DBP		55 (11)	30–83	19:14	28 (3)	23–36	88 (13)	67–107
Accoson Green-light 300	*40*	SBP	51 (15)	56 (16)	34–80	15:18	29 (5)	18–42	142 (26)	95–176
		DBP		55 (16)	34–90	19:14	30 (5)	18–42	88 (21)	51–125
Braun BP 2550	*41*	SBP	37						146 (22)	102–181
		DBP		52 (8)	30–82	18:15	24 (6)	16–42	93 (20)	60–127

(Continued)

Table 4 ***(Continued)***

				Age		*Sex*	*Arm circumference*		*Recruitment BP*	
Device	*Ref.*	*BP*	*Recruited*[a]	*Mean (SD)*	*Range*	*M:F*	*Mean (SD)*	*Range*	*Mean (SD)*	*Range*
Oscar 2	*42*	SBP	104	56 (12)	31–86	19:14	31 (5)	25–49		96–180
		DBP	48 (18)	51 (13)	22–78	17:16	30 (-)	21–49		63–125
Omron RX3	*43*	SBP DBP	33	53 (13)		18:15	29 (2)		141 (24) 86 (15)	
SunTech Agilis	*45*	SBP DBP	33	54 (12)	31–74	13:20	29 (3)	23–40	143 (23) 87 (17)	93–173 55–108
Seinex SE-9400	*46*	SBP DBP	≈37	54 (14)		18:15	29 (3)	23–36	138 (15) 85 (14)	
Microlife BP 3AC1-1	*46*	SBP DBP	38	53 (14)		19:14	30 (3)	23–38	137 (21) 90 (16)	
Colson MAM BP 3AA1-2	*47*	SBP DBP	33	47 (10)	32–71	15:18	28 (3)	24–32	142 (27) 88 (16)	100–180 61–120
Omron 637-IT (Adult)	*48*	SBP DBP	59	51 (10)	30–71	18:15	28 (2)	26–36	141 (28) 88 (15)	99–180 62–119
Omron 637-IT (Obese)	*48*	SBP DBP	72	52 (11)	34–73	14:19	38 (4)	34–48	144 (27) 88 (16)	98–180 55–121
Omron 637-IT (Elderly)	*49*	SBP DBP	76	72 (5)	65–80	16:17	31 (5)	25–38	146 (23) 86 (16)	104–180 62–112

(Continued)

Table 4 ***(Continued)***

				Age		*Sex*	*Arm circumference*		*Recruitment BP*	
Device	*Ref.*	*BP*	*Recruited*[a]	*Mean (SD)*	*Range*	*M:F*	*Mean (SD)*	*Range*	*Mean (SD)*	*Range*
BPLab	*50*	SBP	42						145 (32)	82–208
		DBP		51 (12)	30–75	24:18	32 (3)	26–37	88 (21)	56–132
Omron MX3 Plus	*51*	SBP	33						139 (22)	102–178
		DBP		50 (11)	31–73	18:15	30 (3)	24–37	85 (15)	58–112
Microlife BP A 100 Plus	*52*	SBP	44						143 (27)	97–178
		DBP		49 (14)	30–75	17:16	29 (4)	22–40	90 (18)	57–130
PMS Mandaus	*53*	SBP	33						147 (30)	97–206
		DBP		46 (14)	21–73	15:21(sic)	29 (4)	22–39	90 (19)	54–123
Omron M6	*54*	SBP	41							
		DBP		57 (13)		18:15	30 (4)	23–42		
Omron R7	*54*	SBP	35							
		DBP		53 (15)		19:14	30 (2)	26–32		
DINAMAP ProCare	*55*		38						(24)	99–183
		DBP		49 (12)	24–68	17:16	31 (4)	23–38	88 (17)	55–123
Oregon Scientific BPW810	*56*	SBP	33						144 (21)	92–190
		DBP		53 (13)	30–78	19:14	27 (2)	24–31	95 (15)	66–126

[a]In five studies where there were some subjects in which only one pressure (SBP or DBP) was used, the number of subjects in which at least one pressure was used is shown followed in parentheses by the number of subjects in which both pressures were used. For the Oscar 2, there were 104 subjects recruited to get the 48 included. The demographics for the BPLab are for all 42 subjects.

unlikely that these difficulties were not experienced, but this was described in only five studies *(41,42,49,52,55)*. One study stated that no subjects were excluded *(45)*. Many implied that more subjects were recruited, but this was not stated explicitly.

The International Protocol has simplified subject recruitment so as to facilitate the validation process. However, recruitment remains a major problem, with particular difficulty recruiting subjects with low systolic and high diastolic pressures *(46)*. The protocol allows for the use of either systolic or diastolic pressures in different subjects; because only five studies availed of this facility, it may be assumed that this issue should be highlighted in future revisions of the protocol.

A particularly frustrating aspect of recruitment is the fall in blood pressure that may occur between the measurement in clinic and laboratory. A number of factors such as the effect of medication, a white-coat reaction, or anxiety in the clinic may account for this, but the protocol requirement for the subject to relax for 15 min before measurement to reduce variability is the most significant factor. Regression to the mean during the validation procedure will reduce pressures further. It can be anticipated, therefore, that the initial recruitment blood pressure will inevitably be lower during validation. Unless a broad range of subjects with high pressures are recruited, these phenomena tend to result in most of the entry pressures in the high range clustered at the lower end of that range, with the plots showing markedly fewer pressures in the high ranges than would be expected. There should be at least 22 points (two-thirds of the expected number) in each range in the plot. Despite relaxing the range of pressures in the International Protocol, as compared with the BHS and AAMI protocols, the successful treatment of hypertension has reduced the availability of subjects with high blood pressures. Yet this is a critical sector of the population for device validation because this is the range in which monitors are more likely to be inaccurate.

On the other hand, the difficulty of recruiting subjects in the low blood pressure range could be somewhat alleviated by allowing recruitment from a younger population in a future revision of the protocol. The cutoff age of at least 30 yr in the protocol was based on the principle that hypertension is uncommon below this age. A corollary of this argument must be that low blood pressures are more likely in a younger population. A lower limit of 20 yr would be pragmatic without detracting from the principles of the protocol.

The International Protocol stipulated strict criteria for recruitment according to blood pressure ranges so that by standardizing subjects in

this manner validation studies from different centres would be comparable with each other. In this respect the International Protocol has realized this aim. In the 21 studies that provided mean entry blood pressure measurements, the systolic pressures ranged from 137 to 147 mmHg, with an overall mean blood pressure of 143 mmHg; the median pressure was 143 mmHg and there were two mode pressures at 142 and 144 mmHg. This is considerably higher than validation studies performed according to the AAMI standard in which blood pressures tend to be some 20 mmHg lower. The mean diastolic pressures in these studies ranged from 84 to 95 mmHg, with an overall mean of 88 mmHg, a level that reflects the difficulty in recruiting subjects with high diastolic pressures; median and mode pressures were both 88 mmHg. In the studies examined, both systolic and diastolic overall mean pressures were close to the target mean pressures of 145 and 90 mmHg. It would seem, therefore, that the subjects recruited for device validation according to the International Protocol are for the greater part hypertensive, thus providing validation for devices in the circumstances most likely to be met in clinical practice.

Results From Validation Studies Using the International Protocol

Overall, the pass rate from studies using the International Protocol was extremely high, with only 2 of 26 devices failing to meet the protocol recommendations *(18,39)*. (One of these subsequently passed a later study *[44]*.)

The International Protocol introduced two innovative phases to facilitate the validation process. Phase 1 allowed assessment of a device after 15 subjects had been evaluated so that clearly inaccurate devices could be identified in order not to have to proceed with unnecessary validation. Phase 2.2 was introduced with the purpose of ensuring that accurate measurements were distributed randomly rather than being subject dependent. It is timely, therefore, to examine the validation results to determine if these innovative phases are serving the purposes for which they were designed.

Relationship Between Phase 1 and Phase 2.1

The relationship between phase 1 and phase 2.1 for the 26 studies is shown in Table 5. The values in parentheses are the projected phase 2.1 values derived from phase 1. Allowing for band-dependent tolerances, 55% of the 156 values are accurately predicted (shown in boldface),

Table 5
Phase 1 and Phase 2.1 Results

Device	*Study*	*Phase*	*BP*	*Within 5 mmHg*	*Within 10 mmHg*	*Within 15 mmHg*	*Result*	*Mean (SD)*
A&D	*35*	1	SBP	32	40	44	Continue	
UA-631			DBP	43	45	45	Continue+	
		2.1	SBP	**72** (70–71)	**89** (87–89)	**96** (96–97)	Pass	2 (5)
			DBP	**93** (94–95)	**99** (98–99)	**99** (98–99)	Pass+	1 (3)
A&D	*36*	1	SBP	38	42	43	Continue+	
UA-787			DBP	35	39	45	Continue	
		2.1	SBP	*65* (83–84)	*80* (92–93)	**95** (94–95)	Pass	1.0 (5.3)
			DBP	**78** (76–78)	*92* (85–86)	**99** (98–99)	Pass	0.7 (5.3)
Omron	*37*	1	SBP	35	43	45	Continue+	
M5-I			DBP	39	43	44	Continue+	
		2.1	SBP	*68* (76–78)	92 (94–95)	**98** (98–99)	Pass	–0.9 (5.8)
			DBP	**83** (85–86)	**95** (94–95)	98 (96–97)	Pass+	–0.8 (4.8)
Omron	*37*	1	SBP	38	43	44	Continue+	
705IT			DBP	31	42	45	Continue	
		2.1	SBP	**83** (83–84)	**96** (94–95)	98 (96–97)	Pass+	–0.2 (4.5)
			DBP	74 (68–69)	**94** (92–93)	97 (98–99)	Pass	–2.0 (4.8)
Rossmax	*38*	1	SBP	21	31	38	Stop	
			DBP	36	43	45	Continue+	
		2.1	SBP	51 (46–47)	*73* (68–69)	*86* (83–84)	Fail	–4.5 (9.5)
			DBP	*71* (79–80)	**93** (94–95)	**98** (98–99)	Pass	–1.8 (5.0)

(Continued)

Table 5 ***(Continued)***

Device	*Study*	*Phase*	*BP*	*Within 5 mmHg*	*Within 10 mmHg*	*Within 15 mmHg*	*Result*	*Mean (SD)*
Tonoport V	*39*	1	SBP	28	37	40	Continue	
			DBP	26	38	44	Continue	
		2.1	SBP	56 (61–62)	78 (81–82)	**88** (87–89)	Fail	–1.4 (8.7)
			DBP	**60** (57–58)	**83** (83–84)	**97** (96–97)	Pass	–0.2 (6.8)
Tonoport V	*44*	1	SBP	38	42	45	Continue+	
			DBP	39	45	45	Continue+	
		2.1	SBP	**83** (83–84)	**93** (92–93)	**98** (98–99)	Pass+	–0.7 (4.6)
			DBP	80 (85–86)	96 (98–99)	97 (98–99)	Pass+	–0.8 (4.4)
Accoson Green-light 300	*40*	1	SBP	40	44	45	Continue+	
			DBP	31	40	44	Continue	
		2.1	SBP	84 (87–89)	**95** (96–97)	**98** (98–99)	Pass+	—
			DBP	74 (68–69)	**90** (87–89)	**96** (96–97)	Pass	—
Braun BP 2550	*41*	1	SBP	32	42	45	Continue	
			DBP	37	44	45	Continue+	
		2.1	SBP	75 (70–71)	**94** (92–93)	**98** (98–99)	Pass	–1.5 (4.8)
			DBP	78 (81–82)	**98** (96–97)	**99** (98–99)	Pass	2.2 (3.8)
Oscar 2	*42*	1	SBP	33	40	44	Continue	
			DBP	34	41	44	Continue	
		2.1	SBP	**71** (72–73)	**86** (87–89)	*94 (96–97)*	Pass	0.9 (2.3)
			DBP	**72** (74–75)	88 (90–91)	**96** (96–97)	Pass	–0.5 (2.2)
Omron RX3	*43*	1	SBP	40	44	45	Continue+	
			DBP	43	45	45	Continue+	
		2.1	SBP	**86** (87–89)	**95** (96–97)	**99** (98–99)	Pass+	0.8 (4.1)
			DBP	**92** (94–95)	**99** (98–99)	**99** (98–99)	Pass+	–0.4 (3.0)

(Continued)

Table 5 ***(Continued)***

Device	*Study*	*Phase*	*BP*	*Within 5 mmHg*	*Within 10 mmHg*	*Within 15 mmHg*	*Result*	*Mean (SD)*
SunTech Agilis	*45*	1	SBP	35	42	45	Continue+	
			DBP	35	44	45	Continue+	
		2.1	SBP	**78** (76–78)	**91** (92–93)	*96* (98–99)	Pass	–0.7 (4.7)
			DBP	*70* (76–78)	*92* (96–97)	*96* (98–99)	Pass	–3.0 (4.1)
Seinex SE-9400	*46*	1	SBP	34	40	45	Continue	
			DBP	40	40	45	Continue+	
		2.1	SBP	**76** (74–75)	92 (87–89)	**98** (98–99)	Pass	–0.9 (5.2)
			DBP	*79* (87–89)	*93* (87–89)	97 (98–99)	Pass	–1.7 (4.7)
Microlife BP 3AC1-1	*46*	1	SBP	36	40	44	Continue+	
			DBP	32	41	43	Continue	
		2.1	SBP	74 (79–80)	**87** (87–89)	98 (96–97)	Pass	–1.3 (5.6)
			DBP	*81* (70–71)	93 (90–91)	*97* (94–95)	Pass+	–0.4 (4.8)
Colson MAM BP 3AA1-2	*47*	1	SBP	37	44	45	Continue+	
			DBP	35	45	45	Continue+	
		2.1	SBP	76 (81–82)	93 (96–97)	**99** (98–99)	Pass	–1.0 (5.0)
			DBP	**79** (76–78)	**97** (98–99)	**99** (98–99)	Pass	–1.1 (4.1)
Omron 637-IT (Adult)	*48*	1	SBP	29	39	41	Continue	
			DBP	39	44	45	Continue+	
		2.1	SBP	69 (63–64)	88 (85–86)	*95* (90–91)	Pass	0.5 (6.2)
			DBP	**86** (85–88)	**98** (96–97)	**99** (98–99)	Pass+	0.1 (3.7)
Omron 637-IT (Obese)	*48*	1	SBP	32	41	44	Continue	
			DBP	37	45	45	Continue+	
		2.1	SBP	**69** (70–71)	*86* (90–91)	95 (96–97)	Pass	1.8 (6.6)
			DBP	77 (81–82)	95 (98–99)	**98** (98–99)	Pass	1.6 (4.7)

(Continued)

Table 5 ***(Continued)***

Device	*Study*	*Phase*	*BP*	*Within 5 mmHg*	*Within 10 mmHg*	*Within 15 mmHg*	*Result*	*Mean (SD)*
Omron	*49*	1	SBP	31	41	43	Continue	
637-IT			DBP	29	43	45	Continue	
(Elderly)		2.1	SBP	**66** (68–69)	87 (90–91)	**95** (94–95)	Pass	–0.3 (6.5)
			DBP	69 (63–64)	92 (94–95)	97 (98–99)	Pass	2.8 (4.8)
BPLab	*50*	1	SBP	35	42	44	Continue+	
			DBP	38	41	44	Continue+	
		2.1	SBP	*68* (76–78)	**92** (92–93)	98 (96–97)	Pass	–2.2 (5.6)
			DBP	80 (83–84)	93 (90–91)	98 (96–97)	Pass+	–1.5 (4.9)
Omron	*51*	1	SBP	34	41	45	Continue	
MX3			DBP	39	44	45	Continue+	
Plus		2.1	SBP	*68* (74–75)	**90** (90–91)	97 (98–99)	Pass	
			DBP	*75* (85–86)	**96** (96–97)	**98** (98–99)	Pass	
Microlife	*52*	1	SBP	32	42	43	Continue	
BP A			DBP	31	45	45	Continue	
100		2.1	SBP	**71** (70–71)	*87* (92–93)	96 (94–95)	Pass	–2.0 (6.0)
Plus			DBP	**71** (68–69)	**98** (98–99)	**99** (98–99)	Pass	–3.1 (4.1)
PMS	*53*	1	SBP	37	43	45	Continue+	
Man-			DBP	39	44	45	Continue+	
daus		2.1	SBP	76 (81–82)	**94** (94–95)	**99** (98–99)	Pass	–3.2 (3.8)
			DBP	**87** (85-86)	**98** (96–97)	**99** (98–99)	Pass+	–1.8 (2.9)
Omron	*54*	1	SBP	35	43	45	Continue+	
M6			DBP	36	41	44	Continue+	
		2.1	SBP	83 (76–78)	97 (94–95)	**99** (98–99)	Pass+	–0.8 (4.2)
			DBP	84 (79-80)	95 (90-91)	98 (96-97)	Pass+	-1.9 (3.8)

(Continued)

Table 5 ***(Continued)***

Device	*Study*	*Phase*	*BP*	*Within 5 mmHg*	*Within 10 mmHg*	*Within 15 mmHg*	*Result*	*Mean (SD)*
Omron	*54*	1	SBP	35	40	45	Continue+	
R7			DBP	39	44	45	Continue+	
		2.1	SBP	**75** (76–78)	**90** (87–89)	**98** (98–99)	Pass	0.2 (5.6)
			DBP	**88** (85–86)	**98** (96–97)	**99** (98–99)	Pass+	0.2 (3.6)
DINA-	*55*	1	SBP	38	42	43	Continue+	
MAP			DBP	29	43	45	Continue	
ProCare		2.1	SBP	78 (83–84)	**91** (92–93)	96 (94–95)	Pass	–2.5 (5.4)
			DBP	*76* (63–64)	**95** (94–95)	**99** (98–99)	Pass	0.5 (4.5)
Oregon	*56*	1	SBP	32	39	44	Continue	
Scien-			DBP	38	45	45	Continue+	
tific 810		2.1	SBP	*77* (70–71)	*90* (85–86)	**96** (96–97)	Pass	–5.1 (1.6)
BPW			DBP	**81** (83–84)	**98** (98–99)	**99** (98–99)	Pass+	5.0 (4.3)
Phase 1			All of	35	40	43	Continue+	
Phase 2.1			All of	80	90	95	Pass+	

Accurate prediction from Phase 1 **Bold** Within 2 Within 1 Exact
Error in prediction from Phase 1 *Italics* Out by 6 Out by 4 Out by 2

29% are fairly predicted, and 16% are poorly predicted (itaicised). Of these poor predictions, the ratio of final result overestimations to underestimations was 3:2. There were no poor predictions in 12 of the studies, one or two in 11 studies, and three or four in 3 studies.

Only one device, the Rossmax, failed phase 1, but the device was not eliminated in order to test the integrity of phase 1; the results of phase 2.1 confirmed that the device could have been eliminated on the basis of phase 1 results. The Tonoport device, which failed phase 2.1 in the first of its two studies, only marginally passed phase 1. The predicted values also indicated a fail and the device did worse than these predictions. However, a performance slightly better than predicted could have yielded a pass. Given these results, it is clear that passing phase 1 does not guarantee a phase 2.1 pass, but it does tend to give a reasonable indication of how the device will fare, and certainly a comfortable "Continue" will end in a Pass, whereas a fail justifies abandoning further validation.

Relationship Between Phase 2.1 and Phase 2.2

The relationship between phase 2.1 and phase 2.2 is shown in Table 6, which shows the actual spread and the corresponding optimal and worst outcomes based on phase 2.1. In the optimal situation, where a device has at least 66 accurate readings, all subjects will have at least 2 accurate readings. Where the errors are subject based, as many subjects as possible will have all three measurements accurate with a knock-on effect of some subjects having no accurate measurements. Using the data from both phases, it is straightforward to calculate the number of subjects with three, two, one, and no accurate measurements, i.e., those with an error of 5 mmHg or less. The 22 of 33 subjects with at least two accurate measurements was not the most difficult to achieve, but, except where the device was extremely accurate in phase 2.1, there was a potential to fail phase 2.2. One particularly interesting situation was the SBP of the UA-787. With a marginal 65 measurements within 5 mmHg, the potential to fail phase 2.2 was high. But with only four subjects having all three measurements accurate, the phase 2.2 results were very close to optimal. On the other hand, the Oscar 2, which passed phase 2.1 more comfortably, for both SBP and DBP, by a poorer spread of results, went to a whisker of failing phase 2.2.

The only device to pass phase 2.1 and fail phase 2.2 was the Tonoport for diastolic pressure in the first Tonoport study *(39)*. The pass was very marginal with only 60 accurate readings, which needed to be very evenly spread in order to pass phase 2.2, which was not the

case. Although the device had already failed the systolic accuracy, the value of this phase is well demonstrated.

Plots

The description of how the plots should be drawn is given carefully in the protocol along with examples. Yet they were not provided properly in nine studies *(35,36,40–42,44,47,50,51)*. The main errors were the lack of vertical reference points and incorrect blood pressure ranges. Even where plots were provided in a technically correct fashion, they were often of a very poor quality that did not permit counting the points in each range or unnecessary extra lines marking, for example, the mean or two standard deviations were included with the effect of cluttering the plot. These plots are standard, widely used difference against mean scatter plots and should not be described as Bland-Altman plots. (In an article in 1986, Bland and Altman simply recommended this form of plotting as the most appropriate to use when plotting paired measurements hypothesized to be the same *[34]*.)

HOW CAN THE INTERNATIONAL PROTOCOL BE IMPROVED?

Issues of Clarification

In the light of experience with the International Protocol and the above analysis, the following issues can be listed for modification in the next revision of the International Protocol:

Improved reporting: it is important that the details of all stages of the validation process be reported, but clearly this does not always happen, and reviewers of submitted papers may also be unaware that some results have not been detailed. A template for results should be provided so as to facilitate investigators and referees.

Subject recruitment: reducing the age restriction from 30 to 20 yr will facilitate recruitment of subjects with low blood pressures without altering the integrity of the protocol.

Observer measurements: the total number of observer pressures used for assessment (excluding the "Observer A measurements") should be at least 22 for each range. This will allow for some flexibility from the entry pressures but prevent "minimal recruiting."

Altered grading: with improvements in technology, devices will tend to pass the requirements with ease. In the BHS protocol, there was a grading system, and manufacturers had begun to aim for an A/A grade rather than a simple B/B pass. A similar system should be introduced

Table 6
Relationship Between Phase 2.1 and Phase 2.2

				Actual values within 5 mmHg				*Optimal within 5 mmHg*				*Worst within 5 mmHg*				*Results*	
Device	*Ref.*	*BP*	*N*	*3*	*2*	*1*	*0*	*3*	*2*	*1*	*0*	*3*	*2*	*1*	*0*	*Phase 2.2*	*Phase 2.1*
A&D UA-631	*35*	SBP	72	18	4	10	1	6	27	0	0	24	0	0	9	Pass	Pass
		DBP	93	27	6	0	0	27	6	0	0	31	0	0	2	Pass+	Pass+
A&D UA-787	*36*	SBP	65	4	24	5	0	0	32	1	0	21	1	0	11	Pass+	Pass
		DBP	78	18	11	2	2	12	21	0	0	26	0	0	7	Pass	Pass
Omron M5-I	*37*	SBP	68	11	14	7	1	2	31	0	0	22	1	0	10	Pass	Pass
		DBP	83	22	7	3	1	17	16	0	0	27	1	0	5	Pass	Pass+
Omron 705IT	*37*	SBP	83	19	12	2	0	17	16	0	0	27	1	0	5	Pass+	Pass+
		DBP	74	18	8	4	3	8	25	0	0	24	1	0	8	Pass	Pass
Rossmax	*38*	SBP	51	12	4	7	10	0	18	15	0	17	0	0	16	Fail	Fail
		DBP	71	15	11	4	3	5	28	0	0	23	1	0	9	Pass	Pass
Tonoport V	*39*	SBP	56	10	9	8	6	0	23	10	0	18	1	0	14	Fail	Fail
		DBP	60	11	11	5	6	0	27	6	0	20	0	0	13	Fail	Pass
Tonoport V	*44*	SBP	83	22	8	1	2	17	16	0	0	27	1	0	5	Pass	Pass+
		DBP	80	19	10	3	1	14	19	0	0	26	1	0	6	Pass	Pass+

(Continued)

Table 6 *(Continued)*

Device	*Ref.*	*BP*	*N*	*Actual values within 5 mmHg*				*Optimal within 5 mmHg*				*Worst within 5 mmHg*				*Results*	
				3	*2*	*1*	*0*	*3*	*2*	*1*	*0*	*3*	*2*	*1*	*0*	*Phase 2.2*	*Phase 2.1*
Accoson	*40*	SBP	84	18	15	0	0	18	15	0	0	28	0	0	5	Pass+	Pass+
Greenlight 300		DBP	74	17	10	3	3	8	25	0	0	24	1	0	8	Pass	Pass
Braun	*41*	SBP	75	12	18	3	0	9	24	0	0	25	0	0	8	Pass+	Pass
BP2550		DBP	78	17	12	3	1	12	21	0	0	26	0	0	7	Pass	Pass
Oscar 2	*42*	SBP	71	17	7	6	3	5	28	0	0	23	1	0	9	Pass	Pass
		DBP	72	16	9	6	2	6	27	0	0	24	0	0	9	Pass	Pass
Omron RX3	*43*	SBP	86	21	11	1	0	20	13	0	0	28	1	0	4	Pass+	Pass+
		DBP	92	27	5	1	0	26	7	0	0	30	1	0	2	Pass+	Pass+
SunTech Agilis	*45*	SBP	78	18	9	6	0	12	21	0	0	26	0	0	7	Pass+	Pass
		DBP	70	13	14	3	3	4	29	0	0	23	0	1	9	Pass	Pass
Seinex	*46*	SBP	76	16	12	4	1	10	23	0	0	25	0	1	7	Pass	Pass
SE-9400		DBP	79	18	11	3	1	13	20	0	0	26	0	1	6	Pass	Pass
Microlife	*46*	SBP	74	14	15	2	2	8	25	0	0	24	1	0	8	Pass	Pass
BP 3AC1-1		DBP	81	21	7	4	1	15	18	0	0	27	0	0	6	Pass	Pass+
Colson MAM	*47*	SBP	76	16	12	4	1	10	23	0	0	25	0	1	7	Pass	Pass
BP3AA1-2		DBP	79	28	8	3	2	13	20	0	0	26	0	1	6	Pass	Pass

(Continued)

Table 6 ***(Continued)***

				Actual values within 5 mmHg				*Optimal within 5 mmHg*				*Worst within 5 mmHg*				*Results*	
Device	*Ref.*	*BP*	*N*	*3*	*2*	*1*	*0*	*3*	*2*	*1*	*0*	*3*	*2*	*1*	*0*	*Phase 2.2*	*Phase 2.1*
Omron 637-IT	*48*	SBP	69	15	8	8	2	3	30	0	0	23	0	0	10	Pass	Pass
(Adult)		DBP	86	24	5	4	0	20	13	0	0	28	1	0	4	Pass+	Pass+
Omron 637-IT	*48*	SBP	69	14	9	9	1	3	30	0	0	23	0	0	10	Pass	Pass
(Obese)		DBP	77	19	8	4	2	11	22	0	0	25	1	0	7	Pass	Pass
Omron 637-IT	*49*	SBP	66	12	12	6	3	0	33	0	0	22	0	0	11	Pass	Pass
(Elderly)		DBP	69	15	9	6	3	3	30	0	0	23	0	0	10	Pass	Pass
BPLab	*50*	SBP	68	10	18	2	3	2	31	0	0	22	1	0	10	Pass	Pass
		DBP	80	18	11	4	0	14	19	0	0	26	1	0	6	Pass+	Pass+
Omron	*51*	SBP	68	10	18	2	3	2	31	0	0	22	1	0	10	Pass	Pass
MX3 Plus		DBP	75	17	11	2	3	9	24	0	0	25	0	0	8	Pass	Pass
Microlife	*52*	SBP	71	15	11	4	3	5	28	0	0	23	1	0	9	Pass	Pass
BP A		DBP	71	17	7	6	3	5	28	0	0	23	1	0	9	Pass	Pass
100 Plus																	
PMS	*53*	SBP	76	15	14	3	1	10	23	0	0	25	0	1	7	Pass	Pass
Mandaus		DBP	87	23	8	2	0	21	12	0	0	29	0	0	4	Pass+	Pass+
Omron M6	*54*	SBP	83	20	10	3	0	17	16	0	0	27	1	0	5	Pass+	Pass+
		DBP	84	24	5	2	2	18	15	0	0	28	0	0	5	Pass	Pass+
Omron R7	*54*	SBP	75	15	13	4	1	9	24	0	0	25	0	0	8	Pass	Pass
		DBP	88	25	6	1	1	22	11	0	0	29	0	1	3	Pass	Pass+

(Continued)

Table 6 *(Continued)*

Device	*Ref.*	*BP*	*N*	*Actual values within 5 mmHg* 3	2	1	0	*Optimal within 5 mmHg* 3	2	1	0	*Worst within 5 mmHg* 3	2	1	0	*Results* *Phase 2.2*	*Phase 2.1*
DINAMAP	*55*	SBP	78	19	8	5	1	12	21	0	0	26	0	0	7	Pass	Pass
ProCare		DBP	76	18	9	4	2	10	23	0	0	25	0	1	7	Pass	Pass
Oregon	*56*	SBP	77	18	8	7	0	11	22	0	0	25	1	0	7	Pass+	Pass
Scientific		DBP	81	19	10	4	0	15	18	0	0	27	0	0	6	Pass+	Pass+
BPW810																	
				2/3 within 5 mmHg								0/3 within 5 mmHg					
		Pass+		≥26								0					

The number of subjects with 3, 2, and 1 measurements within 5 mmHg (n_3, n_2 and n_1) can be calculated from the total number of measurements within 5 mmHg (N) and the number of subjects with 2 or 3 measurements and zero measurements within 5 mmHg (n_{2or3} and n_0).

$n_3 = N + n_0 - n_{2or3} - 33$

$n_2 = n_{2or3} - n_3$

$n_1 = 33 - n_{2or3} - n_0$

into the International Protocol so that excellent devices can be distinguished from adequate ones.

Acknowledgments: The report should state whether the equipment was purchased for the evaluation or donated or loaned by the manufacturer. The data analysis should ideally be done by the laboratory doing the evaluation. If it has been done by the manufacturers, this should be stated. Any consultancies or conflict of interest should be acknowledged by the investigator.

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II Circadian Variation of Cardiovascular Disease

6 Circadian Rhythmic and Environmental Determinants of 24-Hour Blood Pressure Regulation in Normal and Hypertensive Conditions

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CONTENTS

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INTRODUCTION

The biology of human beings is not constant as assumed by the concept of homeostasis. Instead, most of life's functions vary predictably, and often dramatically, during the 24-h day, the menstrual cycle, and the year. Endogenous circadian (approx 24-h) rhythms, in particular, are of great importance to cardiovascular (CV) medicine because they contribute to the 24-h patterns in blood pressure (BP) and CV events *(1)*. The staging of the peak and trough of prominent circadian rhythms in neural, endocrine, and hemodynamic functions and cyclic day–night differences in physical activity, mental strain, and posture, among others, give rise to an increased vulnerability to thrombotic, ischemic, hemorrhagic, and arrhythmic events in the morning in at-risk hypertensive and normotensive persons *(2)*. In this chapter, we discuss the relevance of these endogenous and cyclic neural, humoral, and environmental determinants to 24-h BP patterns in normal and hypertensive states.

TEMPORAL CONTROL OF CARDIOVASCULAR FUNCTION AND BLOOD PRESSURE

The 24-h variation in CV system physiology and pathophysiology arises from environmental influences, i.e., differences in physical and mental activity and stress during diurnal activity vs nocturnal sleep, and the phase relationships of a variety of endogenous circadian rhythms.

The 24-h sleep–wake cycle, the most evident circadian rhythm, is itself controlled by a multitude of fundamental sensory, motor, autonomic, hormonal, and cerebral rhythms *(3)*. It results from the alternating dominance in time of mutually inhibitory interactions between arousal and activating systems (cholinergic, serotonergic, and histaminergic nuclear groups of the rostral pons, midbrain, and posterior hypothalamus, and cholinergic neurons of the basal forebrain), on one hand, and hypnogenic or deactivating systems (medial preoptic–anterior hypothalamic region and adjacent basal forebrain, medial thalamus, and medulla) on the other. Circadian changes in autonomic nervous system activity play an important mechanistic role in the control of the sleep–wake cycle, and they also mediate the impact of sleep and wakefulness on CV function, per se. For example, serotonin, arginine vasopressin, vasoactive intestinal peptide, somatotropin, insulin, and steroid hormones and their metabolites are involved in sleep induction at night, whereas CRF, adrenocorticotropic hormone (ACTH), TRH, endogenous

opioids, and prostaglandin E_2 are involved in arousal in the morning. The cyclic 24-h pattern of these constituents is surely reflected in the phasic oscillations of CV function and status. Most biologically active substances, e.g., hormones, peptides, and neurotransmitters, among others, exhibit significant circadian variability that is superimposed on feedback control systems. Although the secretion of these substances is typically episodic, i.e., manifesting high-frequency pulses, the occurrence of the secretory episodes is "gated" by mechanisms that are coupled to sleep, itself, or to an endogenous pacemaker clock.

HUMAN SLEEP AND CIRCADIAN BLOOD PRESSURE PROFILE

Sleep is the most important and consistent source of circadian BP variation. BP in healthy normotensive subjects declines during sleep by 10–20% from the mean daytime level *(4)*. Bed-bound subjects, either normotensive *(5)* or hypertensive *(6)*, and patients with fixed heart rate (HR) *(7)*, also exhibit a significant decline in BP during sleep, which is more pronounced in women than men *(8)*. In addition to this profound, sleep-related nocturnal nadir, the typical circadian pattern of BP in diurnally active persons exhibits two daytime peaks—the first in the morning around 9 AM and the second in the early evening around 7 PM—with a small afternoon nadir around 3 PM.

The different stages of sleep depth are associated with differences in BP *(9)*. BP is lowest during the deepest stages (3 and 4) of sleep, whereas BP is more elevated during the less deep stages (1 and 2) or rapid eye movement (REM) sleep periods; however, it is still lower than when fully awake. Fluctuations in BP during REM sleep do not originate in the induction area of REM sleep, i.e., the pontine tegmental area, itself, but in the forebrain, and are likely to be influenced by factors independent of sleep *(10)*.

The question of whether or not BP significantly increases before awakening has been the subject of considerable debate *(11)*. It is difficult to determine the precise timing of arousal in every patient, and this might explain the different interpretations of the BP curves. Deep sleep density is greatest during the first part of the night, when BP rapidly declines. On the other hand, REM sleep and brief episodes of arousal in response to external stimuli are more common during the last half of the sleep span; thus, rises in BP are more frequent during this time of the night. When 24-h recorded intraarterial BP data of a large group of normal subjects

are aligned to each person's time of waking, it can be seen that the early morning rise of BP commences some hours before actual awakening from nighttime sleep. Thus, it is highly implausible that the morning BP rise results from arousal alone. Moreover, two distinct patterns of morning BP rise have been identified: a gradual rise during the latter portion of sleep that is characteristic of younger persons, and a steep rise after waking that is characteristic of older persons, which is highly responsive to mental stress *(12)*.

There is no doubt that physical and mental activity accounts for the predominant proportion of the day–night variation in BP *(13)*, as demonstrated by the close linkage between activity and BP in rotating shift workers *(14,15)*. However, there is also an intrinsic circadian component of the 24-h BP pattern, which is masked by dominant external influences *(16)*. For example, lesioning of the suprachiasmatic nucleus (SCN), the anatomical site of the body's master circadian clock, abolishes the 24-h BP and HR rhythms without affecting the sleep–wake and motor activity cycles *(17,18)*.

Important additional influences of sleep on BP may be exerted through patterns of respiration. Breathing often becomes periodic, and sporadic central apneas are frequently observed after sleep onset and during light non-REM (NREM) sleep. Oscillations in breathing occur periodically, every 20–30 s, and are associated with synchronous oscillatory fluctuation in cortical EEG activity, BP, HR, and O_2 saturation. In contrast, breathing becomes regular and BP and HR drop during deep NREM sleep. During REM sleep, breathing and HR become irregular and central apneas or hypopneas lasting 20–30 s occur sporadically, often in association with bursts of rapid eye movements. Hypertensive BP peaks, sometimes as great as 30–40 mmHg, suddenly appear and continue for the whole duration of the REM sleep stage *(19)*.

NEUROENDOCRINE INTEGRATION OF CIRCADIAN RHYTHMS AND THEIR EFFECTS ON CARDIOVASCULAR PHYSIOLOGY

The mechanisms of biological time-keeping involve a variety of neuro-humoral components that affect CV function and rhythms. For this reason, it is worthwhile to briefly review the mechanisms of biological timekeeping. Autonomic and, in general, monoaminergic systems are responsible for integrating the mechanisms and systems of biological timekeeping. The temporal organization of these systems exhibits complex interactions with the pineal gland, from which the

hormone melatonin emanates, and the SCN—the major pacemaker generator of endogenous circadian rhythms—which play key roles. The SCN is a self-sustaining oscillator whose period approximates 24 h. Three key components form the basis for biological time-measuring and time-keeping mechanisms: endogenous oscillators, photoreceptor cells synchronized by the environmental light–dark cycle, and neuroendocrine/ neuronal effectors.

The main neuroendocrine effector, melatonin, is produced by pinealocytes of the pineal gland only during environmental darkness, with a surge during the second part of the night *(20,21)*. Melatonin is not stored after synthesis; rather, it is released into the general circulation immediately after its formation *(22)*. Thus, it spreads important neuroendocrine information as to the onset, offset, and duration of darkness to the entire biology of vertebrate organisms. In mammals, photoreceptor cells in the retina convey information about the environmental light and dark cycle throughout the 24 h to the SCN and thereafter to the pineal gland via neural signals, thereby regulating the circadian rhythm of melatonin synthesis *(23,24)*. The SCN receives modulatory input from the periventricular nucleus of the thalamus *(25)*. Its norepinephrine content exhibits significant circadian rhythmicity, with the peak occurring at the beginning of the light period *(26)*. Also, circadian variation in endogenous tyrosine hydroxylase and dopamine β-hydroxylase activity, and thus catecholamine and dopamine synthesis, is demonstrated by the pineal gland *(27,28)*. Monoamines (serotonin, histamine, norepinephrine, and dopamine) play a modulatory role in regulating the neurotransmission of environmental light signals via the retinohypothalamic pathway to the SCN *(29)*. Adrenergic agonists stimulate melatonin production in the pineal gland late, but not early, during the nighttime, although this effect requires the priming of darkness during the appropriate circadian phase of their application *(30)*. Rhythmic adrenergic signals determine circadian fluctuation in cAMP-induced transcription *(31)*. At night, postganglionic fibers originating from the superior cervical ganglia release norepinephrine *(32)*. Norepinephrine regulates melatonin synthesis through β-adrenergic receptors *(33)* by mechanisms acting distal to the SCN that generate the melatonin rhythm. Hence, it seems to be involved in the regulation of melatonin output by the SCN, but it is not implicated in the regulation of the pacemaker by light *(34)*.

Altogether, the results of numerous studies suggest that sympathetic and, in general, monoaminergic mechanisms are involved in the modulation of the endogenous (master) brain and peripheral (cell and tissue)

biological clocks and rhythms. This implies that physical and emotional stimuli that drive autonomic activation may also influence the expression of endogenous circadian rhythms. The opposite is also true. The pineal gland mediates the circadian rhythm of catecholamine secretion from the adrenal medulla, as reflected by the disrupted temporal pattern of nucleolar diameters in adrenomedullary chromaffin cells after pinealectomy *(35)*. Melatonin directly modulates norepinephrine and serotonin synthesis through hypothalamic (mediobasal hypothalamus) and extrahypothalamic (amygdala and pontine brain stem) pathways *(36)*. Finally, food intake and ambient lighting conditions interact as controllers of the sympathetic nervous system, and these interactions are modulated by the ventromedial hypothalamus *(37)*. However, hypothalamic (paraventricular nucleus) norepinephrine, together with neuropeptide Y and galanin, can control the total amount and the macronutrient selection of food intake at different stages of the circadian cycle *(38)*. It is of interest that experiments on rats demonstrate that lesions of the SCN abolish circadian BP, HR, and food intake rhythms *(17)*.

In conclusion, the interactions between feedback responses to occasional environmental stimuli and endogenous circadian rhythms on monoaminergic systems result in two different effects: changes induced by external stimuli on monoaminergic neurotransmitter synthesis cause release of chemical mediators, resulting in immediate biological responses, and inherent activity in autonomic activity modulates endogenous rhythms. Feedback responses to environmental stimuli serve to synchronize endogenous rhythms of the CV system; however, under certain circumstances, their expression may be masked. Overall, the immediate adaptation of CV function to the demands of the environment is modulated by the circadian-time-dependent responsiveness of biological oscillators.

AUTONOMIC NERVOUS SYSTEM AND CIRCADIAN BLOOD PRESSURE PROFILE IN NORMAL CONDITIONS

Circadian rhythms in the functioning of the autonomous nervous system are well known; sympathetic tone is dominant during diurnal activity, whereas vagal tone is dominant during nocturnal sleep *(39–42)*. The plasma level of norepinephrine and epinephrine is greatest in the morning during the initial span of daytime activity and lowest during nighttime sleep *(43)*. Urinary catecholamine excretion also exhibits marked circadian rhythmicity of comparable phasing *(44)*. There is a strong temporal relationship between the 24-h pattern in plasma dopamine and norepinephrine/epinephrine level, indicating a

dopaminergic modulation of the circadian rhythm of sympathetic nervous system activity *(45)*.

In human beings, catecholamine sulfates are biologically inactive. In normotensive recumbent subjects, their circadian pattern is opposite that of biologically active free catecholamines *(46)*. Plasma noradrenaline and adrenaline sulfates peak during the initial portion of the sleep span. Before awakening the concentration of both free noradrenaline and adrenaline suddenly increases; while their sulfoconjugate counterparts decline. Thus, the nocturnal decrease in the concentration of biologically active catecholamines may be the consequence of the activation of an endogenous system of sulfoconjugation; conversely, deactivation of the same system late during the sleep span may contribute to the significant morning increase in the concentration of biologically active catecholamines. Temporal modulation of the gene expression of these enzymes most likely contributes to the circadian rhythm in sympathetic activity.

Environmental factors, especially the alternation of light and darkness in conjunction with the activity/sleep cycle, significantly influence the 24-h pattern of catecholamine concentration. Plasma levels of norepinephrine and its metabolite 3-methoxy-4-hydroxyphenylglycol, but not epinephrine, are strongly affected by activity, arousal, and posture *(47,48)*. Indeed, the nocturnal decrease in norepinephrine is observed even in healthy volunteers kept awake for 24 h by means of a regimented routine of forced activity and food consumption every hour. This suggests that the circadian change in norepinephrine secretion is controlled by a biological clock whose activity is apparent only when the influence of sleep, posture, and activity is removed *(49)*. Nonetheless, the evidence is convincing that the observed 24-h changes in autonomous nervous system activity and biogenic amines are not explained by a single controlling influence. Temporal patterns in external stimuli are at least, if not more, important as endogenous clock mechanisms.

NORMAL CIRCADIAN ORGANIZATION OF HUMORAL FACTORS AFFECTING THE CARDIOVASCULAR SYSTEM

Renin–Angiotensin–Aldosterone System

Circadian rhythms in prorenin, plasma renin activity (PRA), angiotensin II, and aldosterone are well documented in both normotensive and hypertensive conditions. They are demonstrable even in subjects restricted to long-term recumbence *(50–53)*. In diurnally active persons, the rhythms of plasma renin and aldosterone peak in the

morning, and they persist, although with reduced amplitude, even in persons deprived of sleep for an entire 24 h *(54)*. However, some investigators have failed to detect circadian patterns in PRA *(55,56)*, finding instead high-frequency (ultradian) oscillations of about 100-min duration that are strongly correlated with sleep-stage patterning—PRA declining during REM sleep and peaking during the transition between deep and light sleep stages *(55,57)*. This relationship is even preserved in narcoleptic patients with disrupted sleep organization *(58)*.

Circadian rhythms in renin, angiotensin II, and aldosterone *(59–61)*, but not 18-hydroxycorticosterone *(62)*, are partly dependent on dopaminergic mechanisms. The sympathetic nervous system also modulates renin-aldosterone release *(63)*. In the rat pineal gland, angiotensin-converting enzyme exhibits circadian rhythmicity in activity, with the peak occurring at the end of the daily rest span. This rhythm is under negative control by norepinephrine released from the sympathetic nerves of the pineal gland *(64)*. The endogenous circadian rhythm in PRA determines the magnitude of the response of the organism to external challenge; in this regard, the exercise-induced PRA response is markedly higher in the afternoon (4 PM) than at 4 AM *(65)*. The circadian rhythm in plasma aldosterone is predominantly modulated by the circadian rhythm in ACTH; the renin–angiotensin and dopaminergic systems play only a minor role. ACTH, which is secreted in greatest quantity during sleep, is a potent stimulus of aldosterone secretion at night. During the daytime, aldosterone is regulated in addition by the renin–angiotensin system *(61)*.

Renal Function

Circadian rhythms of renal blood flow, glomerular filtration rate, urine volume, and urinary excretions of Na, K, and Cl are well known. These rhythms are independent of temporal patterns in posture, meal timings, sleep, and activity during the 24 h *(66,67)*. In contrast, the excretion of creatinine is constant. Renal blood flow, vascular resistance, and glomerular filtration rate decline at night, but the decrease of urine flow is much more pronounced than expected, suggesting the existence of a circadian rhythm of tubular reabsorption with a nighttime peak *(68)*. A greater amount of sodium, potassium, and aldosterone is excreted during the day than night; in contrast, the natriuretic substance kallikrein is excreted in a fixed rate throughout the 24 h *(67)*. At night, when the balance between sodium-retaining and sodium-sparing mechanisms favors natriuresis, i.e., a decreased

aldosterone:kallikrein ratio, a significant correlation is detectable between sodium and potassium excretion rates as well as BP. The correlation is masked during the waking hours by the prevalence of sodium-retaining factors *(67)*. The circadian rhythm of renal sodium and potassium handling appears to be driven by the circadian rhythm of aldosterone. Dopamine may play a role in the circadian variation of water and sodium handling, as suggested by the close temporal relationship among the circadian rhythms of urinary dopamine, sodium, and water excretion *(69)*. The circadian rhythm of atrial natriuretic peptide, which peaks early in the sleep span, also plays a role as it modulates the rhythm of urinary sodium excretion *(70)*.

In summary, renal hemodynamics exhibits significant circadian rhythmicity, and this contributes to the 24-h BP variation. A number of physiological rhythms are involved, such as the ones in systemic hemodynamics, structure and permoselectivity of the glomerular basement membrane, urinary water excretion, and autonomic nervous and renin–angiotensin systems *(70)*.

Hypothalamic–Pituitary–Adrenal System

The endogenous circadian organization of the hypothalamic–pituitary–adrenal (HPA) system is paradigmatic. Rhythms in ACTH and cortisol secretion are well known, as reviewed in the classical work of Aschoff *(23)*. Moreover, the sensitivity of the adrenal cortex to endogenously produced ACTH is, in itself, circadian-time dependent and is in part responsible for the enhanced secretion of cortisol in the morning in response to stressful stimuli *(71)*. Catecholamines seem to be involved in the modulation of corticotropic function and cortisol rhythmicity. A rise in rat brain stem phenylethanolamine *N*-methyltransferase, the enzyme that converts norepinephrine to epinephrine, precedes the circadian rise in plasma corticosterone by several hours *(72)*. Pharmacological destruction of the ventral noradrenergic-ascending bundle, a pathway originating from the locus coeruleus and the A_1 and A_2 medullary groups of neurons that convey most of the catecholaminergic innervation to the paraventricular nuclei, suppresses the ACTH and cortisol circadian rhythms and causes the emergence of reduced-amplitude ultradian (short, <24-h) oscillations *(73)*. Serotonergic neurons also impart a regulatory effect *(74)*. Nonetheless, circadian variation in plasma corticosteroid level can develop in the presence of either marked norepinephrine or serotonin depletion in areas of the central nervous system that are implicated in the regulation of this periodicity *(75)*.

Hypothalamic–Pituitary–Thyroid System

The activity of this neuroendocrine axis affects the functioning of the CV system at multiple levels via direct positive inotropic and cronotropic actions, stimulation of tissue metabolic rate, and positive modulation of the agonistic sensitivity of the β-adrenergic receptors of the myocardium. Pharmacological manipulations with selective agonists and antagonists confirm that sympathetic modulation of TSH rhythmicity occurs through α_2- and β-adrenoceptors *(76)*. Dopamine inhibits the amplitude of the TSH pulses; however, its level does not decrease during the nighttime. Hence, the neuroendocrine mechanism(s) underlying the nocturnal increase in TSH secretion is not dependent on decreased dopaminergic inhibition *(77)*.

Opioid System

The endogenous opioid system is comprised of various species of peptides, many of which possess potent CV system effects. Multiple forms of opioid peptides and opioid receptors have been identified in the central nervous system and peripheral neural elements. A circadian rhythm exists in the content of free and cryptic met-enkephalin in heart tissue of both normotensive and spontaneously hypertensive rats *(78)*. Plasma β-endorphins (but not met-enkephalin) also are circadian rhythmic *(79)*, as is the binding of ligand to opiate receptors *(80)*. Involvement of both the sympathetic and parasympathetic systems in the actions of these peptides on CV function is established, although little is known to date about the mechanisms of this involvement, especially in humans. In humans, endogenous opioids modulate central nervous system BP control, and they play a role in the nocturnal decline in BP *(81)*. δ-opioid receptors might play a role in the nocturnal suppression of the sympathetic nervous system and HPA axis, considering their known inhibitory effects *(82,83)* and phase relationships of the respective circadian rhythms.

Vasoactive Peptides

Both atrial natriuretic peptide and calcitonin-gene-related peptide are circadian rhythmic, and both exert regulatory control of the 24-h BP pattern.

Atrial Natriuretic Peptide

Atrial natriuretic peptide (ANP) is a 28-amino-acid polypeptide that affects physiological functions and systems involved in BP regulation.

It suppresses angiotensin II, plasma renin activity, aldosterone, and catecholamine concentrations. It increases sodium excretion and plasma and urinary cGMP levels, and it shifts the renal pressure–natriuresis mechanism so that sodium balance can occur at lower arterial pressures. Thus, ANP lowers BP and total peripheral vascular resistance. Conspicuous or sudden elevations of ANP trigger secondary sympathetic nervous system activation, which counteracts its physiological actions. A distinct brain pool of ANP also has been identified, particularly in areas that play a role in the regulation of the CV system. Interactions of both circulating and brain ANP with the autonomic nervous system are well established. A review of the studies on ANP indicates it is principally involved in the short-term control of BP and electrolyte balance, in contrast to and in opposition of the renin–angiotensin–aldosterone system, which is primarily involved in long-term BP control *(84)*. The day–night variation in ANP level of approx 10 pmol/L is unrelated to posture. The ANP rhythm peaks between 11 PM and 4 AM, when in diurnally active normal and hypertensive persons the circadian rhythms of PRA and aldosterone are near or at their lowest levels *(61,85,86)*. In humans, the temporal pattern in plasma ANP concentration is paralleled by the circadian rhythm in the plasma concentration of the second messenger cGMP *(87)*. In chronic renal and congestive heart failure patients *(88,89)*, the circadian BP rhythm is altered in phasing; the nocturnal BP decline is blunted or even reversed. Alterations of the 24-h BP pattern are paralleled by concomitant alterations of the circadian rhythm of ANP, both before and after treatment *(90)*.

Calcitonin Gene-Related Peptide

Calcitonin gene-related peptide (CGRP) is a 37-amino-acid peptide involved in a variety of metabolic and behavioral functions *(91)*. CGRP-containing fibers are found throughout the CV system, in the heart and especially within the coronary arteries, sinoatrial and atrioventricular nodes, and papillary muscles *(92)*. Most likely CGRP blood levels are representative of peptide spillover, with release from nerve terminals that promote vasodilatation. A circadian rhythm in plasma CGRP has been demonstrated in both normotensive *(93,94)* and hypertensive *(95)* persons. In vivo and in vitro studies suggest that CGRP is a potent vasodilator. Intravenous infusion of humans with CGRP in pharmacological doses decreases mean BP and total peripheral resistance and increases HR *(96)*. Bolus injection of the peptide results in increased PRA and plasma aldosterone concentrations *(97)*.

Plasma CGRP levels increase in healthy subjects after assuming an upright position or following low-dose infusion of angiotensin II *(98)*. Thus, the renin–angiotensin system could modulate plasma CGRP secretion either directly through a vasopressor effect on the peripheral blood vessels or indirectly through neurohormonal mechanisms that modulate vascular tone and BP *(99)*.

CIRCADIAN BLOOD PRESSURE CHANGES IN DIFFERENT HYPERTENSIVE CONDITIONS

In many diverse pathological conditions, alterations in the circadian rhythm of the neurohumoral factors known to affect the CV system, either primarily or secondarily to the disruption of autonomic nervous system activity, are reflected by a persistent alteration of the 24-h BP pattern. A reduced or reversed nocturnal decline in BP is common in orthostatic autonomic failure *(100)*, Shy-Drager syndrome *(101)*, vascular dementia *(102)*, Alzheimer-type dementia *(103)*, cerebral atrophy *(104)*, cerebrovascular disease *(105,106)*, ischemic arterial disease after carotid endarterectomy *(107)*, neurogenic hypertension *(108)*, fatal familial insomnia (FFI) *(109)*, diabetes *(110)*, catecholamine-producing tumors *(111,112)*, Cushing's syndrome *(113)*, exogenous glucocorticoid administration *(114)*, mineralocorticoid excess syndromes *(115)*, Addison's disease *(116)*, pseudohypoparathyroidism *(117)*, sleep apnea syndrome *(118)*, normotensive and hypertensive asthma *(119)*, chronic renal failure *(120,121)*, severe hypertension *(122)*, salt-sensitive essential hypertension *(123)*, gestational hypertension *(124)*, toxemia of pregnancy *(125)*, essential hypertension with left ventricular hypertrophy *(126)*, renal *(127)*, liver *(128)*, and cardiac transplantation *(129)* related to immunosuppressive treatment, congestive heart failure *(90,130)*, and recombinant human erythropoietin therapy *(131)*. A circadian profile characterized by daytime hypertension and nighttime hypotension has been described in hemodynamic brain infarction associated with prolonged disturbance of the blood–brain barrier *(132)*. In these patients, the range of variation in BP between the day and sleeptime BP level is significantly increased from expected—to 20% for SBP and 23% for DBP.

Disturbances of the circadian rhythm of autonomic nervous system activity and neurohumoral factors that play a role in central and/or peripheral BP regulation are clearly involved in the genesis of altered BP 24-h patterns. An imbalance of sympathetic vs parasympathetic

activity is the major determinant of the alterations. This is true not only for the various forms of neurogenic dysautonomias, but in diabetes and chronic renal failure where change in the circadian BP pattern is minimal *(133)* or absent *(134)* before the onset of autonomic neuropathy. In chronic heart failure, tonic activation of the sympathetic nervous system throughout the day and night is present and seems to be the major determinant of the observed changes in the BP 24-h pattern. Experiments on rats demonstrate that the altered BP pattern of heart failure is independent of changes in locomotor activity *(135)*. An identical imbalance of the circadian rhythm of autonomic activity has been demonstrated in essential hypertensive patients who exhibit a blunted nocturnal BP decline *(136)*. However, absence of the nocturnal fall in BP, conventionally defined as a sleep-time decrease in BP equal to less than 10% of the daytime mean, does not necessarily imply an obliteration of the 24-h BP rhythm. This has been demonstrated in chronic renal insufficiency *(137)*, where a significant circadian rhythm in BP of reduced amplitude and peak time shifted toward the nighttime hours is frequently found; this type of pattern also is seen in fatal familial insomnia or FFI *(109)*.

FFI is a prion disease with anatomical lesions characteristically found in the thalamus, but not in the SCN *(138)*. The cardinal feature of FFI, a total and sustained disruption of the sleep–wake cycle, constitutes a unique, albeit dramatic, opportunity to observe the effect of the chronic absence of sleep on human circadian rhythms. In FFI, a dominant 24-h rhythm is detectable both in BP and HR *(109)*. However, as a combined result of the decrease in amplitude and shift in phase, the nocturnal fall in BP is lost during an early stage of the disease, when the nocturnal bradycardia is still preserved. Only in the terminal stage of FFI is complete obliteration of any significant 24-h variation found. In addition, no association with the pattern of motor activity or meals can be detected. Important features of FFI are the progressive alterations of neurohormonal *(139,140)* and CV rhythms *(109)*, indicating that this prion disease is able to disturb, and eventually obliterate, the endogenous circadian rhythmicity of those affected. Nocturnal peaks of neurohormonal secretions, similar to those found in FFI and representing the reversal of the normal sleep-related inhibition of secretion, have been produced in healthy subjects with acute deprivation of sleep *(141–143)*.

The previously described findings support the existence of an intrinsic component to the 24-h pattern in BP, which is independent of the sleep–wake and rest–activity cycles. A dissociation of the 24-h BP

pattern peak from any specific behavioral event, as found in FFI, can be observed also among healthy subjects *(144)*. Another study has demonstrated the patterns of BP and HR are dissociated in transgenic rats, with BP being out of phase with the rest–activity and light–dark cycles *(145)*.

Absence of the normal nocturnal decline in BP appears to carry a higher CV and cerebral risk by prolonging the time beyond diurnal waking when the elevated BP load is exerted on target tissues and organs. Recent data support this view; the average nighttime BP level and magnitude of the nocturnal BP fall are significantly correlated with target organ damage, either cardiac *(126,146–151)*, cerebral *(105,152,153)*, or renal *(154–157)*. A large prospective study demonstrated that CV morbidity is higher in nondipper (<10% decline from daytime BP level during sleep) than dipper (10–20% decline from daytime BP level during sleep) hypertensive women *(158)*. Left ventricular structure seems more load-dependent in women than in men with essential hypertension, as demonstrated by higher echocardiographic indices of left ventricular hypertrophy in female, but not male, nondippers than dippers *(151)*. Sodium sensitivity may be a marker of enhanced risk of renal and CV complications, and it is of interest that in sodium-sensitive essential hypertensives there is loss of the normal nocturnal sleep-time BP decline *(159)*.

A growing number of studies also indicate the BP rate of rise coincident with the commencement of diurnal activity is an independent predictor of hypertensive target organ damage, particularly the peak occurrence of acute CV events at this time of day *(160,161)*. Interestingly, studies reveal that the 24-h pattern, with the characteristic morning peak, in the occurrence of both ischemic *(162)* and hemorrhagic *(163)* stroke is the same in normotensive and hypertensive persons. Moreover, other CV events, such as acute aortic dissection, display prominent 24-h variation, with a significant morning peak in both hypertension and normotension *(164)*. Taken together, these findings strengthen the suggestion that the morning surge in BP (whether in the presence or absence of hypertension) is a crucial determinant of the rupture of a vulnerable and critically weakened arterial wall *(165)*.

Based on these data, restoration of the normal circadian BP pattern should be considered a therapeutic goal in all of those conditions in which it is abnormal. However, the feasibility and means of achieving this, plus the means of conducting an evaluation of the prospective significance of such a normalization, have yet to be sufficiently addressed.

CONCLUSION

In the majority of people BP and many other physiological CV functions exhibit a circadian pattern that peaks at the commencement of the activity span in the morning. These 24-h changes are the consequence of the circadian rhythm in autonomic function and activity plus the abrupt rise in sympathetic outflow and circulating catecholamines coincident with the commencement of daytime activity. As such, it appears that external behavioral influences are the main determinants of the day–night BP variation, and neurohumoral modulations as well as anatomo-pathological changes may differentially intervene in normal conditions and various disease states. Nonetheless, the BP rhythm has a clear genetic basis that is driven by a variety of neurohumoral constituents, each exhibiting intrinsic circadian rhythmicity. Moreover, the fact that the BP rhythm loses or reverses its nocturnal fall in a variety of pathological conditions in which sleep and activity show only minor change constitutes additional evidence for an endogenous, although not predominant, component.

The temporal organization of BP over 24 h is relevant, particularly to the treatment of hypertension. Antihypertensive medications may need to be selected for their differential time-dependent effects on hemodynamic mechanisms to achieve efficient control of BP throughout both the day and night; but this issue will be discussed in great detail in a different chapter.

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7 Circadian Variation of Blood Pressure in the Population at Large

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CONTENTS

INTRODUCTION

Ambulatory blood pressure (ABP) measurement has several advantages. ABP readings are obtained outside the medical environment and are free of the so-called white coat effect *(1,2)* often seen when the blood pressure (BP) is conventionally measured. Therefore, the average BP level on ABP measurement provides a better estimate of a subject's usual BP than conventional readings *(3)*. In addition, BP is recorded during the habitual daily activities, both working and resting periods, and during episodes of emotional stress and sleep. The way in which a subject's BP is modulated throughout the day to cope with these

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various levels of physical and emotional activity may provide meaningful pathophysiological information *(4)*. Some investigators have demonstrated that the amplitude of the diurnal BP profile is characteristic for an individual *(5)*, or that a blunted or absent nocturnal fall in BP is correlated with a worse cardiovascular prognosis *(4,6–8)*. These views explain the growing interest in methods to describe the diurnal BP profile and its determinants.

More than 20 yr ago, Raferty et al. already demonstrated that the diurnal BP rhythm is preserved during bed rest and remains present in patients with an artificial pacemaker *(4)*. The autonomic nervous system and other hormonal mechanisms are probably involved in maintaining the diurnal BP profile *(4,9,10)*. For instance, plasma renin activity and the plasma aldosterone concentration show a circadian rhythm in normotensive subjects as well as in hypertensive patients with levels that increase in late afternoon and peak in the early morning *(10)*. This circadian variation of renin and aldosterone might represent a compensatory effect to maintain BP homeostasis during sleep *(10)*. However, the existence of an endogenous circadian BP rhythm remains controversial. Recent studies *(11)* addressed the possible genetic influences on BP variability. For instance, homozygous carriers of the insertion/deletion polymorphism of the angiotensin-converting enzyme gene may show a blunted nocturnal fall in systolic BP *(11)*. Moreover, several external and lifestyle factors, such as physical and mental activity, emotions, smoking, and alcohol intake, also influence the diurnal BP profile. However, even if the circadian BP curve would not be endogenously modulated, it remains possible that the response of the BP to daily activities is an important individual characteristic. Indeed, the amplitude of the BP response is potentiated or dampened by cardiovascular control mechanisms, and the integration of these mechanisms might differ between individual subjects *(4)*.

OVERVIEW OF METHODS USED TO DESCRIBE THE DIURNAL BP PROFILE

Nocturnal BP Fall and Night:Day Ratio

The nocturnal BP fall and the night:day ratio can be computed from the average BP during the day and night. The nocturnal BP fall is usually calculated by subtracting the average nighttime from the average daytime BP. These two measures of the difference between the high and low BP spans of the day are easy to calculate but require the definition of arbitrary daytime and nighttime periods *(4)*.

Clock-Time-Independent Method

The most meaningful and scientifically sound method for defining daytime and nighttime BP would be to calculate the pressures for the intervals during which the subject is awake or asleep. Daytime and nighttime are usually delineated based on the times that subjects go to bed at night and get out of bed in the morning. However, these in-bed and out-of-bed periods do not necessarily coincide with the actual periods of sleep and wakefulness. But because it is virtually impossible to note the time at which one is actually falling asleep and waking up, the times of getting in bed for the night and getting out of bed for the day probably provide the most reasonable approximation for practical purposes. A disadvantage of using the times of going to bed and rising is that the periods during which the subjects are awake during the night or take a nap during the day are not accounted for. Some authors report that the inclusion of daytime sleep in the total asleep period is of great importance. Others did not find a clinically relevant difference in BP between the "real" and "conventional" asleep and awake periods *(12)*. More recently, some investigators used a wrist actigraph (Mini-Motionlogger Actigraph, Ambulatory Monitoring, Inc., Ardsley, NY) to identify all actual awake and asleep periods during the 24-h period *(13)*. Subjects have to wear this compact watch-sized device on the wrist of the nondominant arm. It senses motion in three planes as accelerations above the threshold of normal motion of human beings. This device has been validated to distinguish sleep from wakefulness with over 88% accuracy.

Clock-Time-Dependent Method

Another method consists of predefining fixed clock times to calculate the daytime and nighttime BP. This can be done by the "wide" or the "narrow" approach. In the wide approach, the full 24-h period is covered. For example, the 1990 consensus document of the Scientific Committee *(3)* proposed the daytime to last from 7 AM to 10 PM and the nighttime from 10 PM to 7 AM, but other dividing times have also been used. A drawback of the wide approach is that in most instances these wide clock times do not closely correspond to the waking and sleeping hours and that the day and the night may contain variable proportions of the awake and asleep periods *(12)*. In the narrow approach the morning and evening intervals, during which BP increases and decreases rapidly, are excluded from the analysis. Most often daytime is defined as lasting from 10 AM to 8 PM and nighttime from midnight to 6 AM. Other intervals have also been proposed *(12)*. A drawback of the narrow

approach is that not all available information is used for analysis. Another disadvantage is that it is still possible that subjects go to bed or wake up outside the predefined transition periods *(12)*.

Square-Wave Method

The square-wave method represents an individual 24-h BP profile by a waveform consisting of two alternating contiguous periods of constant low and high pressure. Determination of the times of transition between those two periods is performed individually using a least-square error criterion. However, when this method is applied without limitation, one extreme BP value or a short-lasting increase or decrease in BP may be erroneously identified as the interval of low or high BP. This can be avoided by the implementation of restrictions. For instance, one may require that the high-pressure period has to last at least 10 h and the low-pressure period at least 6 h. A disadvantage of this method is that it identifies periods of high and low BP, which will coincide with the day and the night in most instances, except when the diurnal pattern is reversed. Furthermore, the correspondence of the transition times with the in-bed and out-of-bed times is limited, especially for subjects with small awake–asleep differences in BP *(12,14)*.

Cumulative-Sum (Cusum) Analysis

The cusum method consists of selecting a reference value, such as the mean 24-h BP, and subtracting it from each successive BP measurement. The successive deviations of each ABP reading from the reference value are then added and plotted against time. From these cusum plots, several quantitative measures of the diurnal profile can be derived. The cusum plot height is the difference between the maximum and minimum values of the cusum plot. It reflects both the extent and the duration of the nocturnal fall in BP. The cusum-derived crest and trough BP are defined as the highest and lowest time-weighted mean BP, respectively, sustained during a period of at least 6 h. The cusum-derived alteration magnitude is calculated by subtracting the cusum-derived trough BP from the cusum-derived crest BP *(14)*. The cusum method has the advantage that there is no need to define fixed daytime and nighttime intervals. However, just like the square-wave approach, the cusum method is vulnerable to falsely identifying periods of high and low BP, which do not necessarily coincide with the day and the night. Furthermore, the 6-h crest period is relatively short when it is meant to represent the day, but the method allows specifying longer intervals *(12,14)*.

Fourier Method

The most frequently used strategy for modeling the 24-h BP curve is the cosinor method, which is equivalent to a Fourier series with only one harmonic with a period of 24 h. This method has been criticized, however, because of the incorrect assumption that there are exactly 12 h between the acrophase (peak) and bathyphase (trough) of the wave and that the distances of the peak and the trough to the mean value are identical. The fit of the cosinor method can be markedly improved by adding harmonics with shorter periods than 24 h. The use of a Fourier model with four harmonics (cosine functions with periods of 24, 12, 8, and 6 h) has been recommended for use in all subjects, because this approach standardizes the degree of smoothing of the input data. It also offers an acceptable compromise between the accuracy and the complexity of the mathematical procedures required to adequately describe the diurnal BP profile in most subjects. For each of the four harmonics and for the global Fourier curve, the amplitude and the acrophase can be computed. The amplitude is half the difference between each curve's minimum and maximum, and the acrophase is the time lag between the maximum and midnight. Initially, the application of the Fourier technique necessitated that the data points be equidistant. More recently, a weighting procedure (weighted Fourier analysis) was developed, which takes into account that the interval between successive BP readings is variable. The coefficients of the weighted model are estimated using weighted linear regression analysis with the time interval between successive readings as weighting factor. Prior to the application of Fourier analysis, the presence of a significant diurnal rhythm should be tested against the hypothesis of pure random variation using the one-sample runs test *(14–16)*.

DESCRIPTION OF THE DIURNAL BP PROFILE AND ITS DETERMINANTS

The Belgian Population Study

The ABP was initially measured in 399 subjects (58%) of a random sample of the population of a small town *(5)*. Average (±SD) age was 49 ± 15 yr. The one-sample runs test was compatible with a significant diurnal rhythm in 370 subjects (93%). The daytime period was defined as the interval from 10 AM to 8 PM and nighttime as the interval from midnight to 6 AM. The night:day BP ratio averaged 0.87 ± 0.07 systolic and 0.81 ± 0.08 diastolic. The nocturnal BP fall was normally

distributed and averaged 16 ± 9 mmHg systolic and 14 ± 7 mmHg diastolic. The amplitude of the diurnal BP curve fitted by Fourier analysis averaged 16 ± 5 mmHg systolic and 14 ± 4 mmHg diastolic. The acrophase occurred in most recordings between 9 AM and 9 PM and averaged 15:54 ± 4:47 systolic and 15:11 ± 4:20 diastolic.

In a more extended sample (313 men and 317 women, age 20–88 yr, all without BP-lowering treatment) of the same population, the determinants of the diurnal BP curve were identified *(17)*. Table 1 shows some calculated parameters of the diurnal BP profile, i.e., the nocturnal BP fall, the cusum-derived parameters, and the Fourier amplitudes. Most of these measurements were similar in men and women. Tables 2 and 3 show the correlates of the parameters describing the diurnal BP curve in men and women separately. The main determinants of the crest and trough BP in both sexes were age, body mass index, and pulse rate. These predictor variables were mostly associated with an increase in the crest and trough BP levels. In male and female smokers, the trough systolic BP was 2–3 mmHg lower than in nonsmokers. In both sexes, the nocturnal fall in systolic BP increased with the height of the conventionally measured BP (CBP) and was nearly 2 mmHg greater in male smokers than in male nonsmokers. The nocturnal fall in diastolic BP decreased curvilinearly with advancing age. The cusum-derived circadian alteration magnitude and the cusum-derived plot height increased with a higher systolic and diastolic CBP level, whereas the cusum plot height of the diastolic BP was inversely correlated with age in men and women. The amplitudes of the overall Fourier curve and of the first and second harmonics tended to increase in both sexes with a higher CBP. The amplitude of the first harmonic of diastolic BP was inversely correlated with age in men and women, whereas the opposite was observed for the amplitude of the fourth harmonic of systolic BP. Among men and women, current smokers tended to have slightly greater amplitudes of one or more of the harmonics. In women the amplitude of the fourth harmonic of systolic and diastolic BP increased with greater body mass index.

International Database

An international database *(18)* included the ABP recordings of 4765 normotensive and 2555 untreated hypertensive subjects. The study population consisted of 3730 men and 3590 women with an average age of 48 ± 16 yr. Daytime and nighttime were defined ranging from 10 AM to 8 PM

Table 1
Parameters of the Diurnal Blood Pressure Curve in a Belgian Population Sample

	Men		*Women*
Number	313		317
Variance			
Sys_v $(mmHg)^2$	71 ± 19		69 ± 18
Dia_v $(mmHg)^2$	62 ± 20		63 ± 18
Nocturnal fall			
Sys_{nf}	17.8 ± 8.7		17.3 ± 8.2
Dia_{nf}	14.7 ± 6.9		15.3 ± 6.3
Cusum parameters			
Sys_c	131 ± 11	*	126 ± 11
Dia_c	82 ± 9	*	79 ± 8
Sys_t	107 ± 10	*	103 ± 10
Dia_t	61 ± 8	*	58 ± 7
Sys_{am}	24.2 ± 8.2		23.0 ± 7.4
Dia_{am}	20.4 ± 7.1		20.5 ± 6.2
Sys_{ph} (mmHg × h)	103 ± 36		98 ± 32
Dia_{ph} (mmHg × h)	87 ± 32		88 ± 27
Fourier amplitudes			
Sys_a	17.0 ± 5.0		16.3 ± 4.9
Dia_a	14.4 ± 5.0		14.2 ± 4.2
Sys_1	11.3 ± 4.8		10.8 ± 5.9
Dia_1	9.6 ± 4.2		9.6 ± 4.0
Sys_2	5.8 ± 2.9		5.9 ± 4.1
Dia_2	4.8 ± 2.7		5.0 ± 3.1
Sys_3	3.8 ± 2.1		3.6 ± 2.4
Dia_3	3.4 ± 2.2		3.1 ± 2.2
Sys_4	3.6 ± 2.1		3.6 ± 2.1
Dia_4	3.3 ± 2.1		3.2 ± 2.0

Values are means ± standard deviation.

*$p < 0.001$ for the difference between men and women.

Unless otherwise indicated, variables are expressed in mmHg. Sys, Dia = systolic, diastolic pressure; Sys_v, Dia_v = within subject variance of all ambulatory readings over 24 h; Sys_{nf}, Dia_{nf} = nocturnal fall in pressure; Sys_a, Dia_a = overall amplitude; Sys_c, Dia_c = cusum-derived crest pressure; Sys_t, Dia_t = cusum-derived trough pressure; Sys_{am}, Dia_{am} = cusum-derived circadian alteration magnitude; Sys_{ph}, Dia_{ph} = cusum plot height; Sys_1, Sys_2, Sys_3, Sys_4, Dia_1, Dia_2, Dia_3, Dia_4 = amplitudes of the 1st through 4th harmonic.

From ref. *17*.

Table 2
Correlates of the Parameters Describing the Diurnal Blood Pressure Curve in 313 Men of a Belgian Population Sample

	R^2	*INT (mmHg)*	*BP (mmHg)*	*Age (yr)*	*Age^2 (yr^2)*	*BMI (kg/m^2)*	*Rate (bpm)*	*SCa mmol/L*	*γGT (U/L)*	*SMK (0, 1)*
Blood pressure										
Sys_{24}	0.099	118.4	nc	–0.864	0.00920	0.79	ns	ns	ns	ns
Dia_{24}	0.161	42.3	nc	ns	ns	0.56	0.16	ns	3.57	ns
Sys_{d}	0.093	106.7	nc	ns	ns	0.78	ns	ns	ns	ns
Dia_{d}	0.126	48.5	nc	ns	ns	0.65	0.18	ns	ns	ns
Sys_{ni}	0.093	118.7	nc	–1.191	0.01252	0.63	ns	ns	ns	ns
Dia_{ni}	0.126	33.6	nc	0.082	ns	0.39	0.15	ns	4.35	ns
Sys_{c}	0.088	126.1	nc	–0.828	0.00888	0.89	ns	ns	ns	ns
Dia_{c}	0.108	53.1	nc	ns	ns	0.68	0.16	ns	ns	ns
Sys_{t}	0.090	110.0	nc	–0.865	0.00924	0.63	ns	ns	ns	–1.97
Dia_{t}	0.174	20.0	nc	0.598	–0.00510	0.38	0.15	ns	3.96	ns
Variance										
Sys_{v}	0.049	38.3	0.261	ns	ns	ns	ns	ns	ns	ns
Dia_{v}	—	—	—	—	—	—	—	—	—	—
Nocturnal fall										
Sys_{nf}	0.031	7.5	0.076	ns	ns	ns	ns	ns	ns	2.11
Dia_{nf}	0.030	16.8	ns	ns	–0.00084	ns	ns	ns	ns	ns
Cusum parameters										
Sys_{am}	0.047	11.4	0.097	ns	ns	ns	ns	ns	ns	2.10
Dia_{am}	0.031	15.3	0.089	ns	–0.00064	ns	ns	ns	ns	ns

Sys_{ph}	0.049	43.0	0.452	ns	ns	ns	ns	ns	ns	8.83
Dia_{ph}	0.032	65.5	0.457	–0.271	ns	ns	ns	ns	ns	ns
Fourier parameters										
Sys_a	0.046	23.2	0.054	ns	ns	ns	ns	–5.56	ns	ns
Dia_a	—	—	—	—	—	—	—	—	—	—
Sys_1	0.018	6.2	0.040	ns	ns	ns	ns	ns	ns	ns
Dia_1	0.022	10.7	ns	ns	—0.00043	ns	ns	ns	ns	ns
Sys_2	0.049	1.0	0.036	ns	ns	ns	ns	ns	ns	0.71
Dia_2	—	—	—	—	—	—	—	—	—	—
Sys_3	0.017	10.0	ns	ns	ns	ns	ns	–2.74	ns	ns
Dia_3	—	—	—	—	—	—	—	—	—	—
Sys_4	0.020	2.6	ns	0.021	ns	ns	ns	ns	ns	ns
Dia_4	—	—	—	—	—	—	—	—	—	—

Dependent variables: unless otherwise indicated in this footnote, the dependent variables are expressed in mmHg. Sys, Dia = systolic, diastolic pressure; Sys_{24}, Dia_{24} = 24-h ambulatory blood pressure; Sys_d, Dia_d = daytime blood pressure; Sys_{ni}, Dia_{ni} = nighttime blood pressure; Sys_c, Dia_c = cusum-derived crest pressure; Sys_t, Dia_t = cusum-derived trough pressure; Sys_v, Dia_v = within-subject variance of all ambulatory readings over 24 h ($mmHg^2$); Sys_{nf}, Dia_{nf} = nocturnal fall in pressure; Sys_{am}, Dia_{am} = cusum-derived circadian alteration magnitude; Sys_{ph}, Dia_{ph} = cusum plot height (mmHg × h); Sys_a, Dia_a = overall amplitude; Sys_1, Sys_2, Sys_3, Sys_4, Dia_1, Dia_2, Dia_3, Dia_4 = amplitudes of the first through forth harmonic.

Regression model: INT = intercept. The following explanatory variables were considered: the level of blood pressure on conventional measurement at home (BP), age (linear and squared term), body mass index (BMI), pulse rate in the presence of an observer, serum total calcium (SCa), log. γ-glutamyltransferase (γGT), current smoking habits (SMK, coded 0 for nonsmokers and 1 for smokers) and the urinary Na^+/K^+ ratio. All regression coefficients given in the table were significant ($p < 0.05$). —indicates that none of the correlations between the dependent and explanatory variables was significant. nc = not considered for entry into the regression model. ns = not significant.

From ref. *17*.

Table 3
Correlates of the Parameters Describing the Diurnal Blood Pressure Curve in 317 Women of a Belgian Population Sample

	R^2	*INT (mmHg)*	*BP (mmHg)*	*Age (yr)*	*Age^2 (yr^2)*	*BMI (kg/m^2)*	*Rate (bpm)*	*γGT (U/L)*	*SMK (0, 1)*	*Na^+:K^+*	*Pill (0, 1)*
Blood pressure											
Sys_{24}	0.280	94.0	nc	−0.635	0.00873	0.56	0.13	5.93	ns	ns	4.14
Dia_{24}	0.090	50.4	nc	ns	ns	0.23	0.12	4.52	ns	ns	ns
Sys_d	0.204	88.7	nc	ns	0.00245	0.43	0.14	5.25	ns	ns	5.32
Dia_d	0.074	57.8	nc	ns	ns	0.20	0.11	3.33	ns	ns	2.55
Sys_{ni}	0.236	88.6	nc	−0.989	0.01155	0.60	0.18	6.76	ns	ns	ns
Dia_{ni}	0.119	38.0	nc	0.078	ns	ns	ns	6.75	ns	ns	ns
Sys_c	0.261	84.5	nc	ns	0.00293	0.62	0.17	5.26	ns	ns	5.29
Dia_c	0.090	58.8	nc	ns	ns	0.33	0.13	ns	ns	0.66	ns
Sys_t	0.267	82.8	nc	−0.759	0.00937	0.57	0.17	6.63	−2.91	ns	3.74
Dia_t	0.129	27.1	nc	0.587	−0.00481	ns	0.12	6.00	ns	ns	2.29
Variance											
Sys_v	0.125	19.9	0.375	ns	ns	ns	ns	ns	ns	1.55	ns
Dia_v	0.036	35.1	0.375	ns	ns	ns	ns	ns	ns	ns	ns
Nocturnal fall											
Sys_{nf}	0.047	13.7	0.107	ns	ns	−0.37	ns	ns	ns	ns	ns
Dia_{nf}	0.021	16.0	ns	ns	−0.00069	ns	ns	ns	ns	ns	ns
Cusum parameters											
Sys_{am}	0.093	5.8	0.136	ns	ns	ns	ns	ns	2.53	ns	ns
Dia_{am}	0.079	13.1	0.120	ns	ns	ns	ns	−3.71	2.09	0.50	ns

Sys_{ph}	0.070	35.7	0.488	ns	ns	ns	ns	ns	11.29	ns	ns
Dia_{ph}	0.058	61.0	0.500	–0.252	ns	ns	ns	–14.25	10.40	ns	ns
Fourier parameters											
Sys_a	0.108	3.6	0.102	ns	ns	ns	ns	ns	1.34	ns	ns
Dia_a	0.044	8.0	0.071	ns	ns	ns	ns	ns	ns	0.35	ns
Sys_1	0.023	10.2	ns	ns	ns	ns	ns	ns	1.95	ns	ns
Dia_1	0.052	7.3	0.055	–0.045	ns	ns	ns	ns	1.13	ns	ns
Sys_2	0.042	–0.5	0.054	ns	ns	ns	ns	ns	ns	ns	ns
Dia_2	0.033	0.4	0.062	ns	ns	ns	ns	ns	ns	ns	ns
Sys_3	0.051	6.6	ns	–0.173	0.00191	ns	ns	ns	0.23	ns	ns
Dia_3	—	—	—	—	—	—	—	—	—	ns	ns
Sys_4	0.056	1.1	ns	ns	0.00024	0.08	ns	ns	ns	ns	ns
Dia_4	0.016	1.7	ns	ns	ns	0.06	ns	ns	ns	ns	ns

Dependent variables: Unless otherwise indicated in this footnote, the dependent variables are expressed in mmHg. Sys, Dia = systolic, diastolic pressure; Sys_{24}, Dia_{24} = 24-h ambulatory blood pressure; Sys_d, Dia_d = daytime blood pressure; Sys_{ni}, Dia_{ni} = nighttime blood pressure; Sys_c, Dia_c = cusum-derived crest pressure; Sys_t, Dia_t = cusum-derived trough pressure; Sys_v, Dia_v = within-subject variance of all ambulatory readings over 24 h ($mmHg^2$); Sys_{nf}, Dia_{nf} = nocturnal fall in pressure; Sys_{am}, Dia_{am} = cusum-derived circadian alteration magnitude; Sys_{ph}, Dia_{ph} = cusum plot height (mmHg × h); Sys_a, Dia_a = overall amplitude; Sys_1, Sys_2, Sys_3, Sys_4, Dia_1, Dia_2, Dia_3, Dia_4 = amplitudes of the first through forth harmonic.

Regression model: INT = intercept. The following explanatory variables were considered: the level of blood pressure on conventional measurement at home (BP), age (linear and squared term), body mass index (BMI), pulse rate in the presence of an observer, serum total calcium (SCa), log. γ-glutamyltransferase (γGT), current smoking habits (SMK, coded 0 for nonsmokers and 1 for smokers), the urinary Na^+:K^+ ratio and intake of oestroprogestogens (pill, coded 0 or 1). All regression coefficients given in the table were significant ($p < 0.05$). — indicates that none of the correlations between the dependent and explanatory variables was significant. nc = not considered for entry into the regression model. ns = not significant.

From ref. *17*.

and from midnight to 6 AM, respectively. In all subjects combined, the daytime BP averaged 129 ± 17 mmHg systolic and 79 ± 12 mmHg diastolic and the nighttime BP 113 ± 17 mmHg systolic and 66 ± 12 mmHg diastolic. The nocturnal BP fall averaged 17 ± 11 mmHg systolic and 14 ± 8 mmHg diastolic. The corresponding night:day ratios were 0.87 ± 0.08 and 0.83 ± 0.10, respectively. These estimates were similar to those obtained in the Belgian population study.

Determinants of the Diurnal BP Profile

Age, Sex, and Body Mass Index

The nocturnal BP fall and the night:day ratio showed a curvilinear correlation with age (Fig. 1), compatible with a smaller nocturnal decrease in BP and a higher night:day ratio in older subjects, especially those older than 70 yr. Similar observations for systolic and diastolic BP have been reported in other European *(19–21)* and Asian *(22–24)* populations. In general, older people spend more time in bed than younger people, but they experience reduced slow-wave sleep, more nighttime wakefulness, and increased fragmentation of sleep by awake periods. These age-related changes in the circadian sleep–wake rhythm probably explain why the highest night:day ratios were observed in older subjects. After adjusting for age and other significant covariates (CBP level, continent of residence, and technique of ambulatory measurement), the nocturnal BP fall was greater in men than in women, whereas the systolic night:day ratio was slightly smaller in males. Accounting for body mass index reduced the sex difference in the nocturnal fall of diastolic BP to a nonsignificant level.

Normotension vs Hypertension

A higher diastolic CBP was associated with an elevated night:day ratio, i.e., a lesser nocturnal fall in diastolic BP. This association might be partially explained by the possible inclusion of some subjects with secondary hypertension in the database. Indeed, such subjects usually have a considerably elevated BP, whereas their diurnal BP profile is often flattened or even inverted. After adjusting for significant covariates, hypertensive subjects tended to have a larger nocturnal BP fall than normotensive subjects.

Technique of Ambulatory Recording

After adjustment for significant covariates, the nocturnal BP fall was smaller and the night:day ratios were larger in subjects whose BP had been recorded with an auscultatory rather than an oscillometric technique

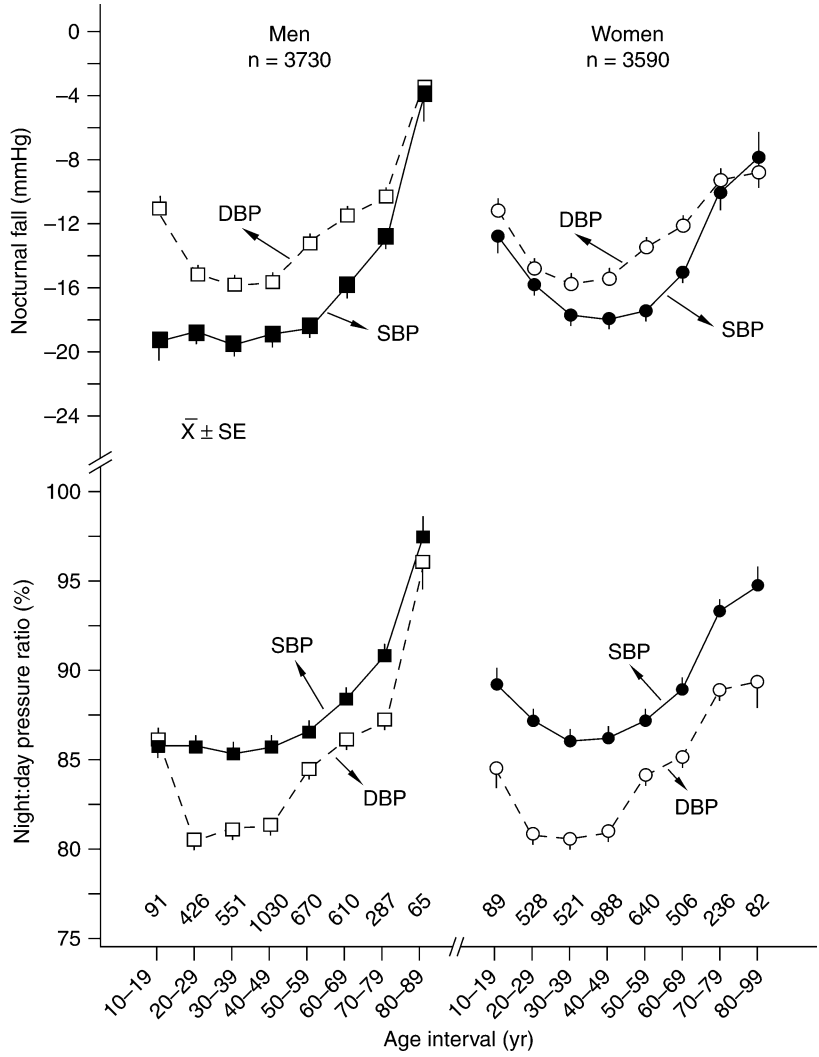

Fig. 1. Nocturnal blood pressure (BP) fall (top) and night:day ratios (bottom) for systolic BP (filled symbols) and diastolic BP (open symbols) in 10-yr age classes in 3730 men (left) and 3590 women (right) from an international database. For each sex and age group, the number of subjects contributing to the mean (±SE) is given. (From ref. *18*.)

for ambulatory BP measurement. However, the international database was not designed to identify differences between two recording techniques, and confounding or aspecific factors could therefore have been involved.

Ethnicity

Of the 7320 subjects, 3799 lived in northern Europe, 757 in southern Europe, 2213 in Asia, and 551 in other continents (South America, Australia, and North America). With adjustments for significant covariates applied, subjects living in northern and southern Europe showed a similar nocturnal BP fall and similar night:day ratios for systolic and diastolic BP. They were therefore pooled for further analysis. The night:day ratios were compatible with larger nocturnal BP falls in Europeans than in Asians (96% Japanese). Selective recruitment, confounding, and methodological differences are some possible explanations for the apparently lesser nocturnal BP fall in the Asians. However, a lesser nocturnal BP fall has been observed in at least four independent studies in the Far East (Japan *[25,26]* and China *[27]*). This suggests that the higher night:day ratios in Asian populations could be real and attributable at least in part to genetic background, lifestyle, or both.

More recently, Profant et al. *(28)* performed a meta-analysis to compare circadian BP patterns between American and non-American blacks and whites. Their meta-analysis revealed that the nocturnal BP fall was smaller in blacks than in whites, but this difference only reached statistical significance in non-American blacks. Although the authors admit that they could not adequately control for several factors known to influence BP (e.g., age, gender, body mass index) and that there were many methodological differences between the studies, they nevertheless concluded that the effect of ethnicity on the BP pattern might be different in Americans and non-Americans of black ancestry.

Nondippers vs Dippers

Nondipping profiles were defined as showing a night:day ratio of 1 or higher for both systolic and diastolic BP. Only 3.2% (233 persons) of all subjects were nondippers. After adjustment for significant covariates, the probability of being a nondipper was significantly correlated with the linear and the quadratic term of age, and it increased 2.8 times from 30 to 60 yr, but 5.7 times from 60 to 80 yr. The odds of being a nondipper were the same in males and females, but were significantly higher in subjects with hypertension as opposed to normotensive subjects.

The Work Site Blood Pressure Study

To study the gender-specific associations between depression and anxiety, awake physical activity, sleep quality, and the diurnal BP variation, Kario et al. *(29)* analyzed ABP measurements and actigraph

(Mini-Motionlogger Actigraph, Ambulatory Monitoring, Inc., Ardsley, NY) data collected in 105 working women and 126 working men enrolled in the Work Site Blood Pressure Study. None of them was taking medication for hypertension, depression, or anxiety or was engaged in shift work. Physical activity was assessed by wearing an actigraph around the waist while awake and on the wrist during sleep. Depression and anxiety were measured by the Brief Symptom Inventory. Sleep BP was defined as the mean BP from the time at which the subject went to bed until the time of awakening and the awake BP as the mean BP during the remainder of the day. The mean awake and asleep BP were lower ($p < 0.001$) in women compared to men, i.e., 119/78 and 104/62 mmHg for awake and asleep BP in women vs 130/84 and 111/76 mmHg for awake and asleep BP in men. However, the sleep:awake ratios were comparable in both sexes. The average depression scores tended to be higher in women than in men, but anxiety scores were on average similar. In all men, with adjustments applied for age, BMI and the awake and asleep activity, the sleep:awake systolic BP ratio was significantly and positively correlated with the anxiety and depression scores. When men were subdivided into a more and less depressed group, based on quintiles of the depression scale (more depressed group = fifth quintile, $n = 21$; less depressed group = first to fourth quintile, $n = 105$), the sleep:awake systolic BP ratio was higher in the more depressed than in the less depressed. Sleep systolic BP tended to be higher in the more depressed group (Fig. 2), but there were no significant differences in awake BP, in physical activity during sleep, or in the duration of sleep between the more and less depressed. These results suggest that factors other than activity, such as disregulation of the autonomic nervous balance (increase in sympathetic activity or decrease in parasympathetic activity) or activation of the hypothalamus–pituitary–adrenal axis, might mediate the association in men between the nocturnal BP fall and depression. In contrast the sleep:awake BP ratio was similar in the group of more (fifth quintile) compared to less anxious men (first to fourth quintile). In women, there was no association between the parameters of the ABP profile and the depression scale. However, after controlling for age, BMI, and the awake and sleep activity, in women awake systolic BP was positively correlated with the anxiety scale. Although the awake systolic BP tended to be higher in more as compared to less anxious women, the sleep:awake BP ratio was comparable in the two groups of women. Kario et al. *(29)* suggested that, based on their findings, depression might lead to a lesser cardiovascular risk in women than men.

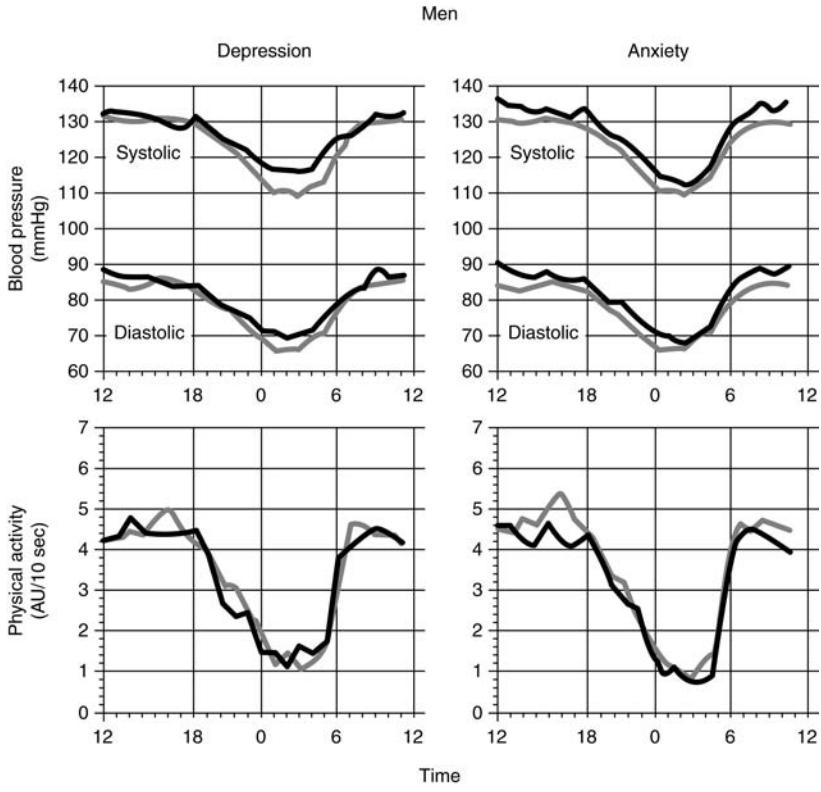

Fig. 2. Diurnal pattern of ambulatory blood pressure and physical activity in men, stratified by depression symptom subgroup (left) and by anxiety symptom subgroup (right). Dark lines show the more depressed or anxious group (the fifth or highest quintile of the depression scale or the anxiety scale), and the light lines show the less depressed or anxious group (first to fourth quintile). AU indicates arbitrary units. (From ref. *29*.)

The Diurnal BP Profile in Children and Adolescents

In children, ABP monitoring is feasible with the application of carefully standardized and specially adapted recording techniques. In 1996, Lurbe et al. investigated the diurnal BP curve and the nocturnal BP fall in 228 normotensive children (116 boys and 112 girls) aged 6–16 yr *(30)*. Normotension (based on conventional BP measurement) was defined according to the criteria proposed by the Task Force on Blood Pressure Control in Children. None of the subjects was taking any medication. Daytime was defined as the interval from 8 AM to 10 PM and nighttime from midnight to 6 AM.

More than 80% of the children in Lurbe's analysis *(30)* showed a diurnal BP rhythm that differed significantly from random variation. The systolic crest pressure, the cusum plot height, and the circadian alteration magnitude for systolic BP were greater in boys than in girls (Table 4). This observation possibly reflects the more vigorous physical activity in male than in female children and adolescents. In most recordings the acrophase of the overall Fourier curve with four harmonics occurred between 9 AM and 9 PM. There were no differences between boys and girls in the other parameters of the overall Fourier curve. The 24-h, daytime and nighttime, crest and trough systolic BP were positively and independently correlated with age and body weight. The 24-h, nighttime, and trough diastolic BP were positively correlated with age, but negatively with body weight (Table 5).

A few years later, the same author studied the possible association of birthweight with the level and variability of ABP in 630 healthy children (369 girls and 261 boys) aged 4–18 yr *(31)*. Day- and nighttime were defined as before *(30)*. The authors mainly focused on (short-term) ABP variability estimated as the SD of BP measurements, but they also reported on the day:night ratio of the daytime and nighttime BP averages. The children were divided into five groups according to their birthweight. After adjustment for significant covariates, 24-h, daytime, and nighttime BPs were significantly higher in the lowest birthweight group when they were compared with those of the other four groups. There were, however, no differences in circadian variation—as estimated by the day:night ratio—for either systolic or diastolic BP within the birthweight groups.

To generate reference values, the German Study Group for Pediatric Hypertension recently assessed the prevalence and the characteristics of physiological circadian (24-h) and ultradian (12-, 8-, and 6-h) rhythms of mean BP *(32)*. The 24-h ABP profiles of 938 healthy school children aged 5–18 yr were analyzed. Circadian (thus 24-h) BP rhythmicity was observed in 90% of the children, with no significant difference according to gender or height. Children exhibiting 24-h rhythms had higher daytime and lower nighttime mean BP. The median 24-h BP amplitude was 10.1 mmHg, and its acrophase occurred at approx 2 PM. Although the circadian rhythmicity seemed to be the major determinant of the overall BP curve, in 63% of the children an ultradian BP rhythmicity was also observed and was usually superimposed on the circadian rhythm. Boys younger than 11 and girls younger than 10 yr were considered to be prepubescent. All others were classified as pubescent. Puberty had marked effects on the prevalence of ultradian rhythmicity: The prevalence of

Table 4
Parameters of the Diurnal Profile in 228 Children

	Boys	*Girls*	*p-value*	*Total*
N	116	112		228
Day–night difference				
SBP (mmHg)	12.6 ± 6.7	11.4 ± 5.7		12.0 ± 6.3
DBP (mmHg)	14.0 ± 6.1	14.4 ± 5.7		14.2 ± 5.9
Day:night ratio				
SBP (mmHg)	1.13 ± 0.07	1.11 ± 0.06		1.12 ± 0.06
DBP (mmHg)	1.25 ± 0.12	1.27 ± 0.12		1.26 ± 0.12
Fourier amplitude				
SBP (mmHg)	12.9 ± 4.4	12.1 ± 3.9		12.5 ± 4.2
DBP (mmHg)	14.0 ± 4.3	13.9 ± 3.9		14.0 ± 4.1
Acrophase				
SBP (h)	13 h 57 ± 4 h 53	13 h 31 ± 4 h 39		13 h 44 ± 4 h 46
DBP (h)	13 h 42 ± 4 h 26	13 h 00 ± 4 h 18		13 h 21 ± 4 h 22
Crest				
SBP (mmHg)	119 ± 8	116 ± 8	0.01	118 ± 8
DBP (mmHg)	75 ± 6	74 ±		± 6

Trough				
SBP (mmHg)	101 ± 7	100 ± 8	0.05	101 ± 7
DBP (mmHg)	56 ± 6	55 ±		± 6
Cusum plot height				
SBP (mmHg × h)	75.7 ± 28.7	68.4 ± 25.1	0.04	72.1 ± 27.2
DBP (mmHg × h)	82.0 ± 28.6	83.0 ± 25.2		82.3 ± 26.9
Circadian alteration magnitude				
SBP (mmHg)	18.0 ± 6.7	16.3 ± 5.6	0.04	17.0 ± 6.2
DBP (mmHg)	19.1 ± 6.3	19.4 ± 5.3		19.2 ± 5.8

Values are expressed as means ± standard deviation.
SBP = systolic blood pressure; DBP = diastolic blood pressure; daytime = 08:00–22:00 h; nighttime = 24:00–06:00 h.
p-value indicates sex differences; only levels ≤0.05 are reported.
From ref. *30*.

Table 5
Correlates of the Parameters Describing Diurnal BP Profile in 228 Children

	R^2	*Intercept*	*Age (yr)*	*Weight (kg)*	*Sex (male = 1, female = 0)*
Blood pressures (mmHg)					
24 h SBP	0.20	97.1	0.66[b]	0.13[b]	
24 h DBP	0.08	75.8	0.77[c]		1.37[a]
Daytime SBP	0.19	100.5	0.68[c]	0.12[a]	1.92[a]
Daytime DBP					
Nighttime SBP	0.16	89.9	0.53[a]	0.15[b]	
Nighttime DBP	0.07	53.3	0.64[b]	–0.11[b]	1.56[a]
Crest SBP	0.19	103.4	0.78[b]	0.12[a]	2.21[a]
Crest DBP					
Trough SBP	0.15	89.4	0.53[a]	0.13[b]	
Trough DBP	0.07	52.5	0.61[c]	–0.12[b]	1.46[a]
Cusum plot height (mmHg × h)					
SBP	0.02	68.5			7.24[a]
DBP					
Circadian alteration magnitude (mmHg)					
SBP	0.02	16.4			1.65[a]
DBP					

SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$.
From ref. *30*.

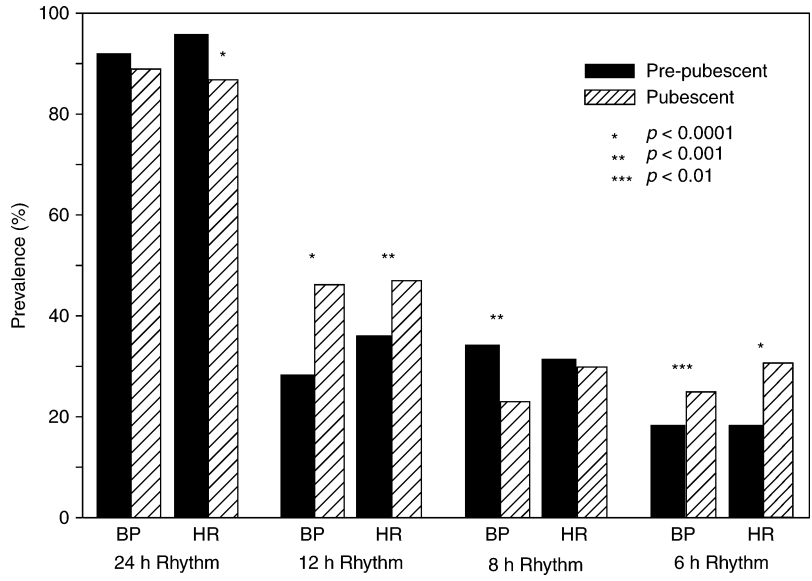

Fig. 3. Prevalence of circadian and ultradian blood pressure and heart rate rhythms before and during puberty. (From ref. *32*.)

12- and 6-h rhythms increased with puberty from 27 to 47% and from 18 to 25%, respectively, whereas the prevalence of an 8-h rhythm decreased from 34 to 23% (Fig. 3). The median amplitudes of the 12-, 8-, and 6-h BP rhythms were 5.9, 5.6, and 5.2 mmHg, with acrophases occurring at about 8 AM, 5:30 PM, and 2 AM, respectively. Some factors possibly implicated in these marked changes of ultradian cardiovascular rhythmicity around puberty include the changes in the intrinsic activity of the autonomic nervous system and endocrine factors, such as the increase in sex hormone production (which also follows ultradian cyclical patterns).

INFLUENCE OF WORKING (TIME) ON THE DIURNAL VARIATION OF BP

The circadian variation of BP is modified by physical as well as mental activities. In contrast to other biological parameters, BP immediately follows changes in the periods of activity and sleep *(33)*. In 1989, Baumgart et al. *(33)* investigated the effects of shift work on the diurnal BP profile of 15 normotensive, healthy, physically working men who were not taking any drugs. They were working according to a slowly rotating three-shift system. Their ABP was recorded during

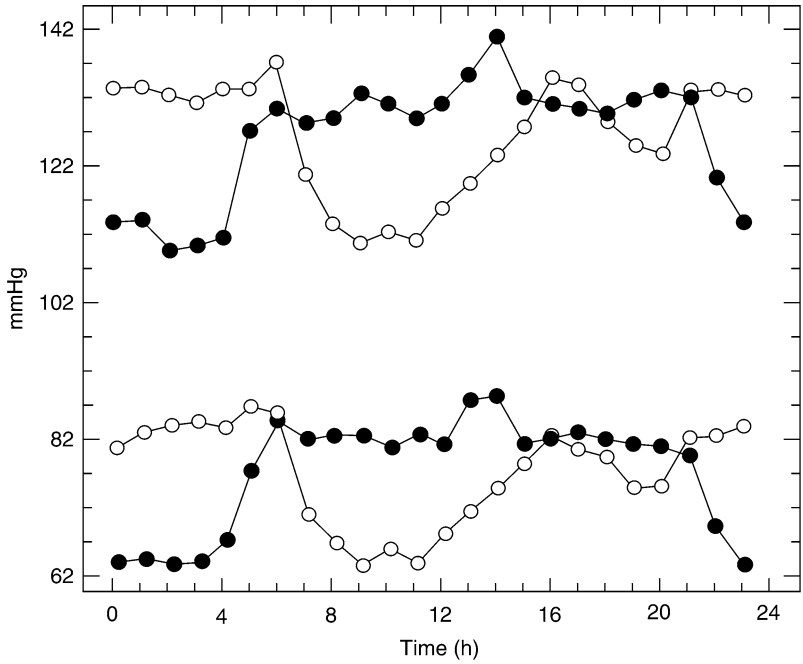

Fig. 4. Hourly means of systolic and diastolic blood pressure of shift workers during the morning (●) and night (○) shifts ($n = 15$). (From ref. *33.*)

shifts with work in the morning and at night. There were no differences between the two shifts in the 24-h BP or in the BP levels during working and sleeping hours. Furthermore, during the two shifts the minimal and maximal hourly means over 24 h were nearly identical, indicating that the amplitudes of diurnal BP fluctuations were of similar magnitude (Fig. 4). In keeping with the lag between the working periods, there was a phase difference of 8 h between the 24-h BP curves. The 24-h BP curves recorded during the first and last day of the night shift were nearly identical. These findings indicate that the adaptation of the circadian BP profile to shifted activity and sleep is immediate and largely independent from an endogenously programmed circadian rhythm.

More recently, Kario et al. *(34)* investigated the possible influence of mental and physical stress on the diurnal variability in BP. They hypothesized that cardiovascular reactivity to acute stress and/or delayed recovery predicted greater diurnal BP variation (i.e., a lower sleep:awake BP ratio). Eighty-seven female nurses, aged 30–59 yr with day or night work shifts, who participated in the Work Site Blood

Pressure Study *(29)* were investigated. In night-shift workers, diurnal BP variation was related to different stress parameters. In day-shift workers, however, diurnal BP variation was associated with exercise-induced BP reactivity. These findings are consistent with the hypothesis that psychological stress predominantly releases noradrenaline to activate sympathetic activity, while physical stress predominantly releases adrenaline from the adrenal glands. The authors concluded that cardiovascular reactivity triggered by psychological and physical stress in the laboratory might be a weak but significant determinant of diurnal BP variation. In addition, day or night work shift appeared to moderate the relationship between these two pressor mechanisms.

REPRODUCIBILITY OF THE DIURNAL BP PATTERN

Several studies compared the reproducibility of various methods for the analysis of the diurnal BP profile *(5,30,35–38)*. The reproducibility of group means was assessed from the signed difference in BP statistics between duplicate measurements and the within-subject repeatability from the repeatability coefficient. The latter is calculated as twice the standard deviation of the individual differences, assuming a mean difference for all subjects of zero. To allow comparisons between various measurements, the repeatability coefficient is often expressed as a percentage of nearly maximal variation, i.e., four times the standard deviation of the measurement under investigation. This index is typically around 50% for clinic BP and around 30% for the mean 24-h BP. The lower the index, the better the repeatability *(12)*.

Reproducibility can be evaluated short-term (over a few weeks) or long-term (over several months). Cuspidi et al. *(36)* evaluated the short-term variability of the diurnal changes in BP (dipping status) by measuring ABP on two occasions over a 3-wk period in 208 nontreated hypertensives. Eighty-five percent showed no change in their dipping status. Of subjects who had a dipping or nondipping pattern on their first ABP monitoring, 90.6 and 72.2%, respectively, did not change their dipping status on the repeat recording. Thus, although the reproducibility of the diurnal BP profile was overall satisfactory in this study, classifying a patient as a nondipper on the basis of a single ABP monitoring was unreliable in about one-third of such patients. In a more recent study, Cuspidi et al. *(37)* extended and refined the previous findings in a much larger sample of similar patients. Stenehjem et al. *(38)* also investigated short-term (4 wk) reproducibility in a group of 74 newly diagnosed, untreated hypertensive patients. Several cusum-derived parameters were

assessed and compared between the two ABP monitorings. Both crest and trough BP and circadian BP alteration magnitudes were similar at both occasions. On average, nighttime BP fall also remained unchanged. Approximately 80% of all patients were classified as having a dipping pattern on systolic ABP measurement. Only a small portion of patients with a dipping pattern converted to a nondipping pattern on repeat measurement, but close to one-third converted from a nondipping to a dipping pattern.

Some investigators assessed long-term reproducibility of the diurnal BP pattern. In the previously mentioned Belgian population study *(5)*, 34 of the 399 participants underwent a repeat measurement of their ABP (mean interval 350 d [range 254 to 430 d]). Expressed as a percentage of maximal variation, repeatability was 37 and 47% for the 24-h systolic and diastolic BP, respectively. Repeatability for the day and nighttime BP levels was comparable. However, repeatability was substantially less for the statistical parameters describing the diurnal BP rhythm. For example, the overall amplitude of systolic and diastolic BP derived by a four-harmonic Fourier series had a repeatability coefficient amounting to 83% of nearly maximal variation. Of the 36 subjects who underwent a repeat ABP measurement, 9 were classified as being strong dippers (night:day ratio < 0.78), 18 as intermediate dippers (night:day ratio between 0.78 and 0.87), and 9 as nondippers (night:day ratio > 0.87). In the strong dippers, the nighttime BP was significantly higher at the repeat than at the initial recording. This was associated with a decrease in the nocturnal BP fall and the amplitude of the BP curve. In the nine nondippers, the nighttime BP fell at the repeat examination, but none of them became a strong dipper. These data suggest that regression to the mean is also observed for the nighttime BP, when ABP recordings are repeated in subjects selected for being a strong dipper or a nondipper. However, the alternative explanation that nondippers become accustomed to the recorder and sleep deeper at the repeat examination and that some dippers may sleep less well must also be considered. The latter explanation seems to be confirmed in a study by Manning et al. *(35)* on the reproducibility of dipper and nondipper status over a 1-yr period. In this study, ABP and dipping status were examined in 79 untreated hypertensive subjects at 0, 6, and 12 mo. Fifty-six percent of all patients were consistently classified as dipper or nondipper on all three ABP monitorings, most of them (53%) showing the normal nocturnal fall in BP. A significant proportion, however, had a variable dipping status when comparing the three ABP recordings.

In this study, the subjects also completed a short questionnaire, which gave an indication of their perceived sleep quality. The results indicated that the BP during sleep was significantly lower and the nocturnal fall in BP was greater in patients who reported good sleep. A repeat ABP recording was also performed in a random sample of 31 of the 228 children and adolescents included in the previously mentioned study by Lurbe et al. *(30)*. The median time between their repeat recordings was 123 d (range 36 to 273 d). Repeat measurements yielded only minor changes in the average 24-h, daytime, and nighttime BP values, making group means thus easy to reproduce. The intraindividual repeatability coefficient for the 24-h systolic and diastolic BP were 32 and 34%, respectively. However, as in adults, the reproducibility of the parameters describing the diurnal BP profile was generally lower than that of the level of the ambulatory measurements.

We can thus conclude that group means for the ABP parameters can be accurately reproduced and that in individual subjects the agreement between paired recordings is satisfactory for the level of BP. By contrast the parameters related to the diurnal BP rhythm are less reproducible in individual subjects. One 24-h ABP recording is thus not sufficient to fully characterize an individual with respect to his or her diurnal BP profile. Increasing the number of recordings per subject or standardizing activity patterns during the recordings may increase the potential of 24-h ABP monitoring to characterize the diurnal BP profile of individual subjects *(5)*. However, repeatability in many studies not only reflects the variability inherent to the measurement technique, but also biological variability. In some studies, variability may have been inflated because of the long interval between the duplicate recordings or by seasonal and random variation in the pattern of daily activities.

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8 Importance of Heart Rate in Determining Cardiovascular Risk

Paolo Palatini, MD

CONTENTS

INTRODUCTION

A body of evidence indicates that subjects with tachycardia are more likely to develop hypertension *(1–3)* and atherosclerosis in future years *(4–6)*. However, the connection between heart rate and cardiovascular risk has long been neglected on the grounds that tachycardia is often associated with the traditional risk factors for atherosclerosis, such as hypertension or metabolic abnormalities *(7)*. A high heart rate is currently considered only an epiphenomenon of a complex clinical condition rather than an independent risk factor. However, most epidemiological studies showed that the predictive power of a fast heart rate for cardiovascular disease remains significant even when its relative risk is adjusted for all major risk factors for atherosclerosis and other confounders *(4–7)*. In this chapter, the results of the main studies that dealt with the relation between tachycardia and cardiovascular

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morbidity and mortality will be summarized, and the pathogenesis of the connection between fast heart rate and cardiovascular disease will be the focus.

EPIDEMIOLOGICAL EVIDENCE

The heart rate was found to be a predictor for future development of hypertension as long ago as 1945 *(8)*. This finding was subsequently confirmed by the Framingham study, in which the predictive power of the heart rate for future development of hypertension was similar to that of obesity *(3)*. Several other more recent reports have confirmed those findings *(1,2,9)*. The heart rate was also found to be a predictor of myocardial infarction *(10,11)* and of cardiovascular morbidity in general *(5,8)*. A body of evidence indicates that tachycardia is also related to increased risk of cardiovascular mortality. This association was shown by Levy et al. in a survey of more than 20,000 Army officers *(8)*. Thereafter, a number of other studies confirmed this finding, showing that the resting heart rate was a powerful predictor of death from cardiovascular and noncardiovascular causes *(4–6,12–15)*. The data related to sudden death were particularly impressive, especially in the Framingham study, in which a sharp upward trend in mortality was found in the men divided by quintiles of heart rate *(6)*. Also, in the Chicago studies a strong association was found between heart rate and sudden death, but the relation was U-shaped because of an excess of mortality in the subjects with very low heart rates *(4)*.

The relationship between heart rate and cardiovascular mortality persists into old age. This was shown by the Framingham *(6,16)* and the NHANES *(5)* studies performed in general populations and by two more recent studies conducted in elderly subjects *(13,14)*. In the CASTEL study *(13)*, the predictive power of heart rate for mortality was 1.38 for the men with a heart rate greater than 80 beats/min (bpm) (top quintile) compared to those of the three intermediate quintiles, and 0.82 for the men with a heart rate less than 60 bpm (bottom quintile). The relation between heart rate and mortality was particularly strong for sudden death, with an adjusted relative risk of 2.45 for the subjects in the top quintile as compared to those in the three intermediate quintiles. In the CASTEL study, no significant association between heart rate and mortality was found in the women. In another study performed on elderly men and women combined *(14)*, a 1.14 times higher probability of developing fatal or nonfatal myocardial infarction or sudden death was found for an increment of 5 bpm of heart rate recorded over the 24 h.

In the Framingham study, the relationship of heart rate to morbidity and mortality was analyzed in hypertensive individuals *(15)* followed up for 36 yr. For a heart rate increment of 40 bpm, the age-adjusted and systolic blood pressure-adjusted relative risk for cardiovascular mortality was 1.68 in males and 1.70 in females. For sudden death, the adjusted odds ratios were 1.93 and 1.37, respectively. These relationships were still significant after adjusting for smoking, total cholesterol, and left ventricular hypertrophy. A more recent analysis of a general population stratified by gender and blood pressure level found that faster heart rate was associated with a higher overall mortality in both normotensive and hypertensive men *(17)*. For cardiovascular and coronary deaths, the associations were stronger for the hypertensives. In contrast, among the women a significant association between heart rate and total mortality was observed only for normotensive individuals. At variance with these results, in the Systolic Hypertension in Europe (Syst-Eur) study, high heart rate was positively associated with a worse prognosis for total, cardiovascular, and noncardiovascular mortality among both elderly hypertensive men and elderly hypertensive women taking placebo *(18)*. Subjects with heart rates higher than 79 bpm (top quintile) had a 1.89 times greater risk of mortality than subjects with heart rate lower than or equal to 79 bpm (95% confidence interval, 1.33–2.68).

The heart rate was also found to be a strong predictor of cardiovascular mortality in patients with myocardial infarction. This association was found in the Norwegian Timolol Multicenter Study *(19)* and in a study by Hjalmarson et al. *(20)* in which the total mortality was 14% in the subjects with an admission heart rate less than 60 bpm, 41% in the subjects with a heart rate greater than 90 bpm, and 48% in those with a heart rate greater than 110 bpm. In a subsequent study, Disegni et al. found a doubled mortality risk in postmyocardial infarction patients with a heart rate greater than 90 bpm compared to subjects with a heart rate less than 70 bpm *(21)*. Two analyses performed in larger datasets confirmed the results of the previously listed studies. In the GUSTO study *(22)*, a high heart rate emerged as a potent precursor of mortality, and in the GISSI-2 trial *(23)*, the predischarge heart rate was a stronger predictor of death than standard indices of risk, such as left ventricular dysfunction or ventricular arrhythmias. It is noteworthy to observe that tachycardia in postmyocardial infarction patients cannot be considered simply as a marker of heart failure, as its predictive power appeared more evident in the subjects with no or mild signs of congestive heart failure *(20,21)*. In a recent study, we found that the predictive power of heart rate for mortality in subjects with acute myocardial infarction

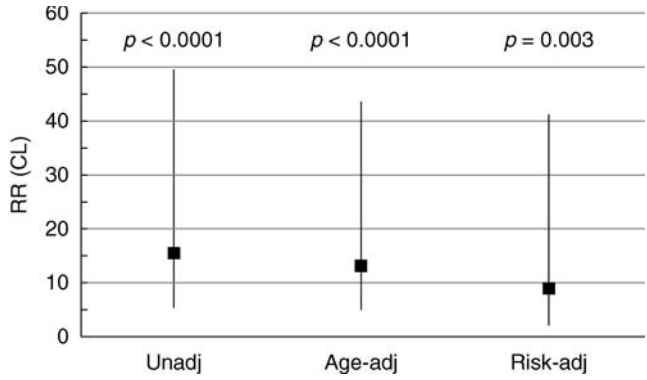

Fig. 1. Relarive risks (RR) and 95% confidence limits (CL) for 1-yr mortality in 250 men divided according to whether their heart rate was <80 bpm or ≥80 bpm on the seventh day after admission to the hospital for acute myocardial infarction. unadj, unadjusted relative risk; age-adj, relative risk adjusted for age; risk-adj, relative risk adjusted for age, CK-MB peak, echocardiographic left ventricular ejection fraction, diabetes, history of hypertension, current smoking, history of angina, Killip class, thrombolysis, and β-blocker therapy. *p*-values relate to the results of Cox regression analyses.

remained significant after adjusting for numerous confounders, including clinical and echocardiographic signs of left ventricular dysfunction (Palatini et al., unpublished observations) (Fig. 1).

PATHOGENETIC CONSIDERATIONS

The pathogenetic connection between fast heart rate and cardiovascular risk can be explained according to several different mechanisms (Fig. 2). The heart rate can be considered as a marker of an underlying clinical condition related to the risk or a consequence of a latent chronic disease. However, experimental evidence suggests that a high heart rate should be regarded as a pathogenetic factor in the induction of the risk as well. In fact, tachycardia favors the occurrence of atherosclerotic lesions by increasing the arterial wall stress *(24)* and impairs arterial compliance and distensibility *(25)*. Moreover, the mean blood pressure has been found to be higher in subjects with faster heart rate *(26)*. This can be explained by the increase in the total time spent on systole because of the shortening of diastolic time.

The experimental evidence for a direct role of tachycardia in the induction of arterial atherosclerotic lesions was provided by studies performed in cynomolgus monkeys. Beere et al. were the first to demonstrate that

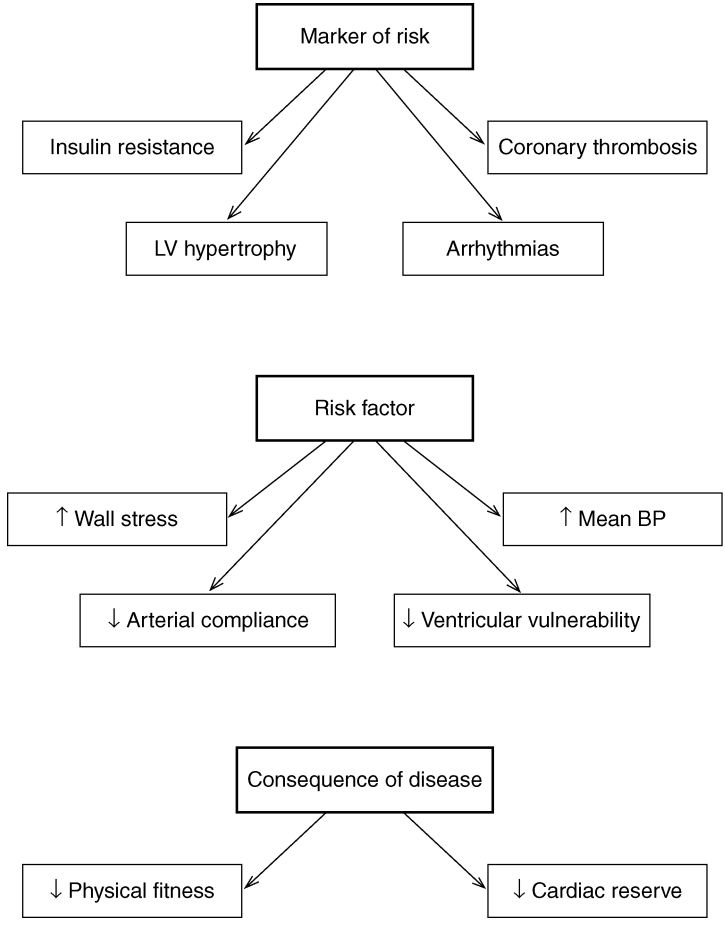

Fig. 2. Mechanisms of the connection between heart rate and cardiovascular morbidity and mortality. The heart rate can be a marker of risk or a consequence of an underlying disease, but can exert direct action in the induction of the risk as well. LV, left ventricular; BP, blood pressure; ↑, increased; ↓, decreased.

reduction of heart rate by ablation of the sinoatrial node could retard the development of coronary lesions in these animals *(27)*.

Bassiouny et al. studied the effect of the product of mean heart rate and mean blood pressure (so-called hemodynamic stress) on the aorta of the monkeys *(28)* and found a striking positive relationship between the hemodynamic stress index and maximum atherosclerotic lesion thickness. Similar results were obtained by Kaplan et al., who found

Table 1
Correlation Coefficients Between Resting Heart Rate and Other Clinical Variables in Three General and One Hypertensive Populations

Population	*SBP*	*DBP*	*BMI*	*CT*	*TG*	*GL*	*INS*
General							
Tecumseh	.27	.26	.11	.16	.13	NS	.19
Mirano	.22	.24	NS	.05	.08	.20*	—
Belgian	.20	.32	.13	NS	NS	.19*	.20
Hypertensive							
Harvest	.26	.10	NS	NS	NS	NS	—

SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; CT = total cholesterol; TG = triglycerides; GL = glucose; INS = fasting insulin; NS = coefficient nonsignificant; * = postload glucose. Data are for men only.
Data from ref. *7*.

a significant relationship between naturally occurring differences in heart rate and atherosclerotic coronary lesions in monkeys *(29)*.

Tachycardia also has a pathogenetic role in precipitating cardiovascular events in subjects at risk. In a group of patients who underwent two coronary angiograms within 6 mo, Heidland and Strauer demonstrated that the hemodynamic forces related to increased heart rate may play a crucial role in coronary plaque disruption *(30)*. Plaque disruption could be prevented in those subjects who had been administered β-blockers.

As mentioned earlier, heart rate can be considered as a marker of an abnormal clinical condition. This is suggested by the relationship found in several studies between heart rate and many risk factors for atherosclerosis *(31–33)*. In four different populations studied in the Ann Arbor laboratory, we found that the heart rate was correlated with blood pressure, degree of obesity, cholesterol, triglycerides, postload glucose, and fasting insulin (Table 1) *(34,35)*. In other words, subjects with a fast heart rate exhibited the features of the insulin-resistance syndrome. If one assumes that a fast heart rate is the marker of an abnormal autonomic control of the circulation, as demonstrated by Julius et al. *(36,37)*, it is easy to understand why subjects with tachycardia develop atherosclerosis and cardiovascular events. In fact, several studies performed in the Ann Arbor and other laboratories indicate that sympathetic overactivity can cause insulin resistance (Fig. 3). This can be obtained through acute *(38)* as well as chronic *(39)* stimulation of β-adrenergic receptors. It has been shown that chronic stimulation of β-receptors causes the conversion from a small to a larger proportion of insulin-resistant fast-twitch muscles *(39)*.

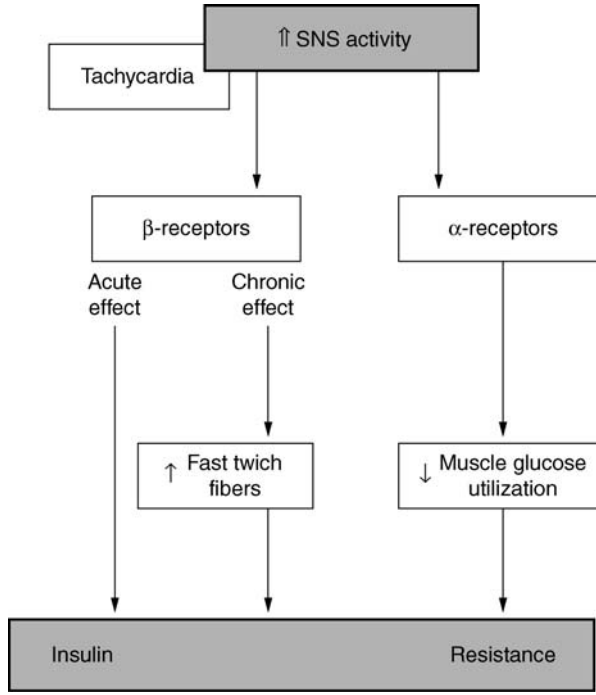

Fig. 3. Pathogenesis of the connection between tachycardia and insulin resistance. Tachydardia is a marker of the underlying sympathetic overactivity. SNS, sympathetic system; ↑, increased; ↓, decreased.

An insulin-resistance state can also be obtained through vasoconstriction mediated by α-adrenergic receptors, as shown by Jamerson et al. in the human forearm *(40)*. Conversely, α-adrenergic blockade can improve insulin sensitivity in patients with hypertension *(41)*.

The connection between high heart rate and mortality can also be explained by an unrecognized underlying disease, and tachycardia can reflect poor physical fitness or loss of cardiac reserve *(4,6,13)*. In fact, impaired left ventricular contractility may be an early clinical finding in asymptomatic hypertensive individuals, as demonstrated in the Padova *(42)* and Ann Arbor *(43)* laboratories. To rule out this possibility, in some studies the subjects who died within the first few years after the baseline evaluation were eliminated *(6,13,16)*. However, in all of those studies, the heart rate–mortality association remained significant, indicating that tachycardia was not only a marker of latent left ventricular failure or of loss of vigor.

Besides causing the development of atherosclerotic lesions, a fast heart rate can also favor the occurrence of cardiovascular events, as shown by the Framingham study *(6,12,16)*. The relationship appeared weak for nonfatal cardiovascular events but was strong for fatal cardiovascular events. Moreover, as mentioned earlier, tachycardia can facilitate sudden death *(4,6,13)*. The reasons for this connection can be of a different nature. Sympathetic overactivity underlying a fast heart rate can facilitate the occurrence of coronary thrombosis through platelet activation and increased blood viscosity *(34)*. Subjects with tachycardia are more prone to ventricular arrhythmias. It is known that a heightened sympathetic tone can promote the development of left ventricular hypertrophy *(44)*, which facilitates the occurrence of arrhythmias *(42)*. Moreover, tachycardia increases oxygen consumption and ventricular vulnerability *(7,46)*. The latter mechanisms are important chiefly in subjects with acute myocardial infarction.

LOOKING FOR A THRESHOLD VALUE

The current definition of tachycardia is a heart rate greater than 100 bpm. Recent results obtained in our laboratory with mixture analysis suggest that this value is probably too high. In fact, in three general and one hypertensive populations, we found that the distribution of heart rate was explained by the mixture of two homogeneous subpopulations: a larger one with a "normal" heart rate and a smaller one with a "high" heart rate. The partition value between the two subpopulations was around 80–85 bpm. Furthermore, in almost all of the epidemiological studies that showed an association between heart rate and death from cardiovascular or noncardiovascular causes, the heart-rate value above which a significant increase in risk was seen was below the 100-bpm threshold *(47)* (Table 2). On the basis of the above data, we suggested that the upper normal value of heart rate should be set at 85 bpm *(47)*.

THERAPEUTIC CONSIDERATIONS

Although there is no doubt that a fast heart rate is independently related to cardiovascular and total mortality, it is not known whether the reduction of heart rate can be beneficial in prolonging life. No clinical trial has been implemented as yet in human beings with the specific purpose of studying the effect of cardiac slowing on morbidity and mortality. This issue was dealt with by Coburn et al. in mice by studying the effect of digoxin administration *(48)*. Survival increased by 29% in the digoxin-treated males and by 14% in the treated females in comparison

Table 2
Heart Rate Threshold Values Above Which a Significant Increase in Mortality was Found in Eight Epidemiologic Studies

Reference	*HR threshold value*		*Results of the study*
	Men	*Women*	
Levy et al., 1945 *(8)*	99	—	Increased 5-yr cardiovascular mortality in men.
Dyer et al., 1980 *(4)*	79	—	Increased 15-yr all-cause mortality in the men of the People Gas Co. study.
Dyer et al., 1980 *(4)*	86	—	Increased 5-yr all-cause mortality in the men of the Heart Association study.
Dyer et al., 1980 *(4)*	89	—	Increased 17-yr all-cause mortality in the men of the Western Electric study.
Kannel et al., 1985 *(6)*	87	87	Increased 26-yr sudden death mortality rate in men.
Gillum et al., 1991 *(5)*	84	84	Increased 10-yr all-cause mortality in black and white men and in black women.
Gillman et al., 1993 *(15)*	84	84	Increased 36-yr all-cause mortality in hypertensive men and women.
Palatini et al., 1999 *(13)*	80	84	Increased 12-yr cardiovascular mortality in elderly men.

HR = heart rate in bpm.

with two groups of untreated mice (control groups), indicating that a heart-rate reduction may confer an advantage in terms of longevity.

A beneficial effect of heart-rate reduction in retarding the development of atherosclerotic lesions was demonstrated by Kaplan et al. with β-blocker administration in cynomolgus monkeys *(49)*. After 26 mo of propranolol treatment, the socially dominant animals showed a reduced development of coronary artery lesions in comparison to a group of untreated monkeys of the control group. This suggests that heart-rate reduction with β-blockers is beneficial in preventing atherosclerotic lesions, but only in animals exposed to a high environmental stress.

Most of the information on the effect of β-blockers on heart rate and morbidity and mortality in human beings comes from results obtained in postmyocardial infarction patients. The reduction in heart rate obtained varied greatly among the trials, from 10.5 to 22.8%. β-Blocking treatment appeared beneficial in those patients in whom the heart rate was reduced by 14 bpm or more, whereas for a heart-rate reduction of less than 8 bpm, no benefit was apparent *(50)*. Moreover, the advantage of treatment was virtually confined to patients with a heart rate of greater than 55 bpm.

In 26 large, placebo-controlled trials with a long-term follow-up, β-blockers proved effective primarily in reducing sudden death and death resulting from pump failure *(50–54)*. An almost linear relationship was found between reduction in resting heart rate and decreased mortality *(51,55)*. β-Blockers with intrinsic sympathomimetic activity, such as pindolol or practolol, showed little effect on mortality.

Similar beneficial effects were obtained in patients with congestive heart failure *(56)*. Carvedilol caused a marked reduction in mortality in subjects with congestive heart failure *(57)*, but only in patients with a high heart rate (>82 bpm).

The results obtained in hypertensive subjects *(58)* were less impressive, probably the result of the untoward effects of β-blockers on high-density lipoprotein cholesterol and triglycerides *(59)*. However, the effect of β-blockers in hypertensive patients was never examined in relation to the subjects' heart rates at baseline.

If the unsatisfactory effects of β-blockers in hypertension are the result of their unfavorable effects on plasma lipids, the use of drugs that reduce blood pressure and heart rate without altering the lipid profile appears warranted. Nondihydropyridine-calcium antagonists *(60,61)* have been shown to be neutral on the metabolic profile and could, thus, be more effective in preventing cardiovascular mortality in hypertensive subjects with tachycardia. In addition to having a peripheral action, some of them can cross the blood-brain barrier and decrease sympathetic outflow *(61)*.

Diltiazem and verapamil have been shown to be effective in reducing the risk of cardiac events *(62–64)*, but their depressive action on cardiac inotropism makes them unsuitable for patients with acute myocardial infarction and severe left ventricular dysfunction. The new long-acting calcium antagonists that selectively block voltage-dependent T-type calcium channels *(65,66)* reduce heart rate without manifesting a depressant effect on myocardial contractility and could, thus, be indicated also for subjects with congestive heart failure *(67)*. Azelnidipine is a third-generation dihydropyridine calcium antagonist that has been

shown to reduce both blood pressure and heart rate *(68)*. A number of studies conducted in hypertensive patients have demonstrated that azelnidipine does not increase plasma catecholamines or plasma renin activity, suggesting that this drug could be used also in hypertensive subjects with high heart rate.

Centrally active antihypertensive drugs that decrease heart rate through reduction of the sympathetic discharge from the central nervous system should have a good potential for the treatment of the hypertensive patient with fast heart rate. Unfortunately, the use of clonidine, α-methyldopa, guanfacine, and guanabenz is limited by the frequent occurrence of side effects, like dry mouth, sedation, and impotence *(69)*. Moxonidine and rilmenidine are new antihypertensive agents acting on the I1-imidazoline receptors of the rostro-ventrolateral medulla of the brain stem and do not have most of the side effects encountered with the centrally acting agents *(69,70)*. Moreover, these drugs proved effective in improving the metabolic profile in the experimental animal *(71)* and also in human studies *(72)*. Because it is difficult to separate the benefit of heart rate lowering from the antihypertensive action with currently available drugs, a "pure" heart-rate-lowering drug would be of great interest in establishing the benefit of heart rate reduction per se. The novel selective heart-rate-reducing agent ivabradine was shown to reduce resting heart rate without modifying any major electrophysiological parameters not related to heart rate, thereby reducing myocardial oxygen demand *(73)*. This action was obtained without any negative inotropic or lusitropic effect, thus preserving ventricular contractility. The goal of antihypertensive treatment should be not only to lower the blood pressure, but also to reverse those functional abnormalities that often accompany the hypertensive condition. Therefore, a therapy that not only reduces blood pressure effectively but also decreases the heart rate and improves metabolic abnormalities should be sought.

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9 Sodium, Potassium, the Sympathetic Nervous System, and the Renin–Angiotensin System

Impact on the Circadian Variability in Blood Pressure

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CONTENTS

INTRODUCTION

Under the typical circumstances of everyday life, the phasing of human circadian clocks and rhythms is set, or harmonized, by the 24-h routine marked by two important variables: sleep-in-darkness and activity-in-light. These time/activity prompts importantly shape the built-in diurnal rhythm for blood pressure (BP). As an example of this, swing-shift workers assigned to night duty quickly develop a timewise

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different sleep-activity/BP pattern than when they are working day shifts *(1)*. In this regard, the diurnal variations of BP are determined by the working and sleeping periods and are largely independent of endogenous rhythm.

The biological time structure of humans is an inherited characteristic for a number of parameters including BP; however, its "final" expression may be influenced by either environmental and/or nutritional factors and/or an individual's neurohumoral status *(2)*. When normal phase relationships change between circadian bioperiodicities, BP patterns may respond in an unpredictable manner *(3,4)*. The purpose of this review is to characterize the neurohumoral and nutritional determinants of the ambulatory blood pressure (ABP) profile in normotensive and hypertensive patients. In particular, this review focuses on the sympathetic nervous system (SNS), the renin–angiotensin–aldosterone system (RAAS), and the role of dietary sodium (Na^+) and potassium (K^+) in determining the structure of circadian BP patterns.

AMBULATORY BLOOD PRESSURE MONITORING AS A TOOL

ABP monitoring is a methodology capable of identifying and methodically evaluating individual differences in BP responses in the natural environment. This approach offers a means for studying an individual in a standardized manner as the patient reacts to the physical, psychological, or sleep-related demands of a representative 24-h day. ABP monitoring has established that most people have low amplitude diurnal variations in BP, with higher pressures during waking hours and lower pressures during sleep *(5,6)*. In normotensive subjects, BP values decline on average by approx 15% during sleep *(7,8)*. In hypertensive subjects, the circadian rhythm is generally preserved, although the 24-h profile for BP moves to higher around the clock values *(9)*.

ABP patterns are seldom fixed with considerable day-to-day variability in nocturnal BP patterns *(10)*. Although direct links have been hypothesized between dietary status and/or neurohumoral alterations and nocturnal BP changes, it is the unusual circumstance where such associations alone explain a particular BP pattern, such as nocturnal nondipping. Neurohumoral and dietary factors should typically be integrated to arrive at a composite explanation for a specific BP pattern. Comments found in this chapter should be viewed accordingly.

ELECTROLYTES AND CIRCADIAN RHYTHMS

Dietary recall and/or urinary excretion parameters are the preferred correlates to BP, because it is widely held that they more accurately represent the state of electrolyte balance *(10–12)*; thus, interpreting the relationship between a plasma electrolyte, such as K^+, and BP is challenging (if even an unrealistic exercise) because a host of factors are known to influence plasma K^+ values, not the least of which is nutritional intake and level of renal function. Additional factors that govern K^+ values include a circadian rhythm for plasma K^+ (average peak–trough difference ≈ 0.60 meq/L with a nighttime nadir) *(13)*, a nocturnal decline in urinary K^+ excretion and a predisposition for K^+ to migrate intracellularly with β_2-adrenergic receptor stimulation *(14)*.

Accordingly, very few reports have endeavored to characterize the relationship between plasma K^+, end-organ events *(15)*, development of hypertension/cardiovascular disease *(16,17)*, and/or BP patterns in patients *(18,19)*. In adults with treated hypertension, hypokalemia (serum $K^+ \leq 3.4$-mmol/L) in the year before a stroke has been associated with an increased risk of incident ischemic and hemorrhagic stroke (odds ratio of 2.04 and 3.29 for ischemic and hemorrhagic stroke, respectively) independent of diuretic use when compared to normal serum K^+ levels *(15)*. A total of 2358 participants (1292 women, 1066 men) in the Framingham Heart Study who were free of hypertension, were not taking drugs affecting K^+ homeostasis, and had serum K^+ measured were longitudinally tracked for BP and development of hypertension over a 4-yr time span from 1979 to 1983. In a logistic regression model adjusting for multiple confounders, serum K^+ quartile was not associated with risk of BP progression. Circadian BP patterns were not established in either of these studies *(15,16)*.

In an early study by Bulpitt et al., plasma K^+ was found to be negatively associated with both systolic and diastolic BP in both men and women. A decrease in plasma K^+ potassium of 1 mmol/L in women was associated with an increase in systolic and diastolic BP of 7 and 4 mmHg, respectively. In men, the corresponding increases were 4 and 2 mmHg *(18)*. The absence of ABP monitoring precluded an assessment of diurnal BP patterns in these first serum electrolyte-related studies. Goto et al. found significant negative correlations between daytime plasma K^+ concentration and 24-h systolic and diastolic BP levels in patients with essential hypertension *(19)*. Plasma K^+ also inversely correlated with both daytime and nighttime systolic and diastolic BP levels,

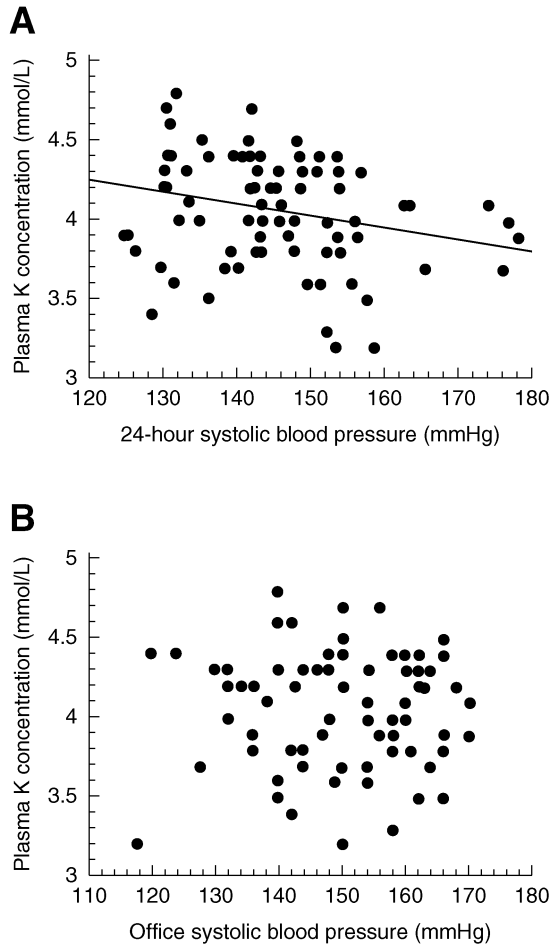

Fig. 1. Relation between plasma K^+ and 24-h systolic blood pressure (**A**, $r = 0.336$, $p < 0.01$) or office systolic blood pressure (**B**, $r = -0.018$, p = NS) in 82 patients with essential hypertension. (Adapted with permission from ref. *19*.)

suggesting that there was no time-wise specificity to the BP increment associated with a reduced plasma K^+ concentration (Fig. 1).

In the studies of Goto et al. there was no correlation between office BP readings and plasma K^+ concentration. As such, it is probable that any relationship with office-based measurements was obscured by the innate variability in such measurements. Goto et al. have offered as a means of explanation for these findings that decreased extracellular K^+ promotes vasoconstriction in hypertensive patients by either enhancing

SNS activity or by increasing the Na^+ content of vascular smooth muscle cells *(18)*. Despite the positive nature of these findings, additional research is needed to better understand the relative contribution of plasma electrolyte concentrations per se to circadian variability in BP.

NEUROHUMORAL PATTERNS AND CIRCADIAN BLOOD PRESSURE RHYTHMS

Daily hormonal profiles are the product of a complex interaction between the output of the circadian pacemaker, periodic changes in behavior, light exposure, neuroendocrine feedback mechanisms, gender, age, and the timing of sleep and wakefulness. The interaction of these factors can affect hormonal secretory pulse frequency and amplitude, with each endocrine system differentially affected by these factors. In turn, it has been speculated that specific hormonal profiles may coordinate the time-wise structure of the 24-h BP pattern. Disease-state related alterations in hormonal profiles also have to be considered in any developed relationship for a specific neurohormone and diurnal BP changes. Twenty-four hormonal profiles and not single point-in-time values are needed to establish a true cause and effect relationship.

Natriuretic Peptides

Natriuretic peptides are intimately involved in the regulation of BP in their regulatory role of volume homeostasis in man. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) release are principally regulated by atrial pressure, although a number of other factors, such as age and level of renal and/or cardiac function, can regulate its plasma concentration. ANP and BNP effectively offset activation of the RAA axis by inhibiting the release of renin and aldosterone while opposing the actions of angiotensin II and aldosterone through effects on vascular tone, cells growth, and tubular Na^+ reabsorption. When ANP or BNP is administered to humans, BP acutely drops, a process that is particularly prominent when the RAAS is activated. For these reasons, a connection between the time structure of ANP/BNP, other neurohormones, and 24-h BP patterns has been envisioned.

The relationship between ANP, BNP, and BP has been an inconsistent one. It has been observed that morning ANP levels may have little relationship to the varied phases of the 24-h BP cycle *(20)*. Alternatively, Kario et al. found plasma ANP/BNP levels to be slightly increased in patients with isolated clinic hypertension compared with elderly normotensives. These authors also observed that sustained hypertensives

showed significantly increased plasma levels of ANP and BNP compared with isolated clinic hypertensives *(21)* and in separate studies that normotensive subjects determined to be nondippers had higher plasma ANP/BNP levels than did normotensive dippers *(22)* Chiang et al. did not find a circadian rhythm for ANP (sampled every 3 h for 24 h) and thus no relationship to diurnal BP changes in a group of 14 healthy volunteers *(23)*. However, in chronic kidney disease (CKD) the loss and possible reversal of the nocturnal decline in BP is associated with the disappearance of any significant circadian variation in the circulating concentrations of ANP *(24)*.

In studies by Portaluppi et al. where subjects were synchronized to the light–dark cycle (and given a controlled diet), a fairly well-defined acrophase for ANP is found at around 4 AM. In these studies, BP and heart rate (HR) rhythms appeared to be in antiphase with that of ANP. The BP and H peaks corresponded to the ANP trough, implying some biological association *(25)*. Alternatively, the other measured neurohormones in these studies including plasma renin activity (PRA), plasma aldosterone (PA), and plasma cortisol were characterized by acrophase asynchrony with ANP, suggesting the absence of a causal relationship. Alternatively, Cugini et al. established an acrophase timing for ANP at about 7 PM in clinically healthy young subjects after synchronization to a light–dark regimen and meal timing. In these same studies no circadian pattern for ANP was evident in elderly individuals *(26)*. There is not a clear way to reconcile these noticeably different findings on the acrophase for ANP. Additional studies will be required if the time pattern of ANP levels and its relationship to specific 24-h BP patterns is to be more definitively characterized.

Plasma Renin Activity

Gordon et al. first described a diurnal rhythm for PRA that was independent of diurnal variations in posture and diet *(27)*. In these seminal studies the highest values for PRA were observed between 2 and 8 PM, and the lowest values between 12 and 6 PM. These early findings have been subsequently confirmed by several other investigators *(25,28–31)*. From these observations emerged the concept of a circadian rhythm in PRA, with a nadir in the afternoon and a peak in the early morning hours; however, several studies have been unable to demonstrate any significant time-wise variation in PRA *(32–34)*.

Further refinement of the concept of a circadian rhythm for PRA requires a definition of the relative role of endogenous circadian

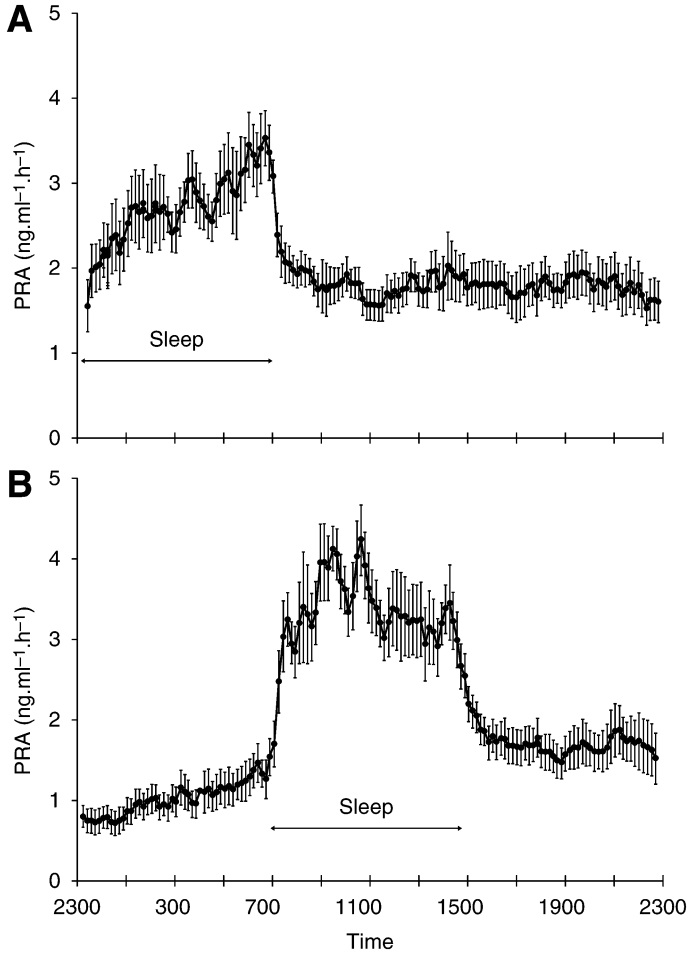

Fig. 2. Effects of an 8-h shift of the sleep–wake cycle on the 24-h plasma renin activity profiles in 10 subjects: **(A)** normal nocturnal sleep from 11 PM to 7 AM and **(B)** daytime sleep from 7 AM to 3 PM after a night of sleep deprivation. Values are expressed as means ± SEM. (Adapted with permission from ref. *34*.)

rhythmicity and the sleep–wake cycle on 24-h PRA variations. The sleep stage itself substantially contributes to time-wise variations in PRA and if not accounted for can conceal the makeup of an endogenous rhythm *(35)*. Brandenberger et al. have recently shown, using an acute shift in the normal sleep time, that increased renin release was associated with sleep whatever time it occurs, an observation not characteristic of an intrinsic circadian rhythm (Fig. 2) *(26)*.

A strong relationship exists between nocturnal oscillations in PRA and internal sleep structure *(33,36)*. Non-rapid eye movement (NREM) is invariably associated with increased PRA levels; conversely, PRA values decrease in tandem with rapid eye movement (REM) sleep. In normal humans, modifying renal renin content (low Na^+ diet or furosemide) modulates the amplitude of the nocturnal PRA oscillations while leaving the relationship to the stage of sleep intact *(37)*. In the case of sleep disorders, sleep apnea flattens PRA profiles and the restoration of a normal sleep pattern by continuous positive airways pressure (CPAP) treatment brings back the PRA oscillations typical of specific sleep cycle components *(38)*. These findings are not disrupted by prolonged bed rest *(31)*.

Although several studies have examined the 24-h cycle of PRA, few have seen fit to examine the relationship between PRA and ABP patterns and those that have fail to identify a consistent relationship. For example, after allowance for the decrease in PRA with age, direct relationships were observed between PRA (log values) and the level of pressure by Watson et al. *(39)*; alternatively, Chau et al. reported significant inverse correlations between upright PRA and 24-h mean BP values *(40)*. Harshfield and colleagues examined the relationship between renin-Na^+ profiles and ABP patterns in a biracial sample of healthy children and adolescents *(41)*. The subjects were classified as low, intermediate, or high renin from a relationship developed between PRA and 24-h urinary Na^+ excretion. The subjects with high renin-Na^+ profiles had a smaller decline in systolic BP with sleep than did subjects with low renin-Na^+ profiles (7 vs 11 mmHg). Subjects with high renin-Na^+ profiles also had greater variance in sleep-associated diastolic BP readings than subjects with either low or intermediate renin-Na^+ profiles. These studies show that the association between the level of RAA system activity and ambulatory BP patterns is complex, with Na^+ sensitivity and/or Na^+ intake as important covariables in this relationship.

The 24-h pattern for PRA varies from that for BP, which tends to fall in the first few hours of sleep and to rise thereafter *(42,43)*. Superimposed on these time tendencies for BP values, periodic changes in BP occur, which coincide with NREM sleep cycles *(42)*. Such changes are characterized by a decrease in mean BP during slow-wave sleep. In contrast, during REM sleep BP readings can reach values similar to those recorded during awakening and are characterized by marked and irregular fluctuations. Pressure-dependent mechanisms are likely causal in the nocturnal PRA oscillations rather than sleep-related processes per se *(43)*.

Plasma Aldosterone

Plasma aldosterone secretion is highest during the night and early morning *(28–31,44)*. The large increase in plasma aldosterone levels and pulse amplitude upon awakening is linked to increased adrenocorticotropic axis activity, reflected by the AM rise in cortisol. Plasma aldosterone values during a 24-h time period are coupled to PRA, with renin secretion being either simultaneous to or preceding aldosterone secretion by 10–20 min. This temporal coupling becomes even more evident with a low Na^+ intake *(44)*. Heretofore a time-wise change in the 24-h profile of aldosterone was viewed as a simple circadian event that is not influenced by prolonged bed rest per se *(31)*. More recently, it has been recognized that the pattern of aldosterone release is clearly influenced by sleep architecture *(45)*.

Under basal conditions sleep deprivation reduces plasma levels and pulse amplitude of plasma aldosterone *(46)*. Moreover, studies with an experimental design of shifting sleep by 8 h show sleep processes to have a strong stimulatory effect on aldosterone release. This is evidenced by the finding of high plasma aldosterone levels together with increased pulse amplitude/frequency during the period of sleep and reduced levels during sleep deprivation (Fig. 3). This pattern of secretion is not dissimilar to that seen with PRA *(35)*. The issue of sleep-related aldosterone change is complex with aldosterone pulses mainly related to PRA oscillations, whereas such pulses are coupled with those of cortisol during awake periods.

The influence of aldosterone circadian patterns on BP and, in particular, nocturnal BP remains poorly defined. Limited information exists that might allow an assessment of the effect of aldosterone receptor antagonism on circadian BP/natriuretic patterns *(46,47)*. A final consideration on the circadian rhythm for plasma aldosterone and BP relates to the aldosterone:ratio and its application as a screening measure for primary hyperaldosteronism. Because of the circadian rhythms for PRA and plasma aldosterone, their measurement should be performed at a standard time (such as between 8 and 9 AM) to improve the sensitivity and reproducibility of this measure *(49)*.

Sympathetic Nervous System

In both normotensive and hypertensive individuals, BP varies according to the mental state and/or the level of physical activity. BP, HR, and SNS activity are generally highest in the awake state and/or

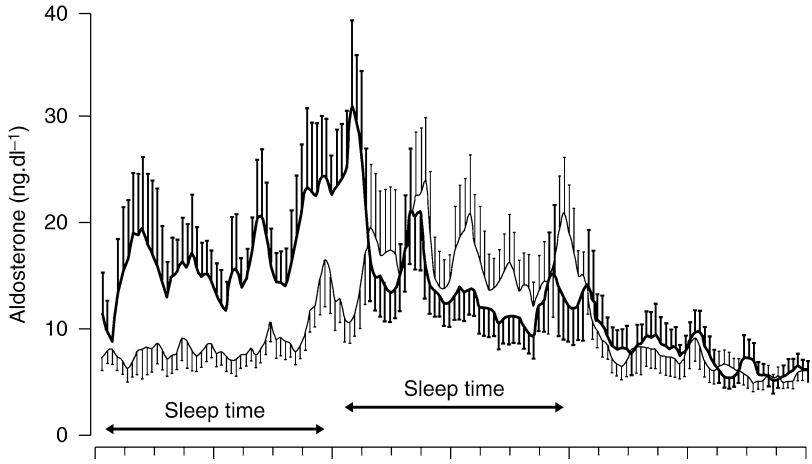

Fig. 3. Effect of an 8-h shift in sleep period cycle on 24-h profiles for plasma aldosterone (mean ± SEM) in seven subjects. Blood was sampled at 10-min intervals. In the daytime sleep condition, the amplitude of the aldosterone pulses was significantly enhanced during sleep. (Adapted with permission from ref. *45*.)

with physical/mental activity. Conversely, these values nadir between midnight and 3 PM *(50–52)*. Although the precise interplay of factors mediating the diurnal BP rhythm remains unclear, nocturnal BP and HR seem to most closely follow SNS activity. Abnormalities in the autonomic nervous system offer insight into the role of the SNS in diurnal BP rhythms. Paraplegics and incomplete tetraplegics typically have a normal diurnal BP pattern. However, the BP rhythm is nonexistent in quadriplegics despite HR variability being preserved. Presumably, this is because cardiac vagal innervation remains intact in the face of a complete high-level cord transection *(53)*.

Testing for level of activity in either the sympathoadrenal or noradrenergic branches of the SNS can prove challenging; thus, defining the role of the SNS in nocturnal BP changes is complicated by important methodological considerations. Plasma catecholamine values, as markers of diurnal changes in SNS activity, are subject to considerable sampling error and can prove difficult to interpret. The application of sympathetic nerve recording techniques and isotope dilution methodology quantifying neurotransmitter release from sympathetic nerves is cumbersome and difficult to apply to the circumstances of sleep. In addition, regional differences in SNS tone may exist that go undetected with whole body sampling.

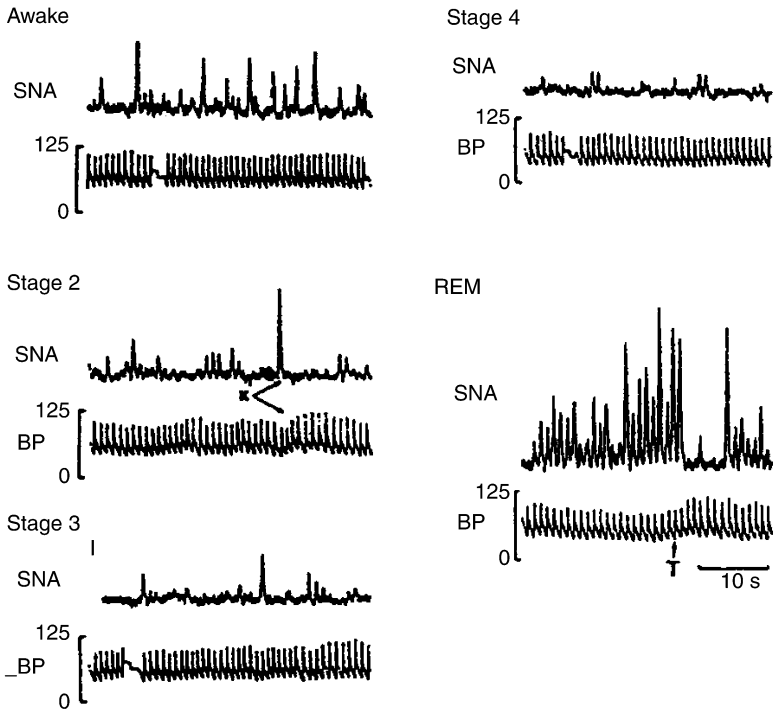

Fig. 4. Recordings of sympathetic nerve activity (SNA) and mean blood pressure (BP) in one subject either awake or in stages 2, 3, 4 and rapid eye movement (REM) sleep. As non-REM sleep deepens (stages 2–4), SNA gradually falls, and both the mean and variability in BP are gradually reduced. Arousal stimuli elicited K complexes on the electrocardiogram (not shown) were accompanied by increases in SNA and BP (indicated by the arrows, stage 2 sleep). In contrast to the changes during non-REM sleep, heart rate, BP, and BP variability increased during REM sleep, in concert with a profound increase in both the frequency and amplitude of SNA. There was a frequent association between REM twitches (momentary periods of restoration of muscle tone, denoted by T on the tracing), sudden inhibition of SNA, and increases in BP. (Adapted with permission from ref. *56*.)

Mindful of these difficulties in reliably establishing the level of SNS activity, it typically decreases while asleep with changes in the sympathoadrenal branch (epinephrine), governed by both posture and sleep, and the noradrenergic branch (norepinephrine), being regulated more by posture *(52)*. Plasma epinephrine concentrations and/or SNS activity decline during NREM sleep; alternatively, epinephrine concentrations increase with morning awakening *(52,54,55)* and episodically during REM sleep (Fig. 4) *(56)*. Plasma norepinephrine concentrations

trend downward with sleep and do not increase until a postural stimulus to norepinephrine release is combined with the arousal process *(52,54)*. Morning plasma norepinephrine concentrations are not necessarily the highest values attained during a 24-h time interval, although they are typically higher than sleep values *(54,55)*.

A higher level of muscle sympathetic nervous activity as determined by microneurography, a specific marker of muscle SNS activity, has been associated with greater daytime BP variability and a steeper decline in BP from day to night. These findings relate to testing undertaken in the late morning or early afternoon *(57)*. When tested in the early morning hours (between 6:30 and 8:30 AM), there appears not to be a specific increase in muscle sympathetic nerve activity in normal volunteers *(58,59)*. Parenthetically, this is a time interval during which the rate of myocardial infarction (MI) is highest *(2,4)*. This suggests that the early morning peak in MI and/or sudden cardiac death could, in part, reflect exaggerated end-organ responsiveness to norepinephrine following the relative downturn in SNS activity that occurs during sleep.

Nocturnal BP can be viewed as either an absolute number or in a proportional relationship to daytime BP readings. Nocturnal BP readings have a number of well-characterized patterns when specifically compared to daytime readings, including: normal dipping (a 10–20% decrease in nighttime BP), extreme dipping (a ≥30% decrease in BP while asleep), and nondipping (<10% drop in nocturnal BP or a rise in BP) *(10,59,60)*. Of these BP patterns, attention for the most part has been directed to a nighttime nondipping BP pattern, because it is believed to be associated with more rapid progression of renal failure *(61)* and a greater tendency to the development of left ventricular hypertrophy *(62)*. Aging, a salt-sensitive phenotype for BP, and African-American ethnicity are viewed as demographic markers for this phenomenon *(10)*.

Insight into the origin of a nocturnal nondipping BP pattern can be obtained from an analysis of sleep architecture and nocturnal SNS activity. HR slows and BP falls during NREM sleep, events marked by a relative increase in parasympathetic or vagal activity *(63–65)*. It is believed that alterations in SNS activity can importantly influence the diurnal BP pattern. Derangements in autonomic nervous system activity, sleep-disordered breathing, and sleep disturbances per se are established causes of changes in the circadian BP profile *(64)*. Schillaci et al. observed that the reported duration of sleep was significantly shorter for both male and female hypertensive "nondippers" than it was for

"dippers" *(66)*. Kario et al. found nondippers to have increased nocturnal physical activity as determined by actigraphy *(67)*; thus, deeper and less fragmented sleep can be expected to be associated with greater BP dipping *(68)*.

Nutritional

The BP impact of modification in cation intake has been most typically assessed by determining changes in casual BP determinations *(69,70)*. Recently, ABP has been used to more carefully describe the 24-h pattern of change with such interventions *(71–77)*. Accordingly, it is only in the last several years that nocturnal BP patterns could serve as targets for dietary intervention *(71,75)*.

Demographic groups exist in whom the equilibrium point for Na^+ balance is set at a higher BP level. Weinberger et al. demonstrated that African Americans and older individuals (>40 yr) more poorly excrete a Na^+ load and require higher BP values for a longer period of time in order to reach Na^+ balance *(78)*. Falkner et al. have also reported in a cohort of young African Americans (18–23 yr) that those with a positive family history for hypertension together with Na^+ sensitivity (≥ 5 mmHg increase in mean arterial pressure after 10 g of NaCl being added to the diet for 14 d) had the greatest weight and mean arterial pressure response *(79)*. Harshfield et al. have also demonstrated that Na^+ intake is an important determinant of ABP profiles in African-American children and adolescents (10–18 yr) *(80)*. African-American subjects displayed a positive correlation between Na^+ excretion and asleep systolic BP, whereas Na^+ excretion was independent of asleep BP in white subjects.

The relationship between salt-sensitivity and the nocturnal decline in ABP has been carefully probed. Wilson et al. explored the relationship between Na^+ sensitivity and ABP in healthy African-American adolescents *(73)*. They classified 30 and 70% of those studied as Na^+ sensitive and resistant, respectively. Sodium-sensitive subjects showed higher daytime diastolic and mean BP values than did Na^+-resistant subjects. A significantly greater percentage of salt-sensitive subjects were classified as nondippers according to diastolic BP (<10% decrease from awake to asleep) as compared to Na^+-resistant individuals (Fig. 5). These findings are consistent with prior observations by de la Sierra et al. *(74)*, which showed higher awake BP values in normotensive Na^+-sensitive as compared to Na^+-resistant adults and a recent meta-analysis, which found African Americans to experience a smaller dip in BP (higher levels of

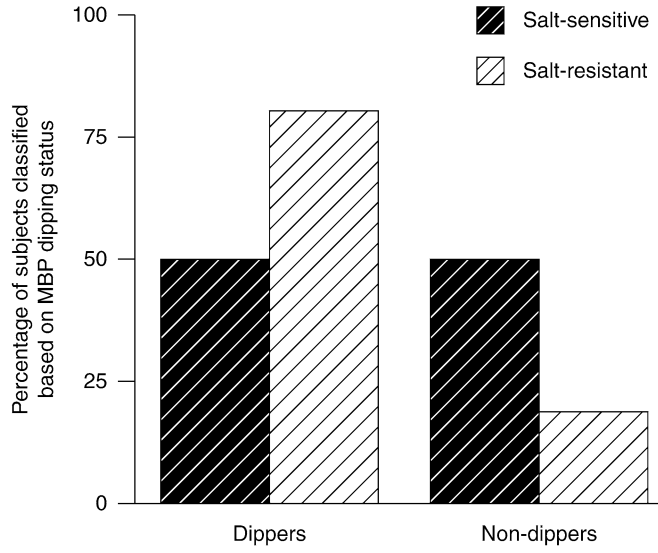

Fig. 5. Percentage of salt-sensitive vs salt-resistant normotensive adolescent African Americans who were classified as dippers (>10% decline in nocturnal blood pressure) or nondippers (<10% decline in nocturnal blood pressure). (Adapted with permission from ref. *73*.)

both systolic and diastolic BP) at night *(81)*. Whether the greater likelihood of nondipping status is a finding only in African Americans is an unresolved issue *(81,82)*.

The mechanism(s) by which Na^+ sensitivity (or Na^+ loading) alters nocturnal BP likely involves some element of increased SNS activity *(83,84)*. Increased SNS activity, in turn, is known to modify Na^+ handling, albeit in a varied fashion. For example, Harshfield et al. have found that normotensive individuals differ in Na^+ handling during SNS activation *(85)*. In one group of adults, termed excreters, Na^+ excretion increased during 1 h of behaviorally induced SNS arousal (competitive video games) with a return to baseline levels within 2 h of stimulation. In a second group of adults, termed retainers, Na^+ excretion decreased in response to SNS arousal and remained below baseline values for at least 2 h following stimulation. The capacity of SNS arousal to decrease renal Na^+ excretion is an observation and that offers an explanation as to how nocturnal BP might be altered *(85–87)*.

The role of Na^+ intake in nocturnal BP patterns is evident from several studies *(71,72)*. Uzu et al. found that a nondipper nocturnal BP pattern in salt-sensitive patients converted to a dipper pattern with Na^+ restriction

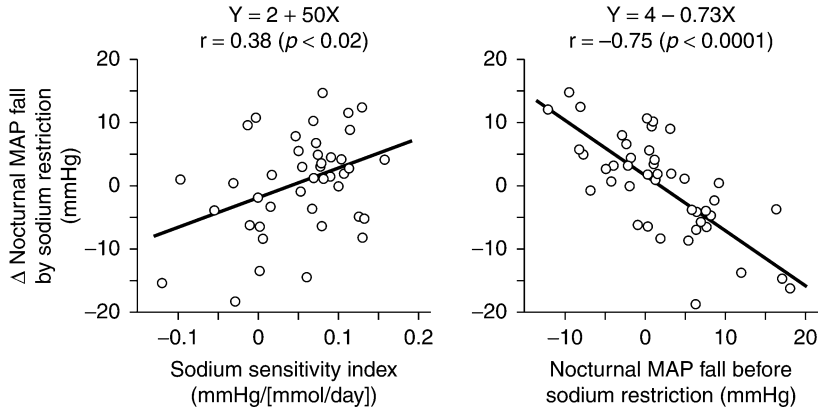

Fig. 6. Relationships of changes in nocturnal MAP fall induced by Na^+ restriction with Na^+-sensitivity index as well as with nocturnal MAP fall before Na^+ restriction. The Na^+-sensitivity index, shown on the left, was calculated as the ratio of the change in MAP over the change in $U_{Na}V$ produced by Na^+ restriction (1–3 g NaCl/d). The nocturnal fall in MAP before Na^+ restriction on the right was calculated as the difference between daytime and nighttime MAP during high Na^+ intake (12–15 g NaCl/d). The change in nocturnal MAP fall with Na^+ restriction was calculated as the difference between low- and high-Na^+ diets and had a positive relationship with the Na^+-sensitivity index ($r = 0.38$, $p < 0.02$) and a negative relationship with the nocturnal MAP fall during the high- Na^+ diet ($r = –0.75$, $p < 0.0001$). (Adapted with permission from ref. *71*.)

(Fig. 6) *(60)*. Higashi et al. *(61)* found that the nocturnal decline in mean BP was significantly smaller in Na^+-sensitive as compared to Na^+-resistant hypertensives during a Na^+-loading protocol, adequate to have elevated ABP levels (Fig. 7). In their studies, nondipping was most commonly seen in Na^+-sensitive hypertensive patients receiving a high-Na^+ diet. These findings suggest that a high Na^+ intake can be an etiologial factor (among several others) for the failure of BP to decline at night in hypertensive patients, particularly in Na^+-sensitive individuals.

The relationship between K^+ intake and BP responses (including ABP) has been delved into in some detail *(10,73)*. A means by which K^+ may influence BP patterns is by way of K^+-related natriuresis. A number of studies have suggested that a change in K^+ intake alters Na^+ balance, such that natriuresis occurs with an increase in K^+ intake, whereas the converse occurs with K^+ restriction *(88–90)*. K^+-related natriuresis can be expected to decrease BP in conjunction with a reduction in plasma volume. A K^+-mediated direct vasodilator effect on BP has also been identified. For example, the local intraarterial infusion of

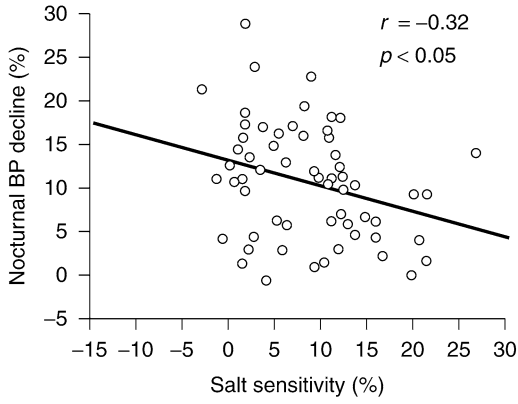

Fig. 7. Scatterplot showing the relationship between the nocturnal decline in blood pressure during a high-NaCl diet (340 mmol/d) (nocturnal blood pressure [BP] decline) and the NaCl-induced increase in blood pressure (salt sensitivity). The NaCl-induced increase in BP was correlated with the nocturnal decline in BP during a high-NaCl diet but not during a low-NaCl diet. (Adapted with permission from ref. *72*.)

K^+ in a dose-dependent fashion decreases forearm vascular resistance while increasing forearm blood flow *(91,92)*. It has also been shown that K^+ supplementation together with a high-Na^+ diet suppresses the catecholamine increase, which occurs in response to Na^+ loading *(84)*. The BP response to an increase in K^+ intake for the most part seems not to be influenced by the type of K^+ salt given *(93)*.

These observations led Wilson et al. to examine the effects of a 3-wk increase in K^+ on ABP responses in healthy African-American adolescents classified as dippers or nondippers according to whether they sustained a >10% decrease from awake to asleep BP. Subjects were randomized to either a high-K^+ diet or a usual diet control group. A significant proportion of nondippers converted from a nondipper to dipper status in response to the high-K^+ diet *(10)*. Although this study did not show a change in nocturnal BP, a follow-up study did show a reversal in nighttime BP as a consequence of a high-K^+ diet in salt-sensitive individuals *(73)*. Finally, Mu et al. have shown a significant increase in nocturnal urinary Na^+ excretion in Na^+-sensitive children given supplemental calcium and K^+ *(94)*.

SUMMARY

Nocturnal BP patterns present as a consequence of both intrinsic circadian rhythms and the quantity and quality of sleep. Although a

variety of neurohumoral factors can have a bearing on the circadian BP pattern, abnormal SNS activity is the one variable most commonly linked to a disappearance of the customary decline in nocturnal BP. Nutritional intake, such as either a high Na^+ or a low K^+ intake, also can eliminate the normal decline in nocturnal BP. The impact of dietary Na^+ intake on nocturnal BP is most prominent in salt-sensitive individuals. Additional studies of an integrative nature are needed to more fully characterize the dynamics of nutrient intake, neurohumoral activity, and the manner in which nocturnal BP patterns evolve.

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10 Prognostic Value of Ambulatory Blood Pressure Monitoring

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CONTENTS

INTRODUCTION

Twenty-four-hour noninvasive ambulatory blood pressure (ABP) monitoring is increasingly used in subjects with essential hypertension *(1,2)*. Traditionally, diagnosis and management of hypertension are based on blood pressure (BP) measurements taken in the physician's office, but several prospective studies conducted in the general population or in hypertensive subjects, either untreated or treated at the time of execution

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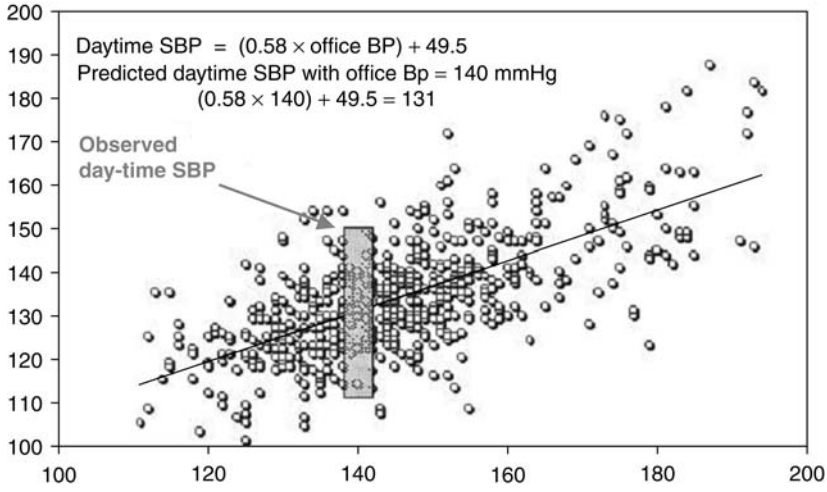

Fig. 1. Graphic representation of the association between office blood pressure and average daytime ambulatory blood pressure in 732 untreated hypertensive patients (our database). The figure shows that the observed ambulatory blood pressure is seldom that predicted by linear regression equation, while it is most often higher or lower than predicted. BP, blood pressure; SBP, systolic blood pressure.

of ABP monitoring, have shown that ABP measurements provide a better prediction of clinical outcome compared with conventional clinic or office BP measurements, especially in mild and moderate hypertension *(3–34)*. The advantages of ABP compared to office BP in predicting clinical outcome and the most appropriate way of interpreting the results of ABP monitoring will be discussed in this chapter.

ASSOCIATION BETWEEN AMBULATORY BLOOD PRESSURE AND TARGET ORGAN DAMAGE

The correlation between clinic BP and hypertension-related organ damage is relatively poor because of two major limitations inherent to clinic BP measurement, namely the marked spontaneous variability of BP measurements and the so-called white-coat effect.

If one plots office BP vs average daytime ABP, it is apparent that for any given value of office BP, the observed ABP may vary considerably, in either direction, from the value predicted by a linear regression equation (Fig. 1). In their landmark longitudinal study, Perloff et al. demonstrated that the risk of cardiovascular (CV) events was significantly higher in the subjects with higher-than-predicted ABP than in those with lower-than-predicted ABP, particularly in the subjects with stage I hypertension *(3,4)*.

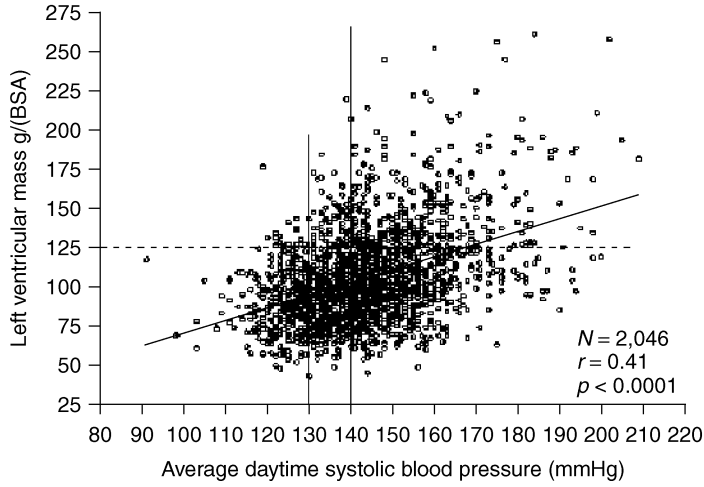

Fig. 2. The plot shows the association between average daytime ambulatory blood pressure and left ventricular mass detected at echocardiography in 2046 untreated hypertensive patients (PIUMA database).

The different prognostic value of office BP and ABP might be expected if one considers their different association with hypertension-related organ damage. Drayer et al. *(35)* and Devereux et al. *(36)* first demonstrated that ABP correlated more closely with left ventricular mass than did casual BP. Now there is general consensus regarding the closer correlation between left ventricular mass and ABP over clinic BP (Fig. 2) *(37–39)*.

Similar results have been obtained when considering microalbuminuria. In young subjects, albumin excretion rate was significantly associated with both 24-h systolic and diastolic ABP, but not with office systolic BP *(40)*. These results suggest that ABP may be more important in predicting albumin excretion rate than traditional BP measurements.

Asmar et al. examined arterial distensibility by carotid-femoral pulse velocity and found a closer association of this parameter with ABP than with office BP *(41)*. On the other hand, carotid intima media thickness has been found to be more closely associated with ABP, particularly pulse pressure (PP), than with office BP *(42)*.

AMBULATORY BLOOD PRESSURE PROVIDES BETTER PREDICTION OF CLINICAL OUTCOME THAN OFFICE BLOOD PRESSURE MEASUREMENT

One of the first studies that addressed the prognostic value of ABP in the general population was the Ohasama study *(19,20)*. In a Japanese

elderly population, after adjustment for age, sex, smoking status, baseline office BP, and use of antihypertensive drugs, ABP was a better predictor of CV mortality than office BP, with subjects in the highest quintile for systolic and diastolic ABP being at greatest risk for CV death. In that study, a U-shaped relationship was noted between the average 24-h BP, both systolic and diastolic, and CV mortality *(20)*, which was interpreted as a possible expression of the link between low BP levels and various morbid conditions in the general population. In a further, long-term analysis of the same population, the U- or J-shaped relation between systolic BP and mortality became more linear after censoring the first 2 yr of observation *(23)*. These data were confirmed in a Danish general population sample in which ABP was a stronger determinant of all-cause and CV mortality than office BP *(24)*. In this study, the relationship between ABP and prognosis was log-linear, with no evidence of a threshold or of a U-shaped relationship.

It appears that a minority of subjects who are normotensive in the clinic have high BP when measured out of the office. This condition is labeled as "isolated ambulatory hypertension" or "masked hypertension." A recent analysis of a population-based sample of Swedish elderly men reported that the outcome of these subjects is worse than that of true normotensives *(25)*. After adjustment for serum cholesterol, smoking, and diabetes, not only sustained hypertension (hazard ratio, 2.94; 95% confidence interval [CI], 1.49–5.82) but also isolated ambulatory hypertension, (hazard ratio, 2.77; 95% CI, 1.15–6.68) were independent predictors of CV morbidity when compared to normotension. In the same study, ambulatory daytime systolic BP was associated with an adverse outcome independently of office systolic BP (hazard ratio for 1 standard deviation increase, 1.47; 95% CI, 1.09–1.97) *(25)*.

In a study of 808 elderly subjects with isolated systolic hypertension followed up for a mean of 4.4 yr, ambulatory systolic BP was a significantly better predictor of CV and cerebrovascular events than conventional BP measurement *(16)*. Briefly, 98 of 808 patients developed a major CV event and after adjustment for age, sex, office BP, active treatment, previous events, cigarette smoking, and residence in the western Europe, the average nighttime systolic BP was a significant predictor of total, cardiac, and cerebrovascular events, whereas the average daytime BP did not yield statistical significance. For every 10 mmHg increase in nighttime systolic BP, the hazard rate for CV events was 1.20 (95% CI, 1.08–1.35) whereas those for cardiac and cerebrovascular events were 1.16 (95% CI, 1.02–1.33) and 1.31 (95% CI, 1.06–1.62), respectively. In the placebo group, the night-to-day ratio of systolic ABP was an

independent prognostic marker even after adjustment for the average 24-h ABP. In this study, the same CV risk was predicted by systolic BP levels of 160 mmHg (office BP), 142 mmHg (average 24-h ABP), 145 mmHg (average daytime ABP), and 132 mmHg (average nighttime ABP) *(16)*.

The first study that demonstrated the prognostic impact of ambulatory BP in patients with resistant hypertension was that published in 1998 by Redon et al. *(18)*. In that study 86 patients with poorly controlled hypertension, defined by an office diastolic BP > 100 mmHg despite treatment with three or more drugs, including a diuretic, underwent 24-h ABP monitoring. Over a mean follow-up of 4 yr, 21 patients suffered a first CV event. After controlling for age, sex, smoking, left ventricular hypertrophy, and office BP, the event rate was significantly higher ($p < 0.02$) in the upper tertile (13.6 events per 100 patient-years) than in the middle (9.5 events per 100 patient-years) and lower (2.2 events per 100 patient-years) tertile of daytime diastolic BP. According to this study, an average daytime diastolic BP ≥ 88 mmHg in a subject with office diastolic BP > 100 mmHg despite treatment with three or more drugs should be considered an adverse prognostic marker.

In a study from our group *(43)*, ABP monitoring was undertaken before therapy and after an average follow-up of 3.7 yr in 790 treated subjects. At the follow-up visit, 27% of subjects achieved adequate office BP control, defined as BP < 140/90 mmHg, and 37% of subjects achieved adequate ambulatory BP control, defined as daytime BP < 135/85 mmHg. After the follow-up visit, 58 patients suffered a first CV event. Event rate was significantly lower among the subjects with adequate ambulatory BP control (0.71 events per 100 person-years) than among those with higher BP levels (1.8 events per 100 person-years) (Fig. 3). Ambulatory BP control predicted a lesser risk for subsequent CV disease, whereas office BP control was associated with a nonsignificant lesser risk of subsequent events.

The Office Versus Ambulatory (OvA) blood pressure study investigated the association between ABP in treated patients and subsequent CV events in 1963 patients *(26)*. The median follow-up was 5 yr. In a multivariate model adjusting for several covariates, including office BP, higher mean values for 24-h ABP were independent risk factors for new CV events.

In the Dublin Outcome Study *(33)*, a large observational registry of subjects who underwent ABP before treatment and were subsequently followed for up to 20 yr, there were 646 deaths, 389 from CV causes. This large number provided the opportunity to examine the value of

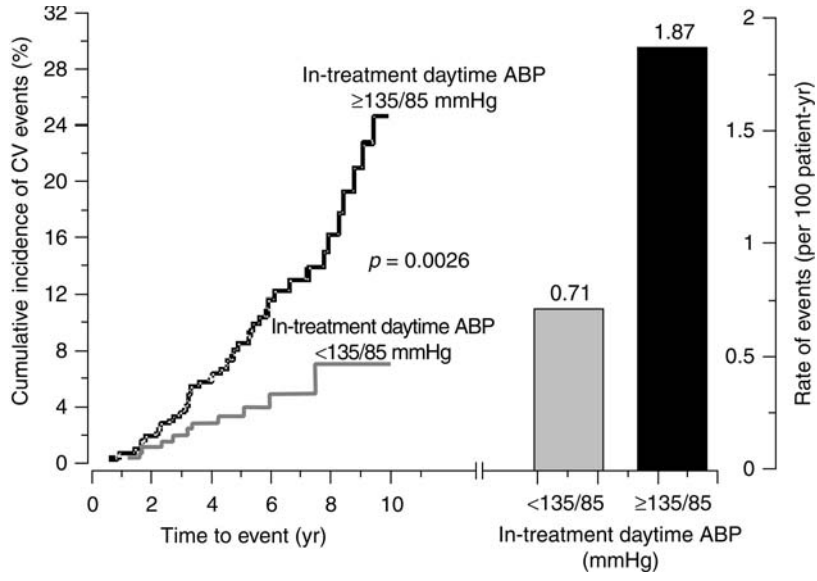

Fig. 3. Incidence of cardiovascular disease in treated hypertensive subjects with and without adequate control of ambulatory blood pressure (ABP).

ABP for prediction of CV mortality in a large hypertensive population. After correction for several confounders, ABP was superior to office BP for prediction of CV mortality and nighttime ABP was the most potent ABP component for prediction of outcome.

In the follow up of the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study *(34)*, a study carried out in a general population sample, nighttime ABP also proved to be superior to daytime ABP for prediction of a composite of fatal and nonfatal CV events. However, the added prognostic information provided by ABP over office and home BP was only modest.

Taken together, these data provide convincing evidence that achieved ambulatory BP is a powerful determinant of subsequent outcome and that its predictive power is superior to that of pretreatment ambulatory BP, and to that of pretreatment or in-treatment office BP.

INTERPRETATION OF RESULTS OF AMBULATORY BLOOD PRESSURE MONITORING

Reference Values

Average 24-h, daytime, and nighttime BP values are the principal components of the ABP profile to be considered as prognostic determinants.

Table 1
Reference Values for Ambulatory Blood Pressure Based on Prospective Outcome Studies

ABP component (ref.)	*ABP measure*	*Reference value*
Average blood pressure		
Northwick Park Study *(7)*	24-h intraarterial	140/90 mmHg
Kario et al. *(11)*	24-h noninvasive	130/80 mmHg
Ohasama Study *(3)*	24-h noninvasive	134/78 mmHg
PIUMA Study *(12)*	Daytime BP (6–22 h)	130/80 mmHg
Syst Eur Study *(13)*	Daytime SBP (10–20 h)	160 mmHg
OvA Study *(26)*	24-h noninvasive SBP	135 mmHg
Day–night BP difference		
PIUMA Study *(14)*	Day–night BP drop	10%
Zweiker et al. *(2)*	Day–night BP drop	10%
PIUMA Study *(15)*	Day–night BP drop	0%
Ohasama Study *(16)*	Day–night BP drop	0%
Nakano et al. *(4)*	Acrophase	20-08 h
Pulse pressure		
PIUMA Study *(8)*	24-h pulse pressure	53 mmHg
Northwick Park Study *(17)*	24-h intraarterial	70 mmHg
SD of daytime BP		
PIUMA Study *(18)*	SD of daytime systolic BP	14 mmHg
Sander et al. *(10)*	SD of daytime systolic BP	15 mmHg

ABP, ambulatory blood pressure; SD, standard deviation.

Although it is generally agreed that the adverse effects of hypertension are related to the average ABP level to which target organs are exposed over time (Fig. 2), reference values are still uncertain because there is a paucity of data allowing an agreed-upon definition of the values of ambulatory systolic and diastolic BP dividing up normotension from hypertension (Table 1). Currently, an average daytime BP < 135 mmHg systolic and <85 mmHg diastolic is generally considered normal, and levels <130/80 mmHg may be considered optimal *(44)*.

White-Coat Hypertension

White-coat hypertension (WCH), also referred to as office hypertension or isolated clinic hypertension *(45,46)*, is generally defined as a persistently elevated office BP in the presence of a normal BP outside the office *(44)*. The previously described definition generally applies to untreated subjects because most available studies dealt with this kind of subjects.

Despite a large number of studies, the definition of WCH remains unsettled. In fact, although the usual definition of elevated office BP is clear (≥140 mmHg systolic and/or ≥90 mmHg diastolic), there is controversy about the definition of normal BP outside the office. It is not easy to find two studies that have used exactly the same definition of WCH based on results of ABP monitoring *(47–64)*. The definition was based on both systolic and diastolic values in some studies and solely on diastolic values in others; some studies used the average ABP during the day and others used the average 24-h ABP *(47–60)*. Still other studies added a measure of the office-ambulatory BP difference in the definition. The upper reference limits of ABP used to define WCH differed across these studies. Such differences might seem small and clinically unimportant, but the prevalence of WCH, and of the associated cardiac target-organ damage, increased markedly when moving from more restrictive (lower) to more liberal (higher) limits of ambulatory BP normalcy over a relatively narrow range *(47)*. The prevalence of left ventricular hypertrophy, virtually absent below 120 mmHg and very low below 130 mmHg (6%), increased to 10.5% when the limit was set to 140 mmHg. Thus, modest swings over a narrow range of presumably normal or nearly normal ambulatory BP may result in remarkable differences in the prevalence of subjects with increased left ventricular mass.

In order to investigate the prognostic significance of WCH in the setting of the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study *(5)*, we followed for up to 7.5 yr 1187 adult subjects with essential hypertension and 205 healthy normotensive controls in whom off-therapy 24-h ABP monitoring had been carried out at entry. Prevalence of WCH was 19.2%. The rate of combined fatal and nonfatal CV events (per 100 patient-years) was 0.47 in the normotensive group, 0.49 in the group with WCH, 1.79 in dippers with ambulatory hypertension, and 4.99 in nondippers with ambulatory hypertension. CV morbidity did not differ between the normotensive group and the group with WCH in a multivariate analysis ($p = 0.83$). These results showed for the first time that CV morbidity is lower in WCH than in ambulatory hypertension and not dissimilar between WCH and clinical normotension. These data have been confirmed in two other prospective studies *(27,28)*. Among 1038 subjects with mild hypertension followed for an average of 4.5 yr, CV event rate in the subgroup with WCH (daytime BP < 135/85 mmHg) was significantly lower than that observed in sustained hypertension (0.38 vs 1.39 events per 100 person-years), and not dissimilar from that of a normotensive control

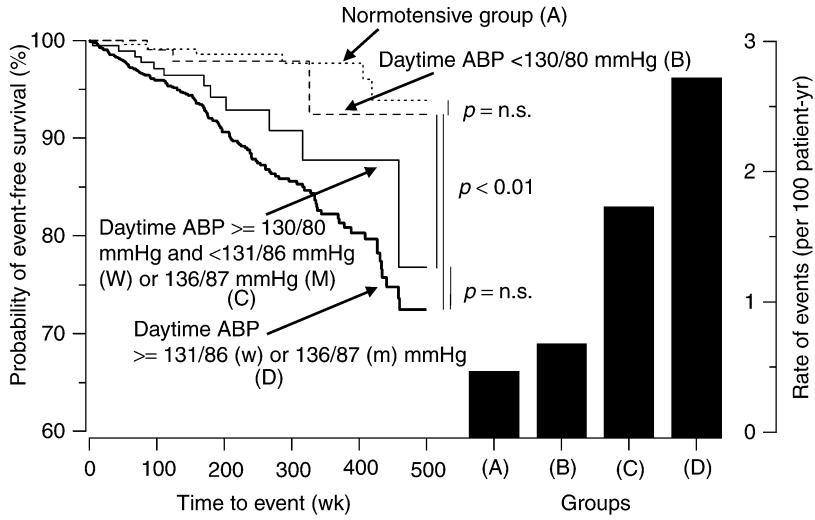

Fig. 4. The figure shows the rate of major cardiovascular morbid events in a normotensive group **(A)**, two groups with white-coat hypertension defined using a restrictive **(B)** or liberal **(C)** criterion, and a group with ambulatory hypertension **(D)**. ABP, ambulatory blood pressure.

group (0.27 events per 100 person-years) *(27)*. In 958 elderly Japanese subjects followed over a 3.5-yr period, the incidence of stroke in WCH was similar to that observed in normotensive subjects (2.0 vs 2.1%) and lower than the risk in sustained hypertension (9.4%, $p < 0.001$) *(28)*.

In a larger analysis of the PIUMA database *(22)*, the subgroup with WCH was divided up into two subsets with very low ABP values (average daytime ABP < 130/80 mmHg) or with intermediate values (between 130/80 and 131/86 mmHg in women or 136/87 mmHg in men). Figure 4 shows that the differences in event-free survival between the normotensive group and the group with WCH defined more restrictively were not statistically significant, whereas the differences between the normotensive group and the WCH group defined more liberally were significant. These data suggest that a daytime ABP < 130 mmHg systolic and 80 mmHg diastolic may be defined optimal in order to identify WCH subjects whose CV risk can be considered low and not dissimilar from clinically normotensive subjects.

To gain further insight into the long-term clinical relevance of WCH, an International collaborative study was initiated, which pooled individual data from four prospective cohort studies from the United States,

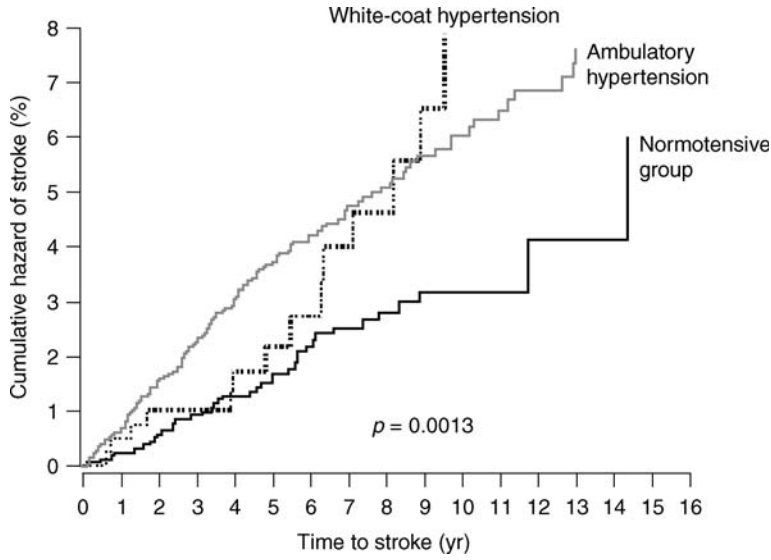

Fig. 5. Cumulative hazard for stroke in normotensive subjects, subjects with white-coat hypertension, and subjects with ambulatory hypertension.

Italy, and Japan *(29)*. In this study, 4406 initially untreated subjects with essential hypertension and 1549 healthy normotensive controls were followed for a median of 5.4 yr. In a multivariate analysis, the adjusted hazard ratio for stroke was 1.15 (95% CI, 0.61–2.16) in the WCH group ($p = 0.66$) and 2.01 (95% CI, 1.31–3.08) in the ambulatory hypertension group ($p = 0.001$) compared with the normotensive group. However, the incidence of stroke tended to increase in the WCH group in the long run, and the corresponding hazard curve crossed that of the ambulatory hypertension group by the ninth year of follow-up (Fig. 5). An obvious limitation of this study was the small number of stroke events after the sixth year of follow-up. Nevertheless, these data raise the hypothesis, to be tested in future studies, that WCH might not be a benign condition for stroke in the long term.

A document issued by the American Society of Hypertension *(1)* suggests using quite restrictive upper limits to define normalcy of ABP (i.e., average daytime BP < 135 mmHg systolic and <85 mmHg diastolic). Furthermore, the cross-sectional results of the PAMELA study *(65)*, a study carried out in the general population, indicate upper reference limits of daytime ABP of 129–132 mmHg systolic and 80–85 mmHg diastolic in men, and 125–129 mmHg systolic and 80–82 mmHg diastolic

in women. The previously listed values correspond to an office BP of 140/90 mmHg.

Khattar et al. *(14)* examined 479 subjects with essential hypertension who had undergone 24-h intraarterial ABP monitoring before therapy. Intraarterial BP monitoring is the gold standard for BP measurement, although not being suitable for general clinical practice. Prevalence of WCH, defined by an average 24-h ABP <140/90 mmHg, was 26%. Over a follow-up period of 9 yr, the rate of CV morbid events was 1.32 per 100 patient-years in the WCH group and 2.56 in the ambulatory hypertension group. These differences were significant after adjustment for age, gender, race, and smoking. In contrast, baseline office BP did not yield statistical significance. In this study, the definition of WCH may not be comparable with that used in noninvasive studies because intraarterial ABP averages may be higher than those resulting from noninvasive monitoring *(66)*. This study was the first to demonstrate, with intraarterial ABP monitoring, the lesser CV risk in the subjects with WCH than in those with higher ABP. Unfortunately, a normotensive control group could not be included because of ethical reasons.

For now, it is reasonable to consider the possibility that antihypertensive drug treatment might be unnecessary in many subjects with WCH *(67)*. It is worth noting, however, that some of the subjects with WCH may be at increased CV risk because of concomitant risk factors such as diabetes, cigarette smoking, elevated cholesterol, or family history of premature CV disease. Withholding antihypertensive drug treatment in these subjects on the basis of a "normal" ABP in the setting of a high office BP may not be justified in the absence of evidence about safety of such intervention. Thus, randomized intervention studies are urgently needed in subjects with WCH in order to compare a regimen based on lifestyle measures without drugs with a standard regimen consisting of lifestyle measures with possible addition of drugs according to current recommendations based on office BP *(68)*. Unfortunately, these studies are unlikely to be supported by institutions other than government agencies and/or scientific or insurance societies.

On the basis of current evidence, we suggest a treatment based on lifestyle measures in the low-risk stratum of subjects with white-coat hypertension under the conditions of correct definition, absence of important co-morbid conditions and target organ damage, and adequate follow-up *(68)*. A correct definition includes an average daytime ABP <135 mmHg systolic and 85 mmHg diastolic, whereas levels <130 mmHg systolic and 80 mmHg diastolic may be defined as optimal *(64)*.

White-Coat Effect

The measurement of BP in the physician's office can trigger an alerting reaction and a rise in BP *(69–72)*. The transient rise in BP from before to during the visit is usually defined as white-coat effect or white-coat phenomenon, whereas the coexistence of persistently high office BP with normal ABP, regardless of the extent of the white-coat effect, is often referred to as WCH. From a practical standpoint, it is worth noting that the white-coat effect is a measure of BP change from before to during the visit, whereas WCH is an operative definition of clinically hypertensive subjects at low potential risk because of apparently normal mean BP levels during daily life. A reliable estimate of the white-coat effect may be carried out through intraarterial *(71,72)* or noninvasive *(73)* techniques, with beat-by-beat measurement of the BP rise from immediately before to during the visit. Mancia et al. have shown that the rise in intraarterial BP during the visit is, on average, 27/14 mmHg, being maximal during the first 4 min of the visit, disappearing within about 10 min, and persisting over several visits *(72,73)*.

The white-coat effect has also been estimated by the difference between office BP and average daytime ABP, based on the belief that average daytime ABP corresponds to the BP immediately before the visit. However, this assumption may be incorrect, and, in fact, no significant association has been found between the beat-to-beat BP rise from before to during the visit and the difference between office BP and daytime ABP *(74)*.

From a prognostic standpoint, in the setting of the PIUMA study the rate of both total and fatal CV disease events did not show any association with the office-ambulatory BP difference *(8)*. These data indicate that the office-ambulatory BP difference, taken as a measure of the white-coat effect, is not a predictor of CV morbidity and mortality in subjects with essential hypertension.

Day–Night Blood Pressure Changes

The clinical significance of day–night ambulatory blood pressure differences has been the subject of an extensive research. Intraarterial studies with beat-to-beat recording in ambulant subjects showed that, in normotensive individuals, BP is characterized by a circadian pattern with values tending to peak during the daytime hours and then falling to a nadir at night *(75,76)*.

Twenty-four-hour noninvasive ABP monitoring appears to be a valid tool to investigate the diurnal BP changes associated with the sleep–wake

cycle *(1,2)*, because it has been demonstrated that intraarterial 24-h BP profile is similar in the absence and in the presence of concomitant noninvasive BP monitoring *(77,78)*.

Day and night have been defined using the waking and sleeping periods from patient's diary or through arbitrarily defined fixed time intervals, either wide (usually from 6 AM to 10 PM for day and from 10 PM to 6 AM for night) or narrow (e.g., from 10 AM to 8 PM for day and from midnight to 6 AM for night). The use of narrow fixed-clock intervals excludes the morning and evening transitional periods, during which a variable proportion of subjects actually is awake or asleep, and seems to be preferable to wide fixed-time intervals because it gives a more accurate estimate of the actual BP values during sleep and wakefulness, at least in subjects going to bed and arising in reasonably well-defined time intervals *(79–81)*.

In recent years several authors have examined the risk of a less than physiological fall in BP during night sleep: according to whether hypertensive patients have a greater or smaller fall in nighttime BP, it has become usual to subdivided them into "dippers" or "nondippers." Generally, nondippers are defined by a reduction in BP by less than a given percentage from day to night, and the subjects out of this definition are classified as dippers. The threshold values for classification ranged from 10% to 10/5 mmHg, up to 0% (i.e., no reduction in BP from day to night or a higher BP during night than during day) *(81)*.

Like all categorizations of continuous variables, the dipper–nondipper classification has been criticized because it implies an arbitrary dichotomization of a continuous variable (i.e., the day–night difference in BP), because it is very difficult to differentiate true "nondippers" from "nonsleepers" without monitoring brain wave activity and also because the definitions of day and night and that of the partition line between dippers and nondippers are arbitrary.

However, such classification appears useful from a clinical standpoint; several reports from independent centers showed that not only left ventricular hypertrophy *(82–87)*, but also ventricular arrhythmias *(88)*, silent cerebrovascular disease *(89,90)*, microalbuminuria *(91,92)*, and progression of renal damage *(93)* were greater in subjects with blunted or abolished fall in BP from day to night than in those with normal day–night BP difference. These results strongly support hypothesis that target organ damage is more advanced and prognosis is worse when the BP load is persistent throughout the 24 h than when it is limited to the daytime hours.

Some studies suggested that nighttime blood pressure is more important than daytime blood pressure in predicting outcome. O'Brien et al. *(94)* reported a more frequent history of stroke in nondippers than in dippers. In older patients with isolated systolic hypertension, CV risk increased with a higher night:day ratio of systolic blood pressure (SDP) (i.e., in patients more likely to be nondippers) independent of the average 24-h blood pressure, with a 10% increase in the ratio giving a hazard ratio for CV end-points of 1.41 (95% CI, 1.03–1.94) *(16)*.

In the PIUMA study, a greater left ventricular mass in nondippers than in dippers was found only in those subjects with abnormally increased ABP values, but not in normotensive subjects or in subjects with WCH *(95)*. Thus, a blunted day–night BP fall may be expected to be harmful for the heart only when the average level of ABP is definitely abnormal.

When dippers and nondippers are compared, it is important to adjust for possible imbalances between the groups in the average 24-h ambulatory BP. If the two groups are matched by daytime ABP only, the average 24-h values will be higher in nondippers than in dippers.

In the PIUMA study *(5)*, hypertensive women with a nondipping pattern at the baseline evaluation had a higher CV morbidity during follow-up than dippers, and this difference remained significant after controlling for traditional risk markers. A nonsignificant trend in the same direction was found in men. In a subsequent analysis of a larger PIUMA sample *(6)*, we examined the relation between CV morbidity and night:day BP ratio, a continuous measure of the nocturnal BP reduction. In this analysis, the rate of CV events significantly increased in both genders with the night:day ratio of systolic BP even after adjustment for age, diabetes, and 24-h systolic ABP (Fig. 6).

The adverse prognostic significance of a blunted day–night rhythm of ABP was confirmed in other studies. In the Ohasama study, Ohkubo et al. *(21)* found an increased CV mortality in nondippers (relative risk 2.56, $p = 0.02$) and inverted dippers (relative risk 3.69, $p = 0.004$) in comparison with dippers. Another Japanese study showed a higher risk of CV events in nondippers than in dippers among subjects with type II diabetes *(31)*. In a small study carried out in 116 treated hypertensive subjects followed for an average of 31 mo, Zweiker et al. *(15)* noted a significantly ($p < 0.001$) higher rate of CV complications in nondippers (4 events in 29 subjects) than in dippers (1 event in 87 subjects). In a study from Japan *(17)*, 105 patients with symptomatic lacunar infarcts underwent 24-h ABP monitoring. Follow-up lasted an average of 3.2 yr.

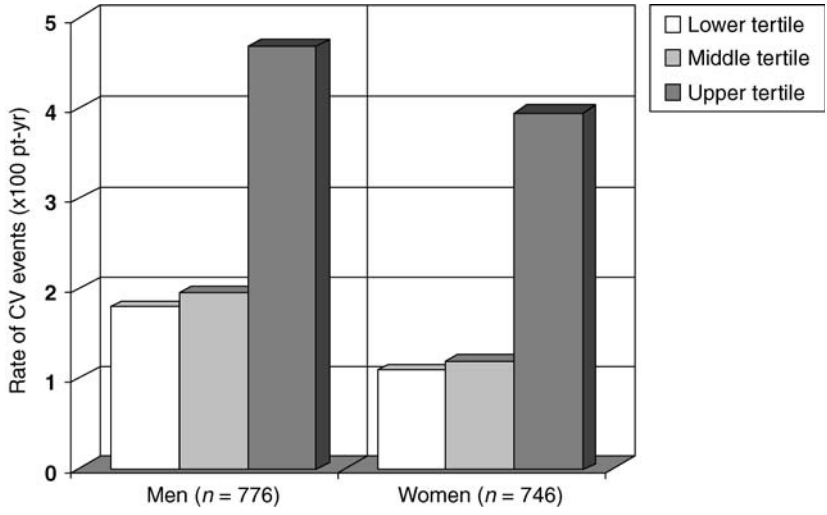

Fig. 6. The bars show the rate of major cardiovascular (CV) morbid events in the three tertiles of the distribution of the night–day ratio of systolic blood pressure.

The degree of ABP reduction from day to night at the baseline assessment was significantly ($p < 0.01$) smaller in the group with subsequent cerebrovascular events (1.3% for systolic BP, 3.3% for diastolic BP) than in the group with no future events and no development of silent lacunae (7.2% for systolic BP, 10.4% for diastolic BP).

In the previously mentioned Dublin Outcome Study, nighttime ABP was the most potent ABP component for prediction of outcome *(33)*. Also in the PAMELA study, nighttime ABP was more potent than daytime ABP for prediction of a composite pool of CV events *(34)*.

These findings indicate that the assessment of day–night BP changes detected with noninvasive ABP monitoring is important in hypertensive subjects because it allows an improvement in CV risk stratification above office BP and other traditional risk markers. Of note, 24-h ABP monitoring is the only practical way to assess the day–night rhythm of BP.

Blood Pressure Variability

The hypothesis that increased short-term BP variability may contribute to increase target organ damage in hypertensive patients is attractive and has received an increased amount of attention. An association between BP variability and organ damage was noted in one

study *(96)*. In the PIUMA study, for any level of 24-h systolic BP, hypertensive subjects were classified at low or high BP variability according to their standard deviation of daytime and nighttime SBP below or above the median. Left ventricular mass at echocardiography did not differ between the groups at low vs those at high systolic BP variability *(97)*. We also used the PIUMA database *(7)* to assess the relationship between blood pressure variability and subsequent incidence of CV morbid events. We followed for up to 8.6 yr (mean 2.92) 1372 individuals with essential hypertension. During follow-up there were 106 major CV morbid events. Event rate was 1.99 and 3.26 events per 100 patient-years, respectively, in participants with low and high variability of daytime systolic pressure and 1.98 and 3.38 events per 100 patient-years, respectively, in those with low and high variability of nighttime systolic pressure (log-rank test: both $p < 0.05$). However, in a Cox multivariate analysis, the variability score for daytime and nighttime systolic pressure failed to enter the model (age, diabetes mellitus, previous CV events, and average nighttime systolic pressure were independently associated with CV events).

Thus, the adverse impact of increased BP variability was largely spurious and resulting from the confounding effect of age, BP, diabetes mellitus, and previous CV morbid events, all potential markers of increased vascular damage and reduced baroceptor sensitivity *(98,99)*. The potential prognostic value of invasive and noninvasive beat-to-beat techniques for assessment of the BP variability remains to be determined.

Ambulatory Heart Rate

Several studies revealed a direct association between resting heart rate and risk of mortality in essential hypertension *(100,101)*. However, resting heart rate, such as BP, is a highly variable measure because it is affected by the alerting reaction to the clinical visit *(71,72)*. To investigate the prognostic impact of heart rate values recorded during the 24 h of ABP monitoring, we followed up 1942 initially untreated and uncomplicated subjects with essential hypertension for an average of 3.6 yr *(9)*. During follow-up there were 74 deaths from all causes (1.06 per 100 person-years) and 182 total (fatal plus nonfatal) CV morbid events (2.66 per 100 person-years). Clinic, average 24 h, daytime, and nighttime heart rates exhibited no association with total mortality. However, the subjects who subsequently died had had a blunted reduction of heart rate on going from day to night during the baseline examination. After adjustment for age ($p < 0.001$), diabetes ($p < 0.001$), and average 24-h SBP ($p = 0.002$)

in a Cox model, for each 10% less reduction in the heart rate from day to night the relative risk of mortality was 1.30 (95% CI 1.02–1.65, $p = 0.04$). Rates of death were 0.38, 0.71, 0.94, and 2.0 per 100 person-years among subjects in the four quartiles of the distribution of the percentage reduction in heart rate from day to night. The baseline day–night changes in the heart rate exhibited an inverse correlation to age and to clinic and ambulatory SBP and a direct association with the day–night changes in blood pressure. The degree of reduction of heart rate from day to night also showed an independent inverse association with total CV morbidity after adjustment for age, diabetes, and left ventricular hypertrophy, but this association did not remain significant when average 24-h SBP and the degree of day–night reduction in SBP entered the equation.

These data suggest that a flattened diurnal rhythm of heart rate in uncomplicated subjects with essential hypertension is a marker of risk for subsequent all-cause mortality, and this association persists after adjustment for several risk factors. For assessing these subjects, a limited and uniformly distributed period of ambulatory heart rate recording for 24 h is a clinically valuable tool.

Ambulatory Pulse Pressure

A significant association has been noted in several studies between PP, the difference between systolic and diastolic BP, and subsequent rate of CV morbid events. Such association was in part independent from the effects of systolic and diastolic BP *(5,102–105)*. In a previous study from our laboratory, such association was also independent of left ventricular mass at echocardiography and WCH *(5)*. However, PP may be affected by the alerting reaction evoked by the clinical visit. Mancia et al. *(71,72)* showed that the rise in intraarterial systolic BP is greater (4–75 mmHg, mean 27) than that of diastolic BP (1–36 mmHg, mean 15). This implies an average rise in PP of about 12 mmHg from before to during visit. Office PP may thus overestimate the usual levels of PP.

To investigate the prognostic value of ambulatory PP, we studied 2010 initially untreated and uncomplicated subjects with essential hypertension from the PIUMA database *(10)*. The rates of total CV events (per 100 persons per year) in the three tertiles of the distribution of average 24-h pulse pressure were 1.19, 1.81, and 4.92, and those of fatal events were 0.11, 0.17, and 1.23 (log-rank test: both $p < 0.01$). After controlling for concomitant risk markers, including WCH and the day–night BP change, survival data were better fitted by the model containing ambulatory PP than by that containing office PP. For any given level of office PP,

CV morbidity and mortality markedly increased with average 24-h ambulatory PP. These data suggest that the alerting reaction to office BP measurement may weaken the relation between PP and CV risk. Consequently, ambulatory PP appears to provide a more precise estimate of risk. These data have been confirmed in a Swedish population-based sample of elderly men *(30)* and in a group of patients with type 2 diabetes *(31)*.

Recently, we analyzed the different prognostic impact of 24-h mean blood pressure and PP on stroke and coronary artery disease in the PIUMA database *(106)*. We examined 2311 subjects with essential hypertension: over a follow-up period of up to 14 yr (mean 4.7 yr), there were 132 major cardiac events (1.20 per 100 person-years) and 105 cerebrovascular events (0.90 per 100 person-years). After adjustment for age, sex, diabetes, serum cholesterol, and cigarette smoking (all $p < 0.01$), for each 10 mmHg increase in 24-h PP, there was an independent 35% increase in the risk of cardiac events (95% CI, 17–55%). Twenty-four-hour mean BP was not a significant predictor of cardiac events after controlling for PP. After adjustment for age, sex, and diabetes (all $p < 0.05$), for every 10 mmHg increase in 24-h mean BP, the risk of cerebrovascular events increased by 42% (95% CI, 19–69%), and 24-h PP did not yield significance after controlling for 24-h mean BP. Twenty-four-hour PP was also an independent predictor of fatal cardiac events, and 24-h mean BP was an independent predictor of fatal cerebrovascular events (Fig. 7).

These findings suggest that in subjects with predominantly systolic and diastolic hypertension, ambulatory mean BP and PP exert a different predictive effect on the cardiac and cerebrovascular complications. Although PP is the dominant predictor of cardiac events, mean BP is the major independent predictor of cerebrovascular events.

Early Morning Rise in Blood Pressure

CV events tend to follow a circadian pattern, with a peak incidence in the early morning and a nadir during the night *(107,108)*. Some years ago we documented a case of acute ischemic stroke in the early morning which followed a steep BP rise in a subject who was wearing ABPM *(109)*. In a small group of elderly hypertensive patients, the early morning rise in systolic BP was positively correlated with left ventricular mass index and inversely correlated with diastolic function *(110)*. In a population of 519 older hypertensive subjects from Japan who contributed 44 stroke events during an average follow-up of 41 mo, a higher morning BP rise was associated with stroke risk independent of ambulatory BP, nocturnal BP

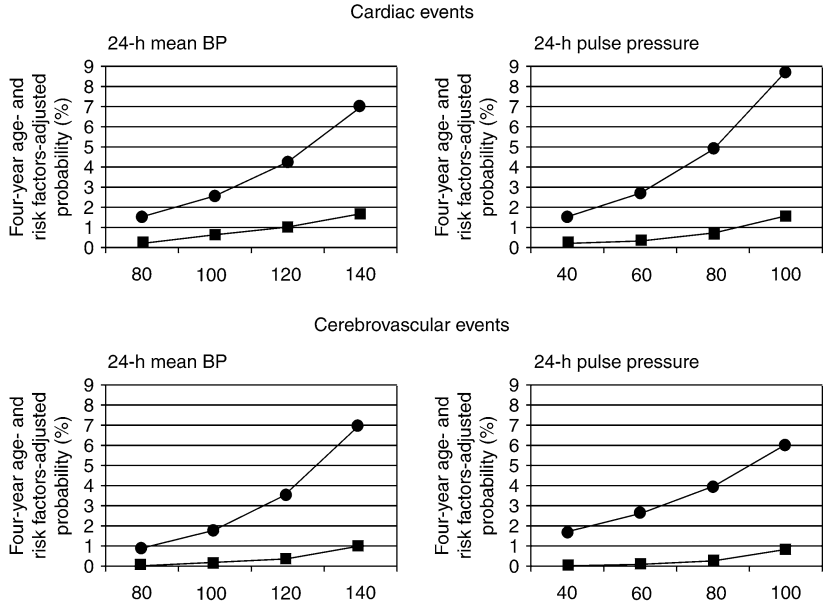

Fig. 7. Four-year age-adjusted and risk factor-adjusted probability of cardiac and cerebrovascular events by increasing levels of 24-h mean blood pressure (BP) and pulse pressure; filled squares denote fatal events and filled circles denote total events.

falls, and silent cerebral infarct *(111)*. These data, to be confirmed in larger samples, different racial groups, and for different end-points, raise the possibility that the early morning rise in BP could be a new therapeutic target for preventing target organ damage and subsequent CV events.

INDICATIONS FOR AMBULATORY BLOOD PRESSURE MONITORING

Indications for ABP monitoring are still unsettled. Both the JNC VII Committee *(112)* and the European Society of Hypertension/European Society of Cardiology Committee *(113)* provided a list of situations in which ABP monitoring might be useful.

According to the JNC VII document *(112)*, these conditions include "the evaluation of (white-coat) hypertension in the absence of target-organ injury," "apparent drug resistance," "hypotensive symptoms with antihypertensive medications," "episodic hypertension," and "autonomic dysfunction."

According to the European Society of Hypertension/European Society of Cardiology document *(113)*, these conditions include considerable variability of office BP over the same or different visits, high office BP in subjects otherwise at low global CV risk, marked discrepancy between BP values measured in the office and at home, and suspected resistance to drug treatment is suspected.

The available evidence supporting the prognostic value of ABP is today remarkable and based mostly on outcome cohort studies in which the qualifying ABP monitoring had been carried out in untreated subjects with essential hypertension. Therefore, ABP monitoring could be increasingly considered for refinement of CV risk stratification above and beyond traditional risk markers in nearly all untreated subjects with essential hypertension as well as in those with resistant hypertension despite three or more drugs *(18)*.

By contrast, there is less evidence that ABP improves CV risk stratification in treated hypertensive subjects, particularly in those well controlled by therapy. The OvA study *(26)*, the most important contribution in this context, has provided evidence that the prognostic value of ABP is superior to that of office BP even in treated patients. In these subjects, an achieved 24-h systolic BP of 135 mmHg or higher was associated with increased CV risk independent of other risk factors *(26)*.

Figure 8 *(68)* presents an algorithm that could be used to refine risk stratification and adapt treatment strategies accordingly. Home BP might be the first line procedure to identify subjects who could be candidates for commencing drug treatment. Indeed, home BP not only has an independent prognostic value *(20)*, but it is also appropriate for self-monitoring of BP in the long run. In subjects with normal home BP, 24-h ABP monitoring might identify low-risk individuals with WCH. These subjects could be suitable for lifestyle measures without antihypertensive drugs if they are free of diabetes, target organ damage, and other CV risk factors. In contrast, a nondipping BP pattern or an increased 24-h PP in subjects with ambulatory hypertension would identify high-risk individuals. In these subjects, drug treatment should be started without delay. Indications from guidelines would remain mandatory in subjects with intermediate risk levels based on ABP, as well as in subjects with WCH and associated risk factors.

PERSPECTIVES

Several years ago, observational surveys identified office BP as a predictor of CV disease, thus justifying the execution of intervention studies targeted at office BP in patients with essential hypertension.

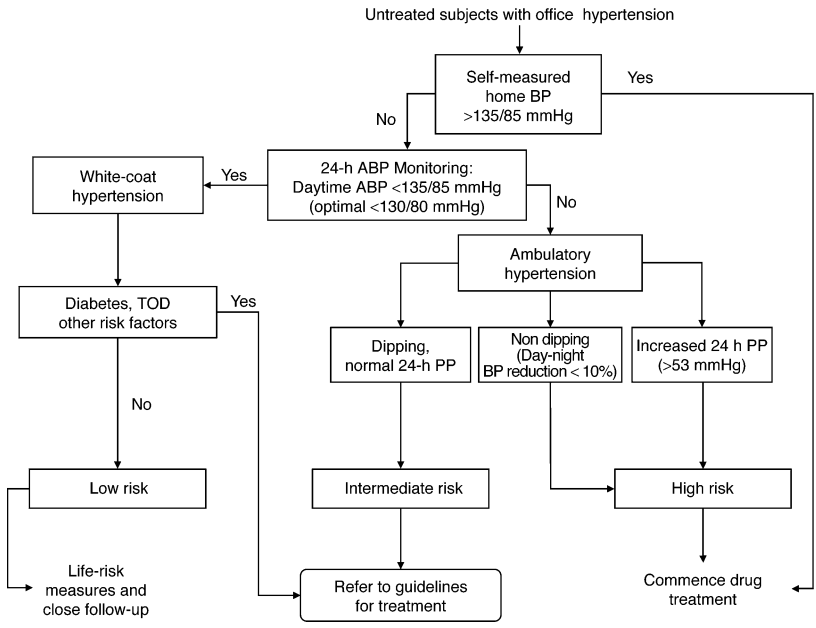

Fig. 8. Operational approach for cardiovascular risk stratification based on ambulatory blood pressure (ABP) in untreated subjects with essential hypertension. PP, pulse pressure.

The stage is now set for prospective intervention studies targeted at ABP within two general areas:

1. In low-risk subjects with WCH, there is a need to ascertain whether standard management of essential hypertension based on office BP differs from no-drug management in terms of development of organ damage and, hopefully, prognosis. The standard management should consist of lifestyle measures and drug treatment when indicated. The no-drug management should consist of lifestyle measures alone, with possible switch to drug treatment beyond predefined ethical thresholds.
2. There is a need to ascertain whether a standard management of hypertension completely based on office BP without execution of ABP monitoring or home BP measurements differs, in terms of development of organ damage and, hopefully, prognosis, from a management targeted on results of ABP monitoring and home BP measurements.

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11 Day/Night Pattern of Myocardial Infarction and Sudden Cardiac Death

Interacting Roles of the Endogenous Circadian System and Behavioral Triggers

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INTRODUCTION: INTERACTING ROLES OF THE ENDOGENOUS CIRCADIAN SYSTEM AND BEHAVIORAL TRIGGERS ON ADVERSE CARDIOVASCULAR EVENTS

Adverse cardiovascular events are the leading cause of mortality in the United States *(1)*. These events do not occur randomly across the day. This chapter reviews the considerable epidemiological evidence that myocardial infarction (MI), ventricular tachyarrhythmias, and sudden cardiac death (SCD) exhibit prominent day/night patterns, with these adverse events occurring more frequently during the morning hours (6 AM to noon). Hematological factors (e.g., increases in aggregability of platelets), vascular endothelial factors (e.g., increase in vascular tone), autonomic factors (e.g., release of catecholamines), and hemodynamic factors (e.g., morning surge of blood pressure and shear forces) have all been implicated in these adverse cardiovascular events. These physiological factors may be altered by behaviors, and several potential behavioral triggers of the adverse cardiovascular events have been identified, including mental stress and anger, the start of activity in the morning, irregular heavy physical exertion, and sexual activity. However, predicting which individuals will suffer adverse cardiovascular events is difficult, and predicting when these will occur is even more challenging. A working group of the National Heart, Lung and Blood Institute met in December 2005 to provide recommendations for developing an algorithm to identify those individuals at high risk for an acute MI or SCD in the near term, i.e., within 1 yr *(2)*. One of the major recommendations that emerged was to perform studies to discover the triggering mechanisms for acute cardiovascular events, i.e., Why did the event happen today, not tomorrow? *(2)*. Clearly the day/night patterns in the occurrence of specific behaviors may not fully explain the day/night pattern of adverse cardiovascular events, suggesting a role for the internal body clock (endogenous circadian pacemaker) affecting cardiovascular vulnerability across the day and the night. We and others have demonstrated that the human endogenous circadian pacemaker (suprachiasmatic nuclei of the hypothalamus) functions to entrain many neurocognitive, behavioral, and physiological systems *(3–7)* to the 24-h solar day and to each other. Our recent data suggest that there is an interaction between behavioral and circadian factors, such that specific behaviors may have different physiological consequences depending on the phase of the endogenous circadian cycle at which they occur. For example, we found that the cardiac response to a standardized stimulus

was greatest at the biological clock time around 9 AM *(8)*. Similarly, others have demonstrated differing physiological responses at different times of day or night (although such studies have generally not followed validated circadian protocols). An example of this interaction is the fact that cortisol responses to exercise were greater at 7 AM compared to 7 PM *(9)*. In many circumstances these physiological variations with behavior and with time of the day may be adaptive. However, in susceptible individuals (e.g., those with vulnerable atherosclerotic plaques), the same behavior could trigger an adverse cardiovascular event. Moreover, because shift work, jet lag, and sleep disorders are exceedingly prevalent in today's society, it becomes of practical importance to determine whether or not there exists an interaction between circadian influences and the impact of behavioral stressors on cardiovascular risk.

This chapter assesses the evidence, outlines the difficulties, and identifies useful approaches when attempting to assess the relative importance of behavioral stressors and endogenous circadian factors and their interaction in causing the robust day/night patterns of adverse cardiovascular events detected in epidemiological studies. For instance, it is generally not possible in clinical situations to study the separate influences of specific behaviors and the endogenous circadian pacemaker because this requires experimentation where the behavioral stressors are scheduled to occur at all phases of the endogenous circadian rhythm. However, it is possible to study such interaction on basic cardiovascular biomarkers on volunteers in a laboratory, and it is sometimes possible to infer a role for the endogenous circadian pacemaker when similar behaviors cause adverse cardiovascular events mainly at one time of day but less frequently at another time of day.

Determination of these independent and interacting mechanisms could lead to better chronobiological therapies for cardiovascular diseases in terms of modification of behavior and activity levels as well as timed pharmacological intervention aimed at reducing the millions of annual cardiovascular insults as well as more than 700,000 cardiac-disease-related deaths in the United States per year *(1)*.

EPIDEMIOLOGICAL EVIDENCE OF DAY/NIGHT PATTERNS IN ADVERSE CARDIOVASCULAR EVENTS

Myocardial Infarction

In many instances MI is not a random clinical event. The onset of MI has a distinct day/night pattern with a peak incidence in the hours after awakening and arising *(10)*. Goldberg et al. *(11)* examined the times of

onset of acute MI in relation to awakening in 137 patients with confirmed acute MI. Approximately 23% of patients reported onset of initial symptoms of MI within 1 h after awakening. Willich et al. *(12)*, using the community-based Triggers and Mechanisms of Myocardial Infarction data, supported this finding with the observation that the increased incidence of MI occurred within the first 3 h after awakening. Many studies have divided the day into quartiles and assessed the proportion of events in each quartile, with midnight to 6 AM being ostensibly the sleeping portion of the day. If events were randomly distributed, 25% of adverse cardiovascular events (MI or SCD) would be expected to occur in any 6-h window. With this in mind, of the 3339 patients entered into the Thrombolysis in Myocardial Infarction II Trial (TIMI II) *(13)*, 34.4% of the heart attacks occurred between 6 AM and noon vs 15.4% between midnight and 6 AM. Genes et al. *(14)* reviewed the data on 2563 patients entered into the USIK trial and noted that 30.6% of the acute cardiac events occurred between 6 AM and noon and only 20.1% occurred between midnight and 6 AM. Cannon and associates *(15)* examined the time of onset of myocardial ischemic pain in 7731 patients who were prospectively identified in the Thrombolysis in Myocardial Ischemia (TIMI) III Registry. The authors documented a statistically significant day/night variation in the incidence of onset of unstable angina and evolving non-Q-wave MI with a peak occurrence rate between 6 AM and noon.

Such epidemiology may be subject to reporting bias caused by events being potentially underreported during sleep or the nighttime. Nonetheless, in some studies serum creatine phosphokinase measurements have been used to objectively derive the time of onset of MI, with similar results. For example, data obtained from 703 subjects in the Multicenter Investigation of Limitation of Infarct Size study *(16)* revealed a marked day/night variation in the incidence of MI with a threefold increase at 9 AM as compared to 11 PM. In the Intravenous Streptokinase in Acute Myocardial Infarction Study (ISAM) *(17)*, Willich et al. used clinical criteria and serial creatine phosphokinase measurements to identify the time of onset of MI in all 1741 patients enrolled. A morning peak in the onset of MI was reported with a 3.8-fold increase in frequency noted between 8 and 9 AM as compared to midnight and 1 AM. The authors stated that the morning was a risk period for patients with mild as well as severe coronary artery disease.

Numerous authors (e.g., refs. *18* and *19*) have suggested that in the evening hours (between 6 PM and midnight), a secondary peak of onset

of MI is present. This may relate to the evening meal or other triggers concentrated in those hours, or possibly endogenous circadian factors.

Arrhythmias

Ventricular tachyarrhythmias are the most common cause of SCD. Cellular hypertrophy compensating for cell loss because of ischemia, intraventricular hypertension, cardiomyopathy, and myocarditis might play a role in arrhythmogenesis, as evidenced by the fact that experimental induction and regression of hypertrophy are paralleled by changes in the inducibility of ventricular tachyarrhythmias *(20)*. As with serum creatine phosphokinase measurements used to objectively derive the time of onset of MI, timing of recorded tachyarrhythmias is accurate and reliable (i.e., not subject to reporting bias such as underreporting events during sleep). Canada et al. *(21)* noted that ventricular ectopy reveals a prominent peak during the daytime hours and a trough at night. Twidale et al. *(22)* observed that the peak incidence of sustained symptomatic ventricular tachycardia in 68 patients occurred between 10 AM and noon. Valkama et al. *(23)* reviewed 24-h long-term electrocardiographic recordings in 34 patients with known coronary artery disease. A day/night pattern was identified for spontaneous ventricular tachycardia (four or more beats of ventricular tachycardia), with a peak incidence at 6 AM. Rebuzzi et al. *(24)* studied 406 patients with 24-h ambulatory electrocardiographic monitoring to assess the time of incidence of ventricular tachycardia. A nonrandom daily distribution of this arrhythmia was described with a peak incidence between 11 AM and noon. D'Avila et al. *(25)* noted that in 22 patients with an implantable cardioverter–defibrillator, 42% of the total appropriate defibrillator shocks occurred during the morning hours. Behrens et al. *(26)* also noted a significant day/night variation of ventricular tachyarrhythmias with a primary morning peak between 7 and 11 AM and a secondary, much smaller peak between 4 and 8 PM. Mallavarapu et al. *(27)* analyzed the stored electrograms from 390 implantable cardioverter–defibrillator recipients who sustained a total of 2692 episodes of ventricular tachycardia or ventricular fibrillation. The peak incidence of the arrhythmia occurred between 10 and 11 AM, with a nadir between 2 and 3 AM. This day/night pattern persisted regardless of age, gender, ejection fraction, or ventricular tachycardia cycle length. Fries et al. *(28)* studied 119 consecutive patients after implantable cardioverter–defibrillator implantation. Over a mean of 3 yr, 1849 ventricular arrhythmic events were detected in 57 patients. The majority of both single episodes of ventricular

arrhythmic events and short-term recurrent tachyarrhythmias were registered between 8 AM and noon and in the evening. Tofler et al. *(29)* studied 483 patients who had a cardioverter–defibrillator implanted in the early 1990s and noted that almost 22% of the ventricular tachyarrhythmias occurred between the hours of 9 AM and noon. Nanthakumar et al. *(30)* reviewed 54 patients with implantable cardioverter–defibrillators who experienced 1012 episodes of ventricular tachycardia with anti-adrenergic medications and 102 episodes of ventricular tachycardia without anti-adrenergic medications. As anticipated, the episodes of ventricular tachycardia without β-blockade followed a day/night variation with a peak incidence of onset at 9 AM, followed by a secondary peak at 4 PM. In contrast to Behrens et al. *(31)*, the presence of a β-blocker did not affect this day/night pattern.

There exist only isolated studies that do not reveal a morning peak in the incidence of malignant ventricular arrhythmias. Wood et al. *(32)* followed 43 patients with implantable cardioverter–defibrillators for a mean of 226 d. The daily distribution of the 830 ventricular tachyarrhythmia episodes recorded was nonrandom with a peak incidence between 2 and 3 PM. Interestingly, this pattern was not observed in subjects receiving antiarrhythmic drug therapy. Lucente et al. *(33)* utilized Holter electrocardiographic recordings to document the time of onset of ventricular tachycardia in 94 subjects with coronary artery disease. A day/night variation in the incidence of ventricular tachycardia was noted with a peak occurrence rate between 2 and 3 PM in patients with a recent MI and between noon and 1 PM in patients with an old MI. The underlying structural heart disease may influence the type and temporal distribution of clinically significant arrhythmias. Wolpert et al. *(34)* studied 28 patients with coronary artery disease and 11 subjects with nonischemic dilated cardiomyopathy who had implantable cardioverter–defibrillators over a mean period of 2 yr. Patients with coronary artery disease manifested a day/night variation in the frequency of malignant ventricular arrhythmias with a peak incidence between 9 and 10 AM. In contrast, the peak incidence of arrhythmias in the subjects with cardiomyopathy occurred in the late afternoon and early evening.

Further evidence of the morning increase in susceptibility to serious arrhythmias comes from defibrillation thresholds. Venditti et al. *(35)* analyzed defibrillation thresholds at different times of day in 134 patients with implantable cardioverter–defibrillators. The morning defibrillation threshold (8 AM to noon) was 15 J vs 13 J in the mid-afternoon (noon to 4 PM) and late (4 to 8 PM) afternoon ($p < 0.02$). This

suggests that greater amounts of energy are required for termination of morning tachyarrhythmias. A similar conclusion was drawn from a separate group of 930 patients with implantable cardioverter–defibrillators with date and time stamps for each therapy, Venditti et al. reviewed 1238 episodes of ventricular tachyarrhythmias treated with shock therapy. There was a significant peak in failed first shocks in the morning compared with other time intervals. Fries et al. *(36)* noted that in 138 recipients of implantable cardioverter–defibrillators, the worst antitachycardia pacing success rates occurred during the time period with the highest episode frequency (the morning hours). In an isolated contra-example, McClelland et al. *(37)* studied 162 subjects with coronary artery disease and found that the time of day during which ventricular stimulation protocols were performed did not affect test results.

Sudden Cardiac Death

Many studies of the timing of the onset of SCD have revealed nonrandom day/night variations with a peak incidence in the morning hours. Data from the Framingham Heart Study *(38)* revealed a significant day/night variation in the occurrence of SCD, with a peak incidence from 7 to 9 AM and a nadir from 9 AM to 1 PM. The risk of SCD was at least 70% higher during the peak period than was the average risk during the other times of the day. Our group *(39)* reviewed the death certificates of 2203 individuals dying out of the hospital in Massachusetts in 1983 and noted a prominent day/night variation of SCD with a low incidence during the night and an increased incidence from 7 to 11 AM. Levine et al. *(40)* identified a morning peak of SCD in out-of-hospital cardiac arrests in the City of Houston Emergency Medical Services. Willich et al. *(41)* prospectively reviewed 94 cases of SCD in four cities and towns in Massachusetts. A day/night variation in the incidence of SCD was demonstrated with a peak from 9 AM to noon. The authors noted that the incidence of SCD during the first 3 h after awakening carried a relative risk of 2.6 compared with the rest of the day. Thakur et al. *(42)* retrospectively reviewed 2250 consecutive patients with witnessed cardiac arrest during a 5-yr period. A day/night variation in the occurrence of SCD was demonstrated with a 2.4-fold increase between the hours of 6 AM to noon. This day/night pattern persisted despite gender, age (above or below 70 yr), and initial cardiac arrest rhythms, and was not evident in the rate of successful resuscitation or the rate of survival. Peckova et al. *(43)* explored the temporal variation of SCD in 6603 out-of-hospital cardiac arrests attended by the Seattle Fire Department. A day/night variation in the occurrence

of SCD was noted with two nearly equal peaks at 8 to 11 AM and at 4 to 7 PM. Mifune and Takeda *(44)* reviewed 90 consecutive patients with prehospital sudden cardiac arrest and noted a day/night pattern, with many cases occurring during the day and few at night. Goudevenos et al. *(45)* prospectively studied 223 SCDs that occurred in a closed population in northwest Greece over a 3.5-yr period. Family physicians and/or relatives of the deceased were interviewed within 12 d of SCD. A day/night variation in the incidence of SCD was noted with the peak occurring between 9 AM and noon. Assanelli et al. *(46)* observed a day/night variation in the incidence of SCD in subjects less than 45 yr of age, with a peak incidence in the morning hours. Pasqualetti et al. *(47)* reviewed 269 cases of SCD over a 17-yr period (1970–1987) in Italy. The authors noted an increased incidence of SCD in the morning hours.

The incidence of SCD from noncoronary causes may also show day/night variation. Maron et al. *(48)* studied 94 patients with hypertrophic cardiomyopathy who died suddenly and whose time of death could be ascertained accurately to the nearest hour. A day/night variation in the incidence of SCD was seen with 46% of the fatalities occurring between 7 AM and 1 PM. A second but smaller peak was noted between 8 and 10 PM. Thirty-nine percent of the SCDs occurred during periods of severe exertion. Sudden cardiac death may occur in as many as 40% of all patients who suffer from heart failure *(49)*. The multicenter trial Veterans Affairs Congestive Heart Failure–Survival Trial of Antiarrhythmic Therapy (CHF-STAT) documented a morning increase of SCD in patients with CHF *(50)*.

Numerous investigators have identified a bimodal distribution of SCDs during the day. Ishida et al. *(51)* reviewed 531 cases of SCD in Kanagawa Prefecture spanning 10 yr. In ischemic heart disease, deaths most frequently occurred between 12 and 1 AM and between 5 and 6 PM. Deaths resulting from acute cardiac failure occurred during sleep. Goto et al. *(52)* investigated 303 patients who suffered SCD in Yamagata city from 1984 to 1987. There was a tendency for SCD to occur in the early morning and evening. Arntz et al. *(53)* studied 703 consecutive patients who suffered SCD during 1988–1990 in Berlin, Germany. The determination of time of day of the event was based on the arrival time of the rescue squad. A striking day/night pattern was identified with a peak incidence between 6 AM and noon and a secondary peak between 3 PM and 7 PM. Martens et al. *(54)* studied the time of the day of calls received for out-of-hospital cardiac arrests prospectively registered by seven major Belgian emergency medical services. An intraday variation

in the incidence of calls for cardiac arrests was observed with a peak incidence between 6 AM and noon, a smaller crest in the early afternoon, and a nadir at night. Hayashi et al. *(55)* noted a bimodal distribution in the daily incidence of SCD with peaks between 6 and 8 AM and between 6 and 8 PM.

Cohen et al. *(56)* performed a meta-analysis on the day/night variation of acute cardiovascular events and noted that 1 out of every 15 SCDs are attributable to the morning excess incidence. Recent data from 112 Minnesota residents who had undergone a clinical diagnostic sleep study and who has subsequently suffered SCD show that people with obstructive sleep apnea are actually more likely to suffer SCD overnight than in the morning hours *(57)*. In that study, SCD occurred in the 6-h window between midnight and 6 AM in 46% of people with obstructive sleep apnea but only 21% of people without sleep apnea, and 16% of people in the general population who had not undergone sleep studies (25% is expected by chance if SCD was randomly distributed). Thus, because both SCD and sleep apnea prevalence increase with age, the morning peak in SCD identified in almost all other epidemiological studies would likely be even higher if people with sleep apnea were excluded from the analysis.

WEEKLY AND SEASONAL VARIATIONS IN MYOCARDIAL INFARCTION AND SUDDEN CARDIAC DEATH

Myocardial Infarction

Numerous authors have reported a weekly variation of MI, with a peak incidence on Monday. For instance, Willich et al. *(58)* noted this increase to be primarily in the working population with a 33% increase in relative risk of MI on this day of the week. In contrast, Spielberg et al. *(59)* observed a Monday increase in both the working and retired subgroups of patients. Some researchers noted an increased incidence of MI on the weekend (e.g., ref. *60*), whereas Sayer et al. *(61)* and Genes et al. *(14)* reported no significant weekly variation in the incidence of MI onset.

Several investigators have reported a seasonal variation in the incidence of onset of acute MI, with a peak in winter (e.g., refs. *59,61–64*). In the 83,541 subjects entered into the National Registry of Myocardial Infarction (NRMI) database between 1990 and 1993, 10% more acute cardiac events occurred in winter or spring than in summer *(63)*.

Spencer et al. *(62)* reviewed the data on 259,891 patients reported to the second National Registry of Myocardial Infarction (NRMI-2) during the 25-mo period beginning July 1, 1994. The authors noted that over 50% more cases of MI were reported in the winter (peak in January) than during the summer (nadir in July). Sayer et al. *(61)* prospectively obtained data on 1225 consecutive patients with acute MI admitted to a general hospital. Overall, a winter peak in the incidence of onset of MI was noted. However, the subgroups of patients who were diabetic, South Asian, or taking β-blockers or aspirin on admission did not demonstrate a seasonal variation. Marchant et al. *(64)* noted a winter peak in the 633 consecutive patients with acute MI admitted to the coronary care unit during a 4-yr period. Interestingly, the authors noted an excess of infarctions on colder days in both winter and summer, suggesting an effect of environmental temperature on the onset of this disease. Ku et al. *(65)* did not identify a significant seasonal variation in the incidence of MI.

Sudden Cardiac Death

Many studies of the timing of the onset of SCD have revealed nonrandom weekly and seasonal variations, with most reporting peak incidences between Saturday and Monday and in the winter. Pasqualetti et al. *(47)* found exactly that pattern after reviewing 269 cases of SCD over a 17-yr period (1970–1987) in Italy. Beard et al. *(66)* studied the records of 1054 cases of SCD in Rochester, MN, during the years 1950–1975. A weekly variation was noted, with a peak incidence on Saturday. Rabkin et al. *(67)* noted an excess proportion of SCDs on Monday in subjects without clinical evidence of coronary artery disease. Patients with ischemic heart disease had a more uniform incidence of SCD throughout the week. Even nocturnal deaths, which are unlikely to be directly related to behavioral triggers, appear to have a nonrandom distribution. Tatsanavivat et al. *(68)* conducted a survey by mail of sudden and unexplained death in sleep that occurred in 60 adults in northeast Thailand during 1988–1989. These deaths were found to have a seasonal variation, with 38% occurring between March and May and 10% between September and October.

BEHAVIORAL TRIGGERS OF ADVERSE CARDIOVASCULAR EVENTS

The robust day/night patterns in adverse cardiovascular events in epidemiological studies previously noted makes it difficult to determine

whether specific behaviors or the phase of the internal body clock are contributing factors to these events. On the other hand, the seasonal patterns in MI and SCD, with most peaks during the winter, do point to an effect of environmental temperature or winter-specific behaviors on the onset of disease. Colder weather has been shown to alter hemodynamic (blood pressure), autonomic (sympathetic tone), and hemostatic (platelet count, fibrinogen) factors favoring arterial thrombosis (e.g., ref. *69*). This is supported by Marchant et al. *(64)*, who noted that acute MIs increased on colder days in both winter and summer, and is further supported by the exceptions to the winter peak in MIs that occurs in stable climates such as subtropical regions (e.g., ref. *65*). Finally, the weekly patterns in MI and SCD do clearly point to behavioral triggers being involved, as behaviors and stresses are unlikely to be evenly distributed throughout the week.

The Myocardial Infarction Onset Study (MIOS) investigators have identified four triggers of onset of MI: start of activity in the morning, anger, heavy physical exertion, and sexual activity *(70–72)*. These four triggers alone account for more than 15% of infarctions, totaling more than 250,000 events in the United States each year.

Anger and Mental Stress

People who possess a high potential for hostility in response to a mental stress and an inability to express that anger outwardly appear to be at significant risk for the development of coronary artery disease *(73)*. Acute mental stress induced, for instance, by tragic personal events or interpersonal confrontations, by occupational events such as being laid off, or by natural disasters such as earthquakes, may be a trigger of transient myocardial ischemia *(74,75)*, MI *(76)*, and SCD *(77–80)*.

The Determinants of Myocardial Infarction Onset Study investigators interviewed 1623 subjects approx 4 d after an acute MI to assess the intensity and timing of anger (and other triggers) during the 26 h before the acute event *(72)*. Anger was objectively assessed by the onset anger scale (a single-item, seven-level, self-report scale) and the state anger subscale of the State-Trait Personality Inventory. The onset anger scale identified 39 patients (2.4%) who experienced anger within the 2 h prior to onset of MI. This corresponded to a relative risk of MI of 2.3, using the case-crossover study design developed by Maclure *(81)*. The state anger subscale corroborated these findings with a relative risk of 1.9.

The risk of anger triggering MI may be modulated. For instance, increasing levels of educational attainment are associated with a reduced

risk of anger-induced MI. The relative risk was twice as high among patients with less than high school education (3.3) compared with those with some college education (1.6) *(82)*. This suggests that behavioral therapy such as anger management may be effective in some cases.

Reich et al. *(83)* noted that anger was the probable trigger for 15% of the life-threatening arrhythmias identified in 117 patients. Fear, anxiety, and bereavement have also been implicated in increased vulnerability to cardiac events *(84)*. Bairey et al. *(74)* noted that 75% of 29 patients with coronary artery disease and exercise-induced myocardial ischemia also demonstrated mental-stress-induced ventricular wall motion abnormalities detected by radionuclide ventriculography. Barry et al. *(75)* performed ambulatory electrocardiographic monitoring with diary in 28 subjects with coronary artery disease and identified 372 episodes of ST-segment depression over a span of 5–6 wk. At least 22% of the ischemic episodes occurred at high levels of mental stress but low physical activity. In addition, transient ischemia was more likely to occur as the intensity level of mental activity increased. An increase in coagulation factors VII and VIII, fibrinogen, von Willebrand factor, and platelet activity has also been observed in patients subjected to mental stress and may play a role in precipitating acute cardiac events *(85,86)*.

Behar et al. *(76)* studied 1818 consecutive patients with acute MI. Exceptional heavy physical work, a violent quarrel at work or at home, and unusual mental stress were the three most frequent possible triggers of MI that occurred within 24 h of symptom onset. Within the first week of missile attacks on Israel during the 1991 war with Iraq, 20 people developed an acute MI at one hospital compared to eight MIs during a control period *(87)*. Leor and Kloner *(88)* identified a 35% increase in the number of hospital admissions for acute MI in southern California in the week following the major earthquake that occurred in Northridge in 1994, which caused extreme mental stress in the city's inhabitants. Most of these events were associated with mental rather than physical stress. Mental stress also may trigger the onset of SCD, as the Northridge earthquake precipitated 24 SCDs in 24 h, a sharp increase from the average of 4.6 SCDs per day usually seen *(80)*. Acute mental stress may be a trigger of adverse cardiovascular events via neural/neuro-hormonal activation and sympathetic stimulation *(77–79)* precipitating malignant arrhythmias *(85,89)* in the presence of structural heart disease.

Irregular Heavy Exertion and Sexual Activity

In the Multicenter Investigation of Limitation of Infarct Size (MILIS) *(90)*, TIMI II *(13)*, and MIOS *(70)* trials, heavy physical exertion was

identified as a trigger of acute MI. In the MILIS trial *(90)*, 14% of patients engaged in moderate physical activity and 9% engaged in heavy physical activity prior to sustaining an MI. In the TIMI II trial *(13)*, moderate or marked physical activity was reported to occur at onset of MI in 18.7% of patients. Compared with patients whose infarction occurred at rest or during mild activity, those with exertion-related infarction had significantly fewer coronary vessels with >60% stenosis and were significantly more likely to have an occluded infarct-related vessel after thrombolytic therapy. The profile of the patient with exertion-related infarction was a nonsmoking, Caucasian male with preexisting exertional angina, who did not use nitrates or calcium blockers in the 24 h prior to infarction.

Fifty-four (4.4%) of 1228 patients enrolled in the MIOS trial *(70)* reported heavy exertion (six or more metabolic equivalent units) within 1 h of the onset of MI. The cardiac symptoms often began during the activity. The estimated relative risk of MI in the hour after heavy physical activity, as compared with less strenuous or no physical exertion, was 5.9. Among people who usually exercised less than one, one to two, three to four, or five or more times per week, the respective relative risks were 107, 19.4, 8.6, and 2.4. Therefore, habitually sedentary individuals were at greatest risk of MI after heavy exertion, and increasing levels of regular physical exercise were associated with progressively lower coronary risk. Indeed, regular physical activity has a favorable effect on the lipid profile by lowering total serum cholesterol and triglycerides and raising high-density lipoprotein cholesterol. In addition, regular physical activity is associated with reduced resting blood pressure, improved glucose tolerance, increased insulin sensitivity, and reduced blood coagulability *(91)*.

Physical exertion may also trigger the onset of SCD. Hayashi et al. *(92)* found that the incidence of SCD was low while sleeping, resting, or doing light work and was high while using the toilet, engaged in sports, or performing heavy work. Maron et al. *(93)* noted that the incidence of SCD in highly trained athletes, such as marathon runners, was exceedingly small (approx 1 in 50,000). Young athletes who suffer SCD during strenuous physical exertion usually have underlying occult structural heart disease such as hypertrophic cardiomyopathy, coronary artery anomalies, or myocarditis (e.g., ref. *94*).

As with MI, habitually sedentary individuals are at greatest risk of SCD after heavy exertion, and increasing levels of regular physical exercise are associated with progressively lower risk of SCD *(95,96)*.

Sexual activity provides both an emotional and physical challenge to the cardiovascular system. The MIOS trial identified 3% of patients

who experienced the onset of MI within 2 h after sexual activity. Case-crossover analysis calculated a relative risk of 2.5 for onset of MI during this time period *(71)*. Nine percent of the patients engaged in sexual relations within 24 h of symptom onset. The relative risk of MI during sexual activity is no different for patients with known cardiac disease than for people without heart disease.

Absolute vs Relative Risk

Although anger, mental stress, irregular heavy physical exertion, and sexual activity have been identified as triggers of the onset of MI, the absolute risk of infarction with each trigger is low, because baseline risk is low. For example, the risk of MI may double in the 2 h after sexual activity, but because the baseline risk of MI for a healthy 50-yr-old male in any given hour is 1 in 1 million, the absolute risk increases only to 2 in 1 million. Similarly, the risk of SCD in people engaging in vigorous exercise is 10 times higher in cardiac patients than in apparently healthy people. Nonetheless, the absolute risk of SCD during vigorous exercise is low in the healthy individual (1:565,000 person-hours) and still low in the cardiac patient (1:60,000 person-hours) *(97)*. Indeed, Murray et al. *(98)* found no difference in risk of cardiac events between individuals who attended cardiac rehabilitation programs in the morning and those who attended in the afternoon. Thus, it appears that the benefit of physical exercise, whatever the time of day, outweighs the risk for most individuals.

PHYSIOLOGICAL RESPONSES UNDERLYING ADVERSE CARDIOVASCULAR EVENTS

The relevant hemodynamic, autonomic, hemostatic, and vascular endothelial biomarkers that may contribute to adverse cardiovascular events, including MI and SCD, are shown in Fig. 1. This figure portrays the independent cardiovascular effects of behavioral stressors and the circadian system and the possibly interaction between the circadian system and behavioral stressors on cardiovascular function. Significant physical activity or emotional stress may lead to (1) hemodynamic stress of hypertension, (2) tachycardia from autonomic sympathetic stimulation, (3) a prothrombotic state characterized by platelet activation, a reduced fibrinolytic response, and reduced prostacyclin release, and (4) endothelial dysfunction-induced coronary vasoconstriction with increased shear forces. We hypothesize that the circadian system

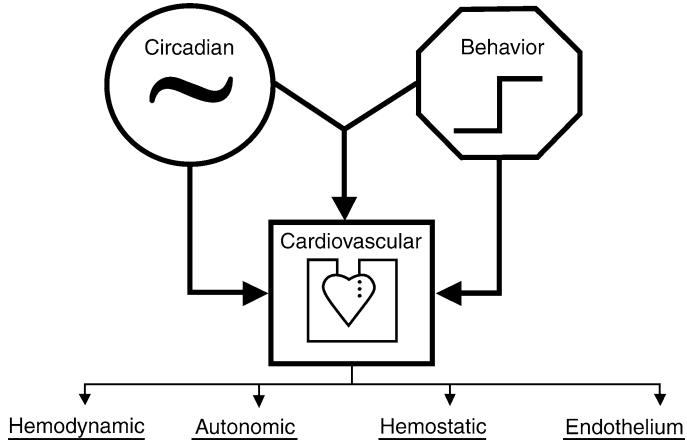

Fig. 1. The cardiovascular effects of the circadian system and of the interaction between the circadian system and behavioral stressors. The acute effects of behaviors (right side of model) have been well documented. The effects of the human circadian pacemaker are largely unknown (left side of model). The interactions between circadian pacemaker and behaviors are unknown (top = arrows joining). In most situations in healthy individuals, the effects of the behavioral and circadian systems on cardiovascular variables may be adaptive; e.g., higher blood pressure during exercise is required to oxygenate the contracting muscles. Similarly, increased cortisol orchestrated by the circadian pacemaker usually precedes awakening such that an individual awakens metabolically prepared for the waking activities. However, in individuals with a collection of risk factors for cardiovascular events, such as obesity, baseline hypertension, smoking history, vulnerable plaque, and so on, the same "adaptive" physiological responses to behaviors or circadian phase may become "maladaptive" as they could trigger an adverse cardiovascular event. By using appropriate circadian techniques that schedule specific behaviors at all phases of the body clock, it ought to be possible to experimentally evaluate the independent circadian and behavioral effects on these cardiovascular parameters, particularly in healthy individuals. However, it is largely unfeasible to study in humans the separate circadian and behavioral factors that contribute to the day/night pattern in actual cardiovascular events.

also affects many of these variables and may alter the influence of behaviors at specific circadian phases (discussed further next).

We recognize that the biomarkers shown in Fig. 1 have physiological fluctuations that promote homeostasis in most situations in healthy people. For instance, higher blood pressure during exercise is required to oxygenate the contracting muscles, and increased cortisol orchestrated by the circadian pacemaker usually precedes awakening such

that an individual awakens metabolically prepared for the waking activities. However, in individuals with a collection of risk factors for cardiovascular events, such as obesity, baseline hypertension, smoking history, vulnerable atherosclerotic coronary plaque, and so on, the same "adaptive" physiological responses to behaviors or circadian phase may become "maladaptive" as they could trigger an adverse cardiovascular event. For example, sympathoexcitation can be regarded as a double-edged sword, which leads to an appropriate fight-or-flight response in most people and situations, but could trigger deleterious changes in blood pressure, vasoconstriction, platelet aggregation, and endothelial function in patients with underlying cardiovascular disease that may lead to MI or fatal coronary thrombosis.

This is exemplified by successful therapeutic studies aimed at reducing such physiological variations across the day. For instance, in the ISAM *(17)* and TIMI II *(13)* trials, the subgroup of patients receiving β-adrenergic receptor-blocking therapy prior to the event did not show a morning excess in the incidence of MI. Hjalmarson et al. *(18)*, after reviewing 4796 cases of acute MI, confirmed the previously described findings and noted that the subgroups of congestive heart failure and prior infarction also had no morning increase in the occurrence of MI, suggesting different mechanisms were at play in these individuals. Ridker et al. *(99)* noted that physicians randomized to aspirin therapy experienced a selective 59% reduction in MI during the morning hours compared with a 34% reduction for the remaining hours of the day.

Similarly, out-of-hospital SCD in the β-blocker Heart Attack Trial demonstrated a marked morning increase in the placebo group with 38% of the SCDs occurring between 5 and 11 AM. However, patients randomized to propranolol therapy received a major protective effect during that same time period *(100)*. Analysis of the Danish Verapamil Infarction Trials (DAVIT I and II) suggests that verapamil is associated with a preferential reduction in morning SCDs *(101)*. The Cardiac Insufficiency Bisoprolol II (CIBIS II) trial *(102)* showed that patients with NYHA class III and IV congestive heart failure randomized to active treatment (bisoprolol) received a 45% reduction in SCD (3.6 vs 6.4%). The study of the patterns of SCD may yield important clues to the pathophysiology of the disease process *(103)*.

Verrier and Mittleman *(104)* attribute the lethal effects of anger to its activation of high-gain central neurocircuitry and the sympathetic nervous system, leading to acute sinus tachycardia, hypertension, impaired myocardial perfusion, and a high degree of cardiac electrical instability. Olshausen et al. *(105)* analyzed the Holter Monitor tapes of 61 patients

who experienced SCD while being monitored. Monomorphic ventricular tachycardia was seen in 43%. Other rhythm disturbances noted were polymorphic ventricular tachycardia (including torsades de pointes), primary ventricular fibrillation, and 1:1 conducting atrial tachycardia. Thus, some of these same physiological changes that accompany MI, such as increased sympathetic nervous system activity, can also lead to malignant arrhythmias *(85,89)* and SCD, particularly in the presence of structural abnormalities of the heart *(106)*. Thus, for simplicity, we sometimes group MI and SCD as adverse cardiovascular events when conceptualizing the interaction of behavioral triggers and circadian influences on the cardiovascular system.

DAY/NIGHT PATTERNS IN RELEVANT CARDIOVASCULAR VARIABLES

This section outlines the current knowledge of day/night patterns in relevant cardiovascular biomarkers that may underlie cardiovascular morbidity and mortality. The presence of a day/night variation in specific biomarkers suggests an effect of behaviors occurring on a regular schedule throughout the 24-h period (e.g., standing up after a night of sleep usually occurs in the morning) or an effect of the endogenous circadian pacemaker itself. By using appropriate circadian techniques that schedule specific behaviors at all phases of the body clock, it ought to be possible to experimentally evaluate the independent circadian and behavioral effects on these cardiovascular parameters, particularly in healthy individuals. The most common validated circadian techniques are termed a "constant routine" protocol *(3,7)* and a "forced desynchrony" protocol *(3,6)*. Both protocols are performed in dim light to avoid resetting the endogenous circadian pacemaker. In the constant routine, subjects are studied over 24 h while the environment and all behaviors are constant (e.g., by maintaining wakefulness in a constant semi-recumbent posture and providing constant nutrition via a drip, or small identical snacks every hour rather than larger sporadic meals). This constant routine reveals underlying circadian rhythms in measured variables, but some variables are affected by the accruing sleep deprivation. The virtue of a forced desynchrony protocol is that all behaviors and durations of prior wakefulness occur evenly spread across all phases of the endogenous circadian pacemaker, achieved by scheduling recurring behavior schedules that are different from 24 h, and repeating this pattern across a number of days. In this way, behavioral factors can be ignored when assessing independent circadian effects (because the

same behaviors occur at all circadian phases). Similarly, all circadian effects can be ignored when assessing independent behavioral effects. Finally, the interaction between behaviors and the endogenous circadian system can be statistically examined as well (e.g., ref. *4*). However, it is not feasible to study in humans the separate circadian and behavioral factors that contribute to the day/night pattern in actual cardiovascular events. Thus, most day/night studies to date were not designed to measure the independent contributions of the endogenous circadian pacemaker vs behaviors (such as sleep–wake state, posture, or activity) to cardiovascular regulation. Next, we examine the day/night patterns in relevant cardiovascular biomarkers that may underlie cardiovascular morbidity and mortality, and, where possible, we derive conclusions regarding whether these are caused by behavioral patterns or the endogenous circadian system.

Hemodynamic Factors

Increased blood pressure is well recognized as a mechanism that elevates cardiovascular risk (e.g., ref. *107*). There is a large body of evidence demonstrating a day/night variation of blood pressure and heart rate (e.g., ref. *108*). The peak blood pressure and heart rate occur at approx 9–10 AM with a minimum at approx 3 AM. Blood pressure and heart rate both change acutely with many behaviors, including sleep and exercise. To assess endogenous circadian effects, it is necessary to "uncouple" the effects of the endogenous circadian cycle and any behaviors, for example, by keeping behaviors constant across the entire circadian cycle. Using 24-h bedrest protocols, several studies have attempted to elucidate the endogenous regulation of blood pressure *(109–111)*. These studies show that under bedrest conditions a day/night variation in blood pressure still exists, suggesting a role for the endogenous circadian clock. However, these studies did not account for independent effects of light, sleep/wake, diet, or social interaction or make accurate measurements of the circadian phase. A subsequent "constant routine" study *(112)* concluded that there was no endogenous circadian rhythm in blood pressure when these potential masking effects were controlled. However, a limitation in the latter study was the lack of an objective marker of circadian phase, and differences in phase alignment among subjects likely decreased the signal to noise ratio in the analyses. In addition, light levels were bright enough to suppress/shift the phase of the circadian pacemaker. Thus, the effect of the endogenous circadian system on blood pressure is disputed. Heart rate is the end product of many endogenous inputs, including catecholamines, cortisol, cardiac

vagal and sympathetic tone, blood pressure (baroreceptors), and core body temperature. Core temperature can be used as a phase marker of the endogenous circadian system when behaviors are kept constant and sleep is not permitted. Heart rate is certainly affected by most behaviors and has a robust endogenous circadian rhythm with the minimum heart rate aligned with the minimum core body temperature around 5 AM, increasing steeply to a peak body clock time of approx 1 PM *(6,112,113)*. Elevated blood pressure and heart rate may have deleterious effects in vulnerable individuals, such as increasing vascular shear stress, which may precipitate plaque rupture and occlusive thrombosis and increased myocardial oxygen demand, contributing to the day/night variation in ischemic episodes.

Autonomic Factors

It is well accepted that there are day/night variations in the autonomic nervous system (e.g., refs. *114–119*). Increases in sympathetic tone are proposed as a potential mechanism potentiating SCD and MI via increased heart rate, cardiac contractility, vascular tone *(120)*, and positive cardiac inotropic and chronotropic effects, which in turn decrease cardiac electrical stability (e.g., refs. *121* and *122*). The day/night sympathetic rhythm has a minimum between 4 and 6 AM and peak at 9 AM to midday *(114–118,121–124)*. Additional evidence supporting a sleep–wake rhythm in sympathetic activity has been provided by studies of peripheral vasodilatation (e.g., ref. *115*), spectral analysis of heart rate (e.g., ref. *116*), and peripheral muscle sympathetic nerve activity (e.g., ref. *117*). The day/night pattern of sympathetic nervous system tone has been measured in ambulant subjects (i.e., not a formal circadian study). Venous catecholamines were collected at 3-h intervals over 24-h from 15 healthy subjects *(119,125)*. Subjects were allowed to sleep between midnight and 8 AM. These data reveal several distinct processes: (1) during the sleep period catecholamine concentrations are low; (2) after awakening at 8 AM there is a sharp rise in catecholamine levels; (3) venous catecholamine concentrations remain high across the course of the day. A similar pattern is seen in coronary artery disease patients *(126)*. Current published reports suggest that the day/night sympathetic nervous system rhythm is principally modulated by posture and/or the sleep–wake cycle with little to no endogenous circadian control (e.g., ref. *127*). However, neuronal evidence links the suprachiasmatic nuclei to the adrenal cortex *(128)*, suggesting the possibility of sympathetic circadian modulation. The role of the human biological clock in generating sympathetic nervous system rhythms has, until now, not been

adequately examined with validated circadian protocols. The ability of β-adrenergic-blocking agents *(17)* to reduce the incidence of myocardial infarction in the morning supports the hypothesis that sympathetic activation contributes to the day/night pattern of acute cardiovascular disease.

Vagal withdrawal is associated with increased cardiovascular risk via increases in myocardial contractile force, heart rate, electrical instability, and removal of pre- and postsynaptic vagal inhibitory actions on adrenergic inputs (e.g., ref. *122*). High-frequency power of the heart rate variability power spectrum is universally regarded as a measure of cardiac efferent vagal tone *(129)*. Such heart rate variability studies have identified a robust day/night rhythm in cardiac vagal tone, with the night being associated with an increase in vagal tone and the waking hours a decrement in vagal efferent outflow with the minimum occurring at approx 9 AM *(109,113,116)*. Burgess et al. *(113)*, using a 24-h constant routine protocol (albeit not performed in dim light), investigated the circadian regulation of cardiac vagal tone by applying heart rate variability analysis. The authors report a significant circadian variation in vagal activity with a minimum of approx 5 h after the minimum core body temperature (approx 9–10 AM). In Burgess's study, during sleep before and after the constant routine protocol, cardiac vagal tone only increased to the same level as that produced by the circadian clock, leading the authors to conclude that the sleep–wake variation in vagal tone is almost entirely a result of the endogenous circadian pacemaker. Based on our data, this appears to be a misleading conclusion, but one that serves to highlight the benefit of a forced desynchrony protocol in which all behaviors are evenly spread across all phases of the endogenous circadian pacemaker. In a 28-d, 20-h forced desynchrony *(6),* we have (1) confirmed the independent circadian input to cardiac vagal regulation, (2) established that sleep per se does increase vagal tone (independent of circadian rhythms), and (3) found that these components do not summate (i.e., when we sleep vagal tone increases to a physiologic maximum, such that there is little circadian component). This interaction effect can only be established in a forced desynchrony study.

The nocturnal decrease in norepinephrine concentrations has been attributed to independent effects of sleep and posture *(119)*. In contrast, although a nocturnal decrease in epinephrine exists, it is relatively unrelated to the presence of sleep or the posture during the night *(119)*. Neuronal evidence links the circadian pacemaker to the adrenal cortex *(128),* suggesting the possible circadian modulation in basal sympathetic tone. In addition, it is very well established that cortisol potentiates

catecholamine effects on vasomotor tone *(124)* and that cortisol has a strong circadian and day/night rhythm, which is maximal in the morning *(130)*. It is plausible that increased cortisol at 9 AM potentiates epinephrine, and thus their combined actions could contribute to the morning increase in MI. To date, there are numerous studies showing acute behaviors that modulate parasympathetic balance and the release of catecholamines from the adrenal medulla, but the effects of the human circadian pacemaker have not been quantified using appropriate circadian techniques.

Hemostatic Factors

A growing body of evidence supports a role for hemostatic factors in triggering cardiovascular events. Higher levels of fibrinogen (e.g., ref. *131*), factor VII *(132)*, factor VIII (e.g., ref. *133*), plasminogen activator inhibitor *(131)*, tissue plasminogen activator (e.g., ref. *134*), and von Willebrand factor (e.g., refs. *131,133,* and *134*) have been documented in patients with atherosclerotic cardiovascular disease. Thompson et al. *(135)* conducted a prospective multicenter trial enrolling 3043 patients with angina pectoris who underwent coronary arteriography and were followed for 2 yr. An increased risk of MI and SCD was associated with higher baseline concentrations of fibrinogen, von Willebrand factor antigen, and tissue plasminogen activator antigen. Interestingly, despite the arteriographic evidence of coronary artery disease and symptomatic angina pectoris, low serum fibrinogen concentrations correlated with a low risk of cardiac events. The authors suggested that impaired fibrinolysis, as well as endothelial cell injury and inflammatory activity, play a pathogenetic role in the progression of coronary artery disease. Blood viscosity *(136)*, factor VII activity and plasminogen activator inhibitor levels *(137)*, heparin potency *(138)*, and thrombolytic drug efficacy *(139)* follow a day/night pattern that favors morning hypercoagulability and hypofibrinolysis.

Enhanced platelet activity has been implicated in the pathogenesis of acute coronary syndromes. In at-risk patients antiplatelet therapy reduces the morbidity–mortality risk by 25% *(140)*. Platelet aggregability *(124)* and in vitro platelet responsiveness to adenosine diphosphate and epinephrine *(141)* increase dramatically after the patient awakens and assumes the upright posture. During this same time period, plasma levels of catecholamines rise, which stimulate the release of platelets from the spleen and amplify platelet activity. There is a large-amplitude day/night rhythm in platelet aggregability, with greater aggregability in the morning around 9 AM in both healthy subjects and coronary artery disease

patients *(99,123,125,142,143)*. This increase in aggregability was found to be most likely a result of a change in posture from supine to standing, suggesting that this maneuver could play a significant role in the morning peak of cardiovascular events. This hypothesis was supported by the finding that aspirin reduces the platelet aggregability response to posture changes and removes the day/night rhythm in MI *(99)*. Exercise itself did not increase aggregability beyond the effect of changes in posture, but did elevate hematocrit, suggesting it could play a role in hemostatic factors and cardiovascular risk. However, in these studies changes in posture always followed a night of sleep, such that the duration of lying down, or the duration of prior sleep, could have affected the results. Also, the circadian effects were only properly assessed over a 3-h period in the morning.

Thus, overall, this day/night pattern in hemostatic factors, occurring possibly through a combination of behavioral and endogenous circadian contributions, mirrors that of the epidemiologically determined day/night pattern of adverse cardiovascular events, suggesting that increased morning hemostasis may contribute to this pattern. For instance, in concert with other factors, the normal morning increase in platelet aggregability may contribute to an overall hypercoagulability, such that once there is a plaque fissure, the size of the resulting thrombus may depend on the time of day via the relative state of coagulability. Although behaviors, including postural changes, clearly affect hemostatic factors, the presence or absence of an endogenous circadian pacemaker input to the regulation of platelet aggregability has not been formally investigated across the whole circadian cycle.

Vascular Endothelial Factors

The measurement of endothelial function is becoming increasingly recognized as a clinically important cardiovascular biomarker. Recent data conclusively demonstrate that endothelial dysfunction is not simply a marker of atherosclerosis but provides independent predictive value from the standpoint of risk of subsequent cardiovascular events. Nitric oxide (NO), a potent endothelium-derived vasodilator in the coronary, pulmonary, and peripheral circulations, inhibits vascular smooth muscle cell proliferation, limits platelet aggregation, inhibits leukocyte adhesion, and opposes the vasoconstrictive effects of catecholamines (e.g., ref. *144*). Reduced bioavailability of NO impairs the protective function of the endothelium and may participate in the development and progression of atherosclerosis *(145)*. Thus, assessment of endothelium-dependent and endothelium-independent vascular dilation

may help us to understand the factors in cardiac risk factors, developing atherosclerotic lesions, and leading to clinical cardiac events. Recent developments in technology allow the assessment of this variable in a serial fashion using noninvasive techniques. Day/night fluctuations in endothelial function have been observed in three studies *(118,146,147)*. There are differences in results among these studies for unknown reasons, although Elherik et al. *(146)* made the most frequent measurements and best described the day/night variability. These authors reported a trough in endothelial-dependent vasodilatation (to acetylcholine) at 8 AM and a peak at 4 PM. The rhythm in endothelial-independent vasodilatation (to sodium nitroprusside) showed a similar pattern. Thus, the reduced vasodilatory capacity of the endothelium may contribute to the cardiovascular risk in the morning. However, further study is clearly required because of the differing results among studies and to assess the independent contributions of behaviors and the endogenous circadian system on endothelial function.

EFFECT OF INTERACTION BETWEEN POTENTIAL BEHAVIORAL TRIGGERS AND ENDOGENOUS CIRCADIAN PHASE ON ADVERSE CARDIOVASCULAR EVENTS

Wakefulness, upright posture, and activity all increase heart rate, blood pressure, platelet aggregation, sympathetic activity, and vascular tone *(146,148,149)*. There is also likely to be an influence from the endogenous circadian system, but this has been less well studied. Comparing the time of occurrence of ischemia during a day with regular day/night activity–inactivity rhythm and a day with delayed arising and activity has shown that the start of activity is the main factor in determining the risk for ischemia *(126)*. Furthermore, during the 2-h period in bed after awakening (from 8 to 10 AM), the risk for ischemia remained increased at least fourfold as compared to the 8-h sleep period before. This finding suggests a morning increase in cardiovascular risk in the absence of a change in posture or activity. Possible explanations include the transition from sleep to wake and/or the endogenous circadian rhythm. From studies of repeated cardiovascular biomarker measurements across the 24-h day, there is some evidence that cardiovascular biomarkers possess a day/night rhythm in sensitivity to behavioral changes—possibly indicating an interaction between the behaviors and the endogenous circadian system. In terms of hemodynamic variables, previous studies identified a day/night rhythm in

orthostatic tolerance (e.g., ref. *150*). Interpreting these findings is confounded by postural history effects (i.e., prolonged recumbence, as occurs during sleep, amplifies orthostatic hypotension *[151]*), and insufficient repeated measurements to permit accurate identification of a specific day/night rhythm. Studies of variations in the cardiovascular response to exercise throughout a waking period have yielded conflicting results. Some studies report that hemodynamic or hemostatic responses to exercise were similar in the morning and in the afternoon *(98,152)*, whereas another study found a significant time-of-day effect of the exercise response *(153)*. The most important confounders among these studies include methodological issues such as nonstandardized exercise levels, comorbidity, and the very limited number of measurements across the 24-h period, such that rhythmical peaks and troughs are likely missed.

In terms of autonomic variables, the increase in serum cortisol in response to exercise is well documented. Kanaley et al. *(9)* compared the exercise-induced cortisol response between morning (7 AM), evening (7 PM), and midnight. Subjects exercised for 30 min at a constant velocity on a treadmill (similar lactate levels of approx 2.5 mmol/L and approx 85% of maximal oxygen consumption). The maximal change in cortisol in response to exercise was found at midnight. Baseline cortisol levels were maximal in the morning. However, the summation of baseline and response to exercise resulted in the highest cortisol levels in the morning. Scheen et al. *(154)* compared the cortisol response to exercise (3 h, 40–60% O_2max, with constant glucose infusion) at three time points. In this study, plasma cortisol concentrations rose in response to exercise in the afternoon (2:30 PM), but not in the early morning (5:00 or 7:40 AM) or at night (11:30 PM or 4 AM). Both of these studies identify a day/night rhythm in the cortisol response. The discordance as to the time for the peak of the cortisol response to exercise may be a result of a difference in exercise intensity, duration, dietary intake, or metabolic state among studies.

As previously noted, platelet aggregability and endothelial function have day/night patterns and changes in response to behaviors, but to our knowledge there have been no studies assessing a day/night variation in the platelet response or endothelial response to a behavioral change.

In an initial attempt to test the hypothesis that myocardial response to a physiological or environmental challenge varies according to circadian phase, we chose a complex but robust stressor with potentially relevant physiological meaning— the arousal from sleep induced by a standard auditory stimulus, namely, an alarm clock. Five healthy

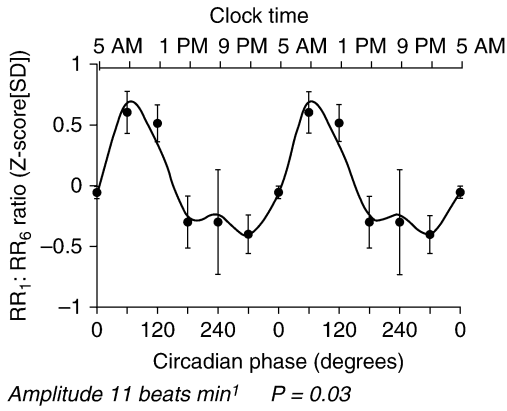

Fig. 2. Cardiac response to arousal from stage II sleep as a function of circadian phase *(8)*. Data are double-plotted to accentuate circadian rhythmicity. Shown are the normalized average data (mean ± SEM) from five healthy subjects who participated in a 10-d "forced desynchrony" protocol, such that by the end of the study the stimulus had been presented evenly distributed across each sleep episode and spanning all circadian phases. Only arousals from stage II sleep were considered for analysis. Arousals reproducibly elicited monotonically increasing heart rate for at least six consecutive beats. The cardiac response to arousal was evaluated in terms of the shortening of the ECG R-R interval from first cardiac cycle (RR_1) to the sixth cardiac cycle (RR_6) after arousal. The data were also normalized to account for baseline differences in heart rate (i.e., by assessing the ratio of RR_1 to RR_6). Circadian phase was determined by core body temperature. The R-R response to arousal from stage II sleep has a significant circadian rhythm with the peak cardiac response at 60-circadian degrees (approx 9 AM). The average instantaneous heart rate increase in response to arousal from sleep was 33 beats per minute at a circadian phase of 60° but only by 22 beats per minute at circadian phases between 180 and 300 (approx 5 PM to 1 AM). These data suggest a circadian window around 9 AM where the myocardium has a maximal response to a behavioral stressor/environmental stimulus.

subjects participated in a 10-d forced desynchrony protocol conducted in dim light (<8 lux) and temporal isolation *(8)*. The subjects' sleep–wake cycles were desynchronized from the endogenous circadian clock by extending the day length to 28-h (9.33-h scheduled sleep). Thus, sleep occurred 4 h later on each subsequent 24-h day. A standardized auditory stimulus was applied to the subjects on three occasions during each scheduled sleep episode. By the end of the study, the stimulus had been presented evenly distributed across each sleep episode and spanning all circadian phases. Figure 2 illustrates that the heart rate response to arousal from stage II sleep has a significant endogenous circadian rhythm with the peak cardiac response at

an endogenous circadian phase that corresponds to approx 9 AM. The increase in heart rate at arousal is likely a result of an increase in the sympatho-vagal balance. These data strongly suggest an interaction between behavioral and circadian effects, and this interaction results in a heightened response of the myocardium to a behavioral stressor around the time of the reported epidemiological peak circadian phase for SCD and MI.

Conceptual Model of Interacting Behavioral and Circadian Factors in Triggering Adverse Events

We propose a model that involves the summation of three cardiovascular risk components: (1) an individual's baseline vulnerability (which is related to the number of risk factors, such as obesity); (2) the summation of any concurrent behavioral triggers, either mental or physical (such as exertion); and (3) the linear or proportional interaction with the circadian system (Fig. 2 provides some evidence for a proportional interaction). For simplicity, we shall refer to the rupture of a coronary atherosclerotic plaque as the "adverse cardiovascular event." An acute coronary syndrome can be triggered by a stress that produces a hemodynamic response sufficient to cause a major plaque disruption, exposing collagen and atheromatous core contents to coronary blood, which results in thrombus formation at the site of the plaque. If the thrombus is large, yet does not totally obstruct coronary blood flow, unstable angina or non-Q-wave MI may result clinically. If the thrombus is large and totally occludes the coronary vessel, acute MI often occurs as does possibly fatal thrombosis, particularly if there exists initial cardiac damage. Thus, as previously noted, many factors that can cause MI can also be implicated in SCD, and thus elements of this model may be equally applicable to both MI and SCD.

The type of coronary plaque most vulnerable to rupture is lipid rich and has a thin fibrous cap that is weakest at its junction with the intima *(155)*, probably the result of increased macrophage activity with elaboration of metalloproteinases *(156,157)*. The acute risk factor is defined as the pathophysiological change (hemodynamic, autonomic, hemostatic, or endothelial) potentially leading to occlusive coronary thrombosis (Fig. 1). A synergistic combination of triggering activities may account for thrombosis in a setting in which each activity alone may not exceed the threshold for causation of infarction. For example, heavy physical exertion producing a minor plaque disruption in a sedentary cigarette smoker (associated with an increase in coronary artery vasoconstriction

and a hypercoagulable state *[158]*) may be needed to cause occlusive thrombosis and disease onset. However, in a patient with an extremely vulnerable plaque, even the nonstrenuous activities of daily living may be sufficient to trigger the cascade leading to the cardiovascular event. It is not known if physical exertion leads directly to plaque rupture or whether the exertion merely adds a thrombotic or vasoconstrictive element to the causal pathway. Given the compelling data on the day/night variation of myocardial event onset, the phase of the internal body clock at which these behavioral triggers occur may influence the vulnerability. This concept is exemplified in Fig. 3, which shows three schematic models of the possible interactions between the circadian system and behavioral stressors that interact to induce cardiovascular variables to surpass a theoretical cardiovascular risk threshold—which itself is adjusted up or down based on an individual's initial vulnerability (e.g., cardiovascular risk factors such as obesity, baseline hypertension, and/or a history of smoking would lower the threshold closer to daily physiological variation). In all three models, the peak in cardiovascular vulnerability is shown to occur around 9 AM based on epidemiological data. The models vary depending on the degree of baseline circadian variation and the interaction with the effect of a behavioral stressor according to the phase of the endogenous circadian rhythm. This model provides a conceptual framework for assessing cardiovascular risk. However, there are several current limitations. For instance, for most cardiovascular variables, the interactions between baseline vulnerability, circadian pacemaker effects, and behavioral effects are unknown. In addition, most cardiovascular variables interact. Thus, this model needs to be developed based on future research.

SUMMARY AND CHRONOBIOLOGICAL THERAPEUTIC IMPLICATIONS

This chapter reviews the evidence that MI and SCD exhibit a prominent day/night pattern, with events occurring more frequently during the morning hours. Hematological, vascular, autonomic, and hemodynamic factors have been implicated in this day/night pattern. These variables are altered by behavioral factors (e.g., mental stress, physical exertion) and by the endogenous circadian pacemaker, and these effects likely summate to trigger an adverse cardiovascular event in susceptible individuals (e.g., those with numerous risk factors such as obesity, hypertension, and/or vulnerable atherosclerotic plaques). Specific behaviors often occur at specific times of the day, and so it has been difficult to

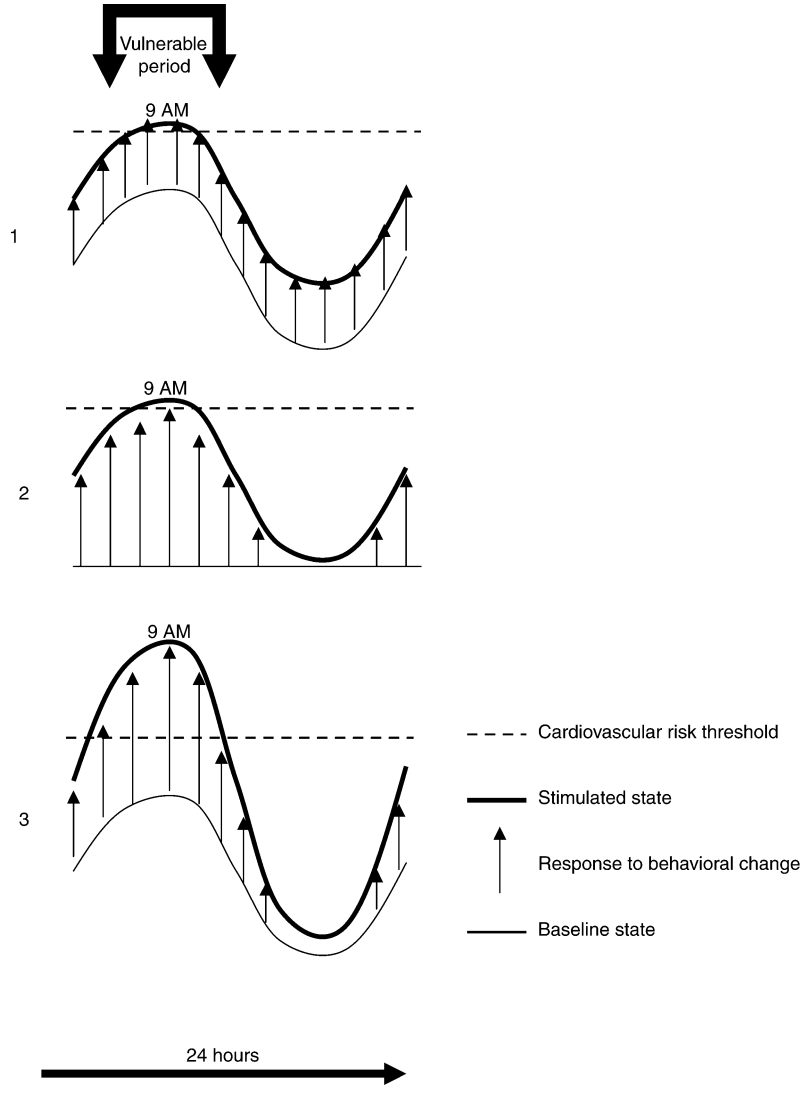

Fig. 3. Three schematic models of the possible interactions between the circadian system and behavioral stressors that may underlie the day/night pattern of adverse cardiovascular events. Depicted on the *y*-axis is any cardiovascular variable that confers physiological vulnerability to an adverse cardiovascular event, such as increased blood pressure, increased platelet aggregability, increased sympathetic nervous system activity, or decreased endothelial function (*see* Fig. 1). Shown as thin lines are the effects on these potential cardiovascular variables of baseline circadian influence. Shown by arrows are the acute effects of behavioral stressors (e.g., exercise, change in posture, arousal from sleep, anger, mental stress). Also

separately assess the independent roles of the behavioral stressors and endogenous circadian factors in causing the robust day/night patterns of adverse cardiovascular events. However, we believe that an understanding of the mechanisms governing the morning peak in cardiovascular events will be important for the following reasons. First, an increasing number of shift workers and travelers across time zones regularly experience shifts in circadian rhythms. Such individuals may or may not experience a morning peak in cardiovascular events depending on the relative importance of and the potential interactions between circadian rhythms and behavioral activities. Shift work has been associated with an increased incidence of MI *(159)*, although the potential mechanism(s) are totally unclear. Second, chronotherapy could be designed to specifically target those time periods at greatest risk for cardiovascular events. For instance, the practical benefit of salicylates to blunt the morning increase in platelet aggregability *(99,143)* and β-blockers *(17,142,160)* to attenuate the morning sympathetic activity attest to the potential role of chronotherapeutics in cardiovascular disease. Moreover, rather than perpetually giving patients the maximum tolerated dose of β-blocker, it may be better to time the β-blockade to coincide with the periods of greatest sympatho-excitation. This may improve exercise tolerance in those with chronotropic incompetence (inadequate heart rate response) by allowing periods of reduced β-blockade during lower-risk periods. Similarly, antiplatelet agents could specifically target the periods of greatest platelet aggregability to reduce thrombotic complications, while minimizing hemorrhagic complications during periods of reduced platelet aggregation. Third, behavioral therapies could be designed

Fig. 3. *(Continued)* shown is a theoretical cardiovascular risk threshold (dashed line). The level of this dashed line could theoretically move up or down based on an individual's initial vulnerability (e.g., cardiovascular risk factors such as obesity, baseline hypertension, and/or a history of smoking would lower the threshold closer to daily physiological variation). In all three models, the peak in cardiovascular vulnerability is shown to occur around 9 AM based on epidemiological data. In model 1 there is a significant baseline circadian variation, and the effect of a behavioral stressor is identical at all phases of the circadian rhythm. In model 2 there is a no baseline circadian variation, but the effect of the same behavioral stressor varies according to the phase of the circadian rhythm. In model 3 there is a significant interaction between the baseline circadian variation and the effect of a behavioral stressor, such that the same behavioral stressor causes a much larger physiological response at specific circadian phases. This model provides a conceptual framework for assessing cardiovascular risk. However, there are several current limitations.

according to periods of greatest cardiac vulnerability. For example, the timing of an exercise program, or more particularly any irregular exertion, could be modified in a predisposed individual to avoid the periods of greatest cardiac risk. Finally, improvements in understanding of mechanism of these rhythms may reveal new therapeutic targets for cardiac patients. For example, if hormones with clear circadian rhythms, such as melatonin and/or cortisol, were found to be important in modulating the times of greatest cardiac risk, interventional studies could be designed with these targets in mind. Thus, we believe that understanding the underlying circadian influences and the interaction between circadian and behavioral influences on cardiovascular biomarkers across the whole circadian cycle is essential for optimizing chronobiological therapies for cardiovascular disease.

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12 Seasonal, Weekly, and Circadian Variability of Ischemic and Hemorrhagic Stroke

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CONTENTS

INTRODUCTION

Circadian rhythms have been recognized in many biological phenomena, including secretion of hormones, activities of the autonomic nervous system, and various cardiovascular pathologies. Transient myocardial ischemia *(1,2)*, acute myocardial infarction *(3)*, embolism *(4)*, rupture of aortic aneurysms *(5)*, sudden cardiac death *(6)*, and death as a result of hypertension, ischemic heart disease, and cerebrovascular disease *(7)* have been shown to follow a certain circadian pattern; the same has been observed in the onset of stroke.

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Stroke onset has been categorized into three general patterns according to their temporal distribution: circadian (rhythm length of approx 24 h), circaseptan (rhythm length of about 1 wk), seasonal or circannual (rhythm with a period of about 1 yr). Newer methods of analyzing temporal variation include the single cosinor method, which adjusts, by least squares, a rhythmic function with a presumed period to data series, providing point and interval estimates of mesor (average values of rhythmic function fitted to the data), amplitude (half the total predictable change defined by the rhythmic function fitted to the data), and acrophase (lag from a given reference time of the rhythm's crest time, defined by the rhythmic function fitted to the data) *(8)*. A summary of the most important studies in this area is provided in Table 1.

SEASONAL VARIABILITY

Seasonal variation in the occurrence of cerebrovascular diseases has been noted since ancient times. The Old Testament suggested that apoplexy ("struck violently") occurred more often during hot weather *(9)*. Over the past two centuries, several authors have addressed the topic of seasonal periodicity in the onset of stroke *(8,10–32)*.

In the subtropical zone, patients 70 yr of age and older have been noted to have more cerebral infarcts on warmer days *(27)*. This could be to the result of increases in thromboembolic mechanisms secondary to physiological changes in response to heat: dehydration, increased blood viscosity and hemoconcentration, decrease in blood pressure, and increased concentration of platelets *(28)*.

In both the Northern and Southern Hemispheres, stroke seems to be associated frequently with cold weather. The cold climate may contribute to a higher incidence of strokes by hemodynamic and nonhemodynamic mechanisms. Blood pressure (as the major hemodynamic factor) is higher during cold weather *(33)*. In addition to increased vasoconstriction in the cold, poor control of hypertension in winter months may result because of delays in outpatient therapy during adverse weather conditions *(19)*. Hypertension by itself is not the only responsible factor for the increased stroke rate in winter, as normotensives have been noticed to also have a higher incidence of cerebral hemorrhage during winter *(27)*. Other (nonhemodynamic) factors that might explain this finding are increased platelet and erythrocyte counts, blood viscosity, and catecholamine secretion, all increasing with the decrease in temperature *(35)*. The possible relation of the seasonal variation of serum cholesterol (higher in winter and lower in summer) *(36–39)*

Table 1
Studies Assessing the Temporal Distribution of Stroke Onset

Author (year)	*Type of study*	*Location*	*No. of patients*	*Age*	*Temporal variability (peak month, day, or hours)*	*Notes*
Perkins (1933)	Hospital	Brooklyn, NY	801	N/A	Seasonal (September–January)	
Aring (1935)	Hospital	Boston, MA	245	N/A	Seasonal (November–March)	
Bokonjic (1968)	Hospital	Sarajevo, Yugoslavia	463		Seasonal (December–January)	
McDowell (1970)	Hospital	New York	1000	N/A	Seasonal (Winter months)	
Alter (1970)	Hospital	Fargo, ND, and Moorhead, MN	408	N/A	Seasonal (April and November)	
Hossmann (1971)	Hospital	Cologne, Germany	127	N/A	Circadian (1–5 AM)	
Olivares (1973)	Hospital	Mexico City, Mexico	206	65	Circadian (6 AM to noon)	Embolic stroke (noon to midnight; March–May)
					Seasonal (August–September)	

(Continued)

Table 1 ***(Continued)***

Author (year)	*Type of study*	*Location*	*No. of patients*	*Age*	*Temporal variability (peak month, day, or hours)*	*Notes*
Agnoli (1975)	Hospital	Rome, Italy	256	N/A	Circadian (6 AM to 2 PM)	
Marshall J (1977)	Hospital	London, UK	707	N/A	Circadian (midnight–6 AM)	Infarct (midnight to 6 AM) Hemorrhage (noon to midnight)
Ramirez-Lassepas M (1980)	Hospital	St. Paul, MN	128	63	Seasonal (January–March)	
Brackenridge CJ (1981)	Hospital and community	Melbourne, Australia	1630	68.8	Circaseptan (Wednesday) Seasonal (mid-July)	
Christie D (1981)	Community	Melbourne, Australia		N/A	Seasonal (July)	
Haberman S (1981)	Hospital and community	England and Wales, UK	864	N/A	Seasonal (January–March)	
Kaps M (1983)	Hospital	Giessen, Germany	563	64	Circadian (7 AM to 7 PM)	
Jovicic A (1983)	Hospital	Belgrad, Jugoslawia	85	N/A	Circadian (8–11 AM) Seasonal (September–November)	

Tsementzis SA (1985)	Hospital	West Midlands and Birmingham, UK	567	<70	Circadian (10 AM–noon)	SAH (10 AM–noon; 6–8 PM)
Suzuki K (1987)	Hospital	Akita, Japan	2168	<67.1	Seasonal (December–February)	
Sobel E (1987)	Hospital and community	Lehig Valley, PA	1944		Seasonal (none for all strokes)	TIA (June–August) Infarct (February–April)
Van der Windt (1988)	Hospital	Utrecht, Netherlands	66	N/A	Circadian (6 AM to 6 PM)	
Gill (1988)	Hospital	West Midlands, UK	30,679	N/A	Seasonal (January)	
Biller (1988)	Hospital	Iowa City, IA	2960	N/A	Seasonal (none for all strokes)	Cerebral infarction (June–August) ICH (December–February)
Marler (1989)	Hospital	MD, MA, CA, IL	1167	68	Circadian (10 AM–noon)	
Marsh E (1990)	Hospital	Iowa City, IA	151	63	Circadian (6 AM–noon)	Thrombotic atroke (mid-night–6 AM)
Arboix (1990)	Hospital	Barcelona, Spain	206	N/A	Circadian (none for all strokes)	

(Continued)

Table 1 ***(Continued)***

Author (year)	*Type of study*	*Location*	*No. of patients*	*Age*	*Temporal variability (peak month, day, or hours)*	*Notes*
						Intraparenchymal hemorrhage (6 AM–noon) Cardioembolic stroke (6 AM to 6 PM)
Argentino (1990)	Hospital	Rome, Italy	426	66	Circadian (6 AM–noon)	
Pasqualetti (1990)	Hospital	L'Aquila, Italy	732	N/A	Circadian (2–8 AM) Circaseptan (Saturday–Tuesday) Seasonal (September–March)	
Shinkawa (1990)	Hospital and community	Hisayama, Japan	308	72	Seasonal (February)	Hemorrhage (January) Infarction (March)
Johansson (1990)	Hospital	Lund, Sweden	497	73	Circadian (9 AM to 1 PM) Circaseptan (Tuesday)	Infarction (July and December) Embolic stroke (March and April)

					Seasonal (none for all strokes)	
Woo (1991)	Hospital	Shatin, Hong Kong	683	N/A	Seasonal (none)	
Ince (1992)	Hospital	Istanbul, Turkey	120	N/A	Circadian (6 AM to 6 PM)	
Wroe (1992)	Hospital and community	Oxfordshire, UK	675	N/A	Circadian (6 AM–noon)	Infarct (6 AM–noon; 2–4 PM) SAH (8–10 AM; 6–8 PM)
Sloan (1992)	Hospital	MA, MD, NY, IL	480	61	Circadian (none for all strokes)	ICH (10 AM–noon; 6–8PM) SAH (10 AM–noon; 2–4 PM)
Ricci S (1992)	Community	Umbria, Italy	368	N/A	Circadian (6 AM–noon) (December–March)	(September–December)
Capon (1992)	Hospital	Brussels, Belgium	236	N/A	Seasonal (November–December)	
Pardiwalla (1993)	Hospital	Bombay, India	182	N/A	Circadian (6 AM to 2 PM)	
Chyatte (1993)	Hospital	Chicago, IL	1487	N/A	Seasonal (late spring women; late fall men)	Intracranial aneurysm
Gallerani (1993)	Hospital	Ferrara, Italy	977	NA	Circadian (7 AM–noon) Seasonal (October)	

(Continued)

Table 1 ***(Continued)***

Author (year)	*Type of study*	*Location*	*No. of patients*	*Age*	*Temporal variability (peak month, day, or hours)*	*Notes*
Vinall (1994)	Hospital	14 countries	685	50	Seasonal (January–March)	SAH secondary to aneurysm rupture
Butchart (1994)	Hospital	Cardiff, UK	96	N/A	Seasonal (December–March) Circadian (6 AM–noon)	
Kelly-Hayes (1995)	Community and hospital	Framingham, MA	635	N/A	Circadian (8 AM–noon) Circaseptan (Monday) Seasonal (January and August)	
Lago (1998)	Hospital	Valencia and Castellon, Spain	1223	72	Circadian (1–6 AM)	
Tuhrim (1998)	Hospital	New York	1148	71	Seasonal (November–January) Circadian (6 AM–noon)	
Casetta (2002)	Hospital	Ferrara, Italy	258	N/A	Circadian (8 AM and 8 PM)	ICH
Casetta (2002)	Hospital	Ferrara, Italy	1656	N/A	Circadian (AM)	Ischemic stroke

ICH, intracerebral hemorrhage; SAH, subarachnoidal hemorrhage; TIA, transient ischemic attack.

with the seasonality of cerebrovascular disease has not been explained. Controversies exist about the seasonal variation observed within the different stroke categories and within different age groups. A seasonal variability for cerebral hemorrhage has been noted by some groups *(17,19,23,24,29,30)* but not by others *(20,21)*; thromboembolic stroke was shown to present with a seasonal pattern in most of the studies *(8,14,15,20–24,27,32)*. The seasonal association with certain types of strokes seems to be dependent, at least partly, with the age of the patients in certain climates: in Japan, younger patients (<64 yr) showed a higher seasonality than elderly patients *(24)*, whereas in Ireland, elderly patients presented a negative correlation between the occurrence of cerebrovascular accidents and the temperature during winter months *(25)*. The rupture of intracranial aneurysms has been reported to occur most often in late fall in men and in late spring in women *(26)*. These differences may be explained by the very heterogeneous populations studied.

CIRCASEPTAN VARIABILITY

Few studies have concentrated on the circaseptan variability in cerebrovascular disease *(23,32,39,40)*. Weekly variability could be related to the change in behaviors that occur during certain periods of the week. The circaseptan variability has been identified as an increase in strokes on Saturday evenings (because of the short-term lifestyle changes during the weekend) *(23)*; on Mondays (in working patients, associated with male sex, alcohol use, cigarette smoking, and hypertension) *(32)*; or on Wednesdays (in hospital-onset strokes when compared with community-onset strokes) *(33)* or Tuesdays (for large vessel infarction) *(40)*.

CIRCADIAN VARIABILITY

Although earlier studies suggested that the onset of stroke was fairly evenly distributed among 24 h of the day *(12)*, more recent studies suggest a circadian variability for all strokes as well as for certain stroke subtypes. However, contradictory data exists regarding the precise onset of stroke. This has been observed to occur more frequently:

1. In the early morning hours (midnight to 6 AM) *(41–43)*.
2. During the late morning hours (6 AM to noon) *(8,15,29,32,44–53, 86,87)*.
3. Between 6 AM and 6 PM *(54–56)*.

The contradictory data presented are explained by the difficulties encountered in determining the exact time of stroke onset (self-report or report by family members, tendency to underreport strokes occurring during a certain time of the day, recalling stroke onset according to its severity) as well as the possible link between the stroke onset and the triggering event, which may be several hours away from the onset of stroke symptoms *(57,58)*.

Stroke categories seem to respect also a certain circadian pattern:

1. Atherothrombotic stroke has been described more often between midnight and 6 AM *(43)* or between 6 AM and noon *(15,29,44,87)*.
2. Intracerebral hemorrhage occurs more often between 6 AM and noon *(15,29,43–46,86)*.
3. Embolic stroke seems to occur more frequently between noon and 6 PM *(15,43)*.

Nevertheless, most data suggest that infarcts occur in the morning hours.

By analyzing the data by the single cosinor method, the peak time (or acrophase) for all strokes has been described as being between 2 and 8 AM *(23)*, between 7 AM and noon *(8)*, and at 11 AM *(40)*. For the different stroke categories, the peak time has been described as being between 11 AM and noon for cerebral infarction *(8,40)*, at 10:24 AM for cardioembolic stroke *(40)*, at 12:41 PM for transient ischemic attacks *(8)*, and at 5:16 PM for subarachnoid hemorrhage *(40)*. No difference in circadian rhythm has been observed between first-time and recurrent stroke *(52)*. The circadian variability of stroke onset has also been described in patients with mitral valve replacement, who present a peak of cerebrovascular events (transient ischemic attacks, reversible ischemic neurological deficits, or strokes) in the morning (and winter months) *(59)*. The mechanisms responsible for the circadian pattern of stroke onset may include variation of the blood pressure, instability of the atherosclerotic plaque, a relatively prothrombotic state, and increased arrhythmogenesis. The presence of a similar circadian pattern for both hypertensive and normotensive patients with hemorrhagic stroke (resembling the physiological circadian rhythm of blood pressure) suggests that blood pressure variations (irrespective of the degree of hypertension) may be paramount in causing the rupture of a weakened arterial wall *(86)*.

It is known that blood pressure presents a circadian variation *(60–64)*, and in hypertensive patients it has been suggested that the early morning onset of cerebral hemorrhage (as well as subarachnoid hemorrhage) is to the result of a rapidly increasing arterial blood pressure in the morning *(45,60,60a)*. The association between intracerebral

hemorrhage and the diurnal variation of blood pressure seems to be very strong in untreated hypertensives *(50)*. The nondipping or dipping pattern of the 24-h monitoring of blood pressure appears to be associated with the cerebrovascular disease.

Nondippers (hypertensives whose 24-h blood pressure does not follow the normal circadian pattern) have a higher risk of stroke *(65)*. The nondipping status conferred risk for stroke even after adjustment for traditional stroke risk factors *(66)*. Sometimes the change from a "dipper" to "nondipper" status may be attributed to a small lacunar infarct *(67)*. The absence of "dipping" or the lower nocturnal blood pressure fall in elderly hypertensives might be associated with silent cerebrovascular disease *(68)*. The diminished nocturnal blood pressure decline in cerebrovascular disease is thought to be caused by specific injury to the central autonomic nervous system (e.g., the striatum, midbrain, pontine tegmentum, or insular cortex) *(69,71)*.

The preserved circadian "dip" in hypertensives (mostly in the early morning) might induce a "critical" local hypotension that can be responsible for the stroke (especially when superimposed on a critical stenosis of the cerebral vessels) *(41,71–72a)*. Silent cerebrovascular lesions are more severe in elderly women with an extreme dipper pattern of circadian blood pressure variation *(73)*.

Factors that may predispose to increased coagulation or vasoconstriction also demonstrate circadian variation:

1. Peak hematocrit and blood viscosity (important factors influencing cerebral flow) have been described to occur at 8 AM *(74)*.
2. The highest fibrinolytic inhibition (and barely detectable tissue plasminogen activity in the blood) occurs between 3 and 8 AM *(75,76)*.
3. Spontaneous increase in platelet sensitivity to epinephrine and the binding affinity of the α_2-adrenoreceptors were maximum at 8 AM *(77)*.
4. Platelet aggregability increases between 9:30 and 11 AM (after assumption of the upright posture) *(78)*.
5. Plasma renin activity of recumbent normal subjects presents the highest values between 2 and 8 AM (with a further increase when assuming the upright posture) *(79)*.
6. Minimum vascular resistance is higher in the morning and night compared to noon and evening *(80)*.

FINAL CONSIDERATIONS

Several observations have shown the existence of a certain temporal (seasonal, weekly, and daily) variability in the onset of acute stroke. Further studies are necessary to better characterize and prevent the

potential triggers of cardiovascular events (vulnerable plaque, refractory hypertension, nondipping status, and so on) *(81)* as well as to provide a better understanding of the role played by certain hormones (e.g., melatonin) in the regulation of various circadian rhythms and stroke onset *(82–85)*.

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III Ambulatory Blood Pressure Monitoring in Special Populations

13 Ambulatory Blood Pressure in Older Patients

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CONTENTS

INTRODUCTION

The treatment of hypertension in elderly patients (60 yr or older) is based on the largest body of data for any group of patients *(1)*. The data are striking for a reduction in strokes and heart failure (Table 1). The benefits have been achieved with the use of multiple antihypertensive drugs in combination *(2)*. Ironically, the elderly have the worst blood pressure control rate.

Ambulatory blood pressure monitoring may provide useful information on blood pressure control and management in this population. It also has potential prognostic utility. In this chapter, we review the various trials utilizing ambulatory blood pressure monitoring in the elderly population.

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Table 1
Double-Blind, Placebo-Controlled Outcome Trials in the Elderly: Percent Change in Events

Trial	*Total mortality*	*Cardiovascular mortality*	*Stroke mortality*	*Fatal myocardial infarctions*	*Heart failure*	*All myocardial infarctions*	*Fatal and nonfatal stroke*	*cardiovascular events*
EWPHE	–26	–38[a]	–43	–47[a]	–63[a]	NS	–46	–34[a]
SCOPE	–4	–6	–7	–5	NS	+10	–24	–11
SHEP	–13	–20	–29	–43	–54[a]	–27[a]	–36[a]	–32[a]
STOP-Hypertension	–43[a]	NS	–73[a]	–25	–51[a]	–13	–47[a]	–40[a]
Syst-Eur	–14	–27	–27	–56	–29	–30	–42[a]	–31[a]

[a]Significant reduction.

EWPHE, European Working Party on High Blood Pressure in the Elderly; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; STOP-Hypertension, Swedish Trial in Old Patients with Hypertension; Syst-Eur, Systolic Hypertension in Europe; NS, not stated.

From ref *1*.

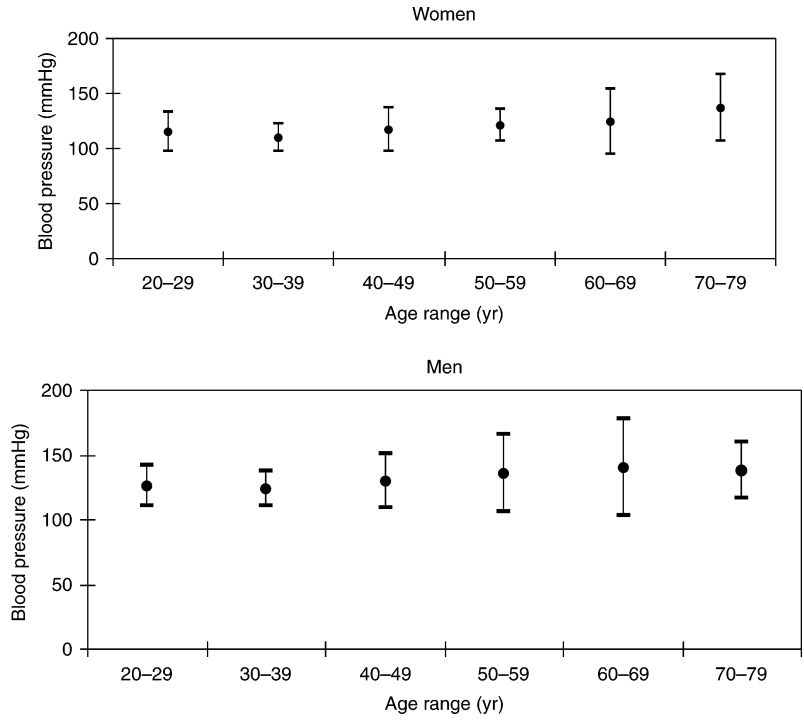

Fig. 1. Variability of blood pressure. Both the upper (women) and lower (men) panels show the increasing blood pressure with increasing standard deviation with aging. (Adapted from ref. *4*.)

OFFICE BLOOD PRESSURE

Several issues should be considered when providing care to older patients: (1) increased variability of blood pressure, (2) orthostatic changes, (3) an auscultatory gap, and (4) pseudohypertension.

Variability of Blood Pressure

The Joint National Committee Report recommends two blood pressure measurements at every visit *(3)*. However, additional measurements may be necessary because of increased variability in older persons possibly because of impaired baroreceptor sensitivity (Fig. 1) *(4)*.

Orthostatic Hypotension

Impaired baroreceptor sensitivity may be a factor in the orthostatic hypotension associated with aging and hypertension *(5)*. Orthostatic

hypotension is defined as a symptomatic fall in blood pressure of 20 mmHg within 3 min of standing. Patients taking certain medications, including antipsychotic medications, antiparkinsonian drugs, α_1-blockers, diuretics and nitrates, and patients with Parkinson's disease and diabetes mellitus with autonomic insufficiency are at increased risk for orthostatic hypotension. Falls and fractures are a consequence of orthostatic hypotension, but there is additionally an increased vascular mortality among home-dwelling elderly persons with orthostatic hypotension *(6)*.

A cohort of 22 healthy elderly normotensive volunteers were studied to assess reproducibility of postural changes *(7)*. Using a Dinamap 8100 (Critikon, Tampa, FL), supine blood pressure and standing blood pressure after 1 and 3 min were measured twice in the morning fasting and in the afternoon 90 min after a light meal and then repeated in 6 wk. After standing 1 min, the systolic blood pressure decline of 7 mmHg was maximal; however, diastolic blood pressure increased as high as 6.8 mmHg 3 min after standing. There was no difference between morning and afternoon measurements or between visits. Reproducibility of postural measurements was poor with differences ranging from 16.4 to 29.3 mmHg for systolic blood pressure and 9.8 to 16.9 mmHg for diastolic blood pressure. Blood pressure reproducibility in the afternoon was less than in the morning.

Of elderly patients with isolated systolic hypertension, 17.3% experienced orthostatic hypotension at 1 or 3 min after standing (Fig. 2) *(8)*. After a high-carbohydrate meal, supine blood pressure declined and heart rate increased without an increase in plasma norepinephrine levels *(9)*.

Auscultatory Gap

The quality of blood pressure measurement is of prime importance for the initial diagnosis and the adjustment of medication *(10)*. The use of a mercury sphygmomanometer remains the gold standard for routine determination of blood pressure *(11)*. Radial artery palpation at the time of the initial cuff inflation will help to identify the level of systolic blood pressure and avoid excessive cuff pressure that might cause pain. Additionally, it may identify the presence of an auscultatory gap. Not recognizing an auscultatory gap can result in an underestimation of systolic blood pressure or an overestimation of diastolic blood pressure. An auscultatory gap is associated with older age, female gender, increased arterial stiffness, and carotid atherosclerotic plaque *(12)*.

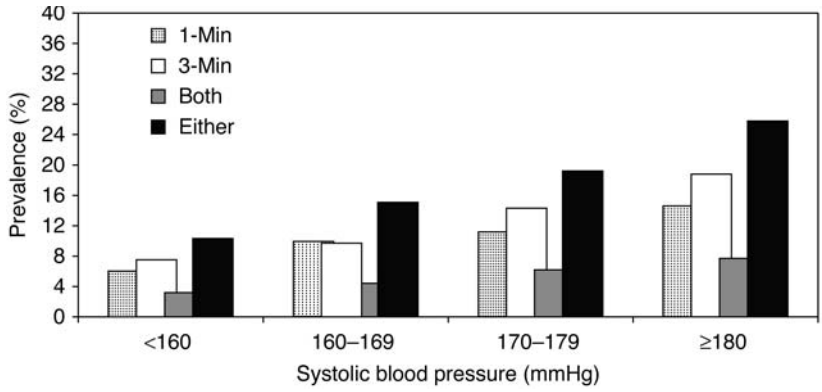

Fig. 2. Prevalence of standing systolic blood pressure decline of ≥20 mmHg. The prevalence of a decline in systolic blood pressure at 1 and 3 min increases with higher levels of systolic blood pressure. (Adapted from ref. *8*.)

Pseudohypertension

A pulseless, but palpable, radial or brachial artery after ipsilateral occlusion by the cuff is described as being "Osler positive," a sign of atherosclerosis *(13,14)*. Pseudohypertension is a spuriously elevated cuff blood pressure with a normal intraarterial measurement. The implication of an Osler-positive sign is that the patient will receive unnecessary antihypertensive drug treatment *(14)*. Higher cuff pressures were observed in Osler-positive (+15.8/+16.4 mmHg) vs in Osler-negative (–3.0/+5.3 mmHg) patients; however, most subjects in this study had systolic blood pressure measurements greater than 140 mmHg. In a study of geriatric patients, the prevalence of an Osler-positive sign was 11% of 205 screened patients *(15)*. When Osler-positive and -negative patients were compared with intraarterial measurements, there was no significant difference in blood pressure. Furthermore, Osler's maneuver did not predict the presence or absence of pseudohypertension *(15)*.

HOME BLOOD PRESSURE MONITORING

Home blood pressure monitoring is increasingly advocated for the diagnosis and management of patients *(16)*. There is also a potential for cost savings.

Twenty-eight elderly patients in random sequence measured their blood pressure with an automatic and semiautomatic device and had their blood pressure measured by a physician three times *(16)*. All

measurements were repeated 3 d later. The automatic device was similar to physician measurements, but the semiautomatic device recorded higher blood pressures than the mercury sphygmomanometer. Thus, automatic devices were recommended for self-measurement.

The Omron HEM-722C and HEM-735C (Omron Healthcare, Inc., Kyoto, Japan) was validated using the revised British Hypertension Society protocol in a population of 30 subjects older than 65 yr *(17)*. For the HEM-722C, the mean difference between the device and a mercury manometer was 0.76/0.41 ± 5/8 mmHg. Comparing the HEM-722C to mercury values, 76% of systolic and 71% differed by less than 5 mmHg. For the HEM-735C, the mean difference between the device and a mercury manometer was 0.24/0.9 ± 8/8 mmHg. Comparing the HEM-735C to mercury values, 68% of systolic and 74% differed by less than 5 mmHg. Both devices passed the British Hypertension Society criteria.

Forty elderly hypertensive men and women (average age 73 yr) were clinically managed by home or clinic blood pressure measurements over a 3-mo period *(18)*. Ambulatory blood pressure was performed at baseline and on completion of the study to assess the effectiveness of each approach. Patients used an Omron HEM-702 device to collect three measurements in the morning and the evening every other day. The information was obtained by telephone by a study nurse every 2 wk. The clinic group had careful blood pressure measurement every 2 wk. Both groups had their drug therapy altered according to a treatment algorithm. Both groups achieved similar levels of blood pressure after 3 mo.

The Hypertension and Ambulatory Recording in the OLD (HAROLD) study is a trial designed to determine whether home blood pressure, 24-h ambulatory blood pressure, left ventricular structure and function, and albumin excretion rate are more accurate predictors of outcome compared with sphygmomanometer measurements in 1000 untreated elderly subjects with a blood pressure between 140/90 and 159/94 mmHg *(19)*. The endpoints are the development of a blood pressure 160/95 mmHg or higher and 5-yr incidence of cardiovascular events. Recruitment is in progress.

AMBULATORY BLOOD PRESSURE

Ambulatory blood pressure has provided new information in the elderly: (1) increased blood pressure variability *(20–22)*, (2) diminished or absent nocturnal blood pressure decline *(23)*, and (3) postural and postprandial hypotension *(24)*.

Demographics

To evaluate ambulatory blood pressure in a community-dwelling, ambulatory elderly Irish population, 75 patients 60–79 yr of age were compared to 81 patients 80–102 yr *(23)*. Hypertensives not receiving drug therapy were included in this study. Age correlated positively with clinic, daytime, and nighttime systolic blood pressure ($p < 0.01$ for each), but not with diastolic blood pressure. There were no gender differences in blood pressure. The old elderly had higher systolic blood pressure levels than the young elderly, a mid-afternoon (postprandial) drop in blood pressure without a decline in heart rate, and a smaller nocturnal decline in systolic blood pressure.

Equipment Validation

To assess agreement between auscultatory blood pressure measurements by an Accutracker II (Suntech Medical Instruments, Raleigh, NC) and mercury manometer using two observers, 103 subjects ages 23–91 yr were studied *(25)*. For the group, the ambulatory blood pressure device was 5.6/6.3 mmHg lower. The systolic blood pressure difference was related to age and the actual level of systolic blood pressure. For example, in a 70-yr-old, a mercury manometer would measure a systolic blood pressure 11 mmHg higher than a simultaneously measured blood pressure with the Accutracker II. Because the authors did not measure intraarterial blood pressure, one can only speculate which device was in error.

Thirty elderly patients underwent an equipment validation of the QuietTrak ambulatory blood pressure recorder (Tycos-Welch-Allen, Arden, NC) using the British Hypertension Society protocol *(26)*. The average difference between the observer and the device was –0.8/–0.2 $\pm$ 3.2/4.5 mmHg. Ninety-five percent of systolic readings and 98% of diastolic readings were within 5 mmHg.

An equipment validation was undertaken in 85 normotensive and hypertensive elderly subjects *(27)*. Using the revised 1993 British Hypertension Society protocol, two observers, using same arm sequential blood pressure measurements, compared the SpaceLabs 90207 (SpaceLabs, Inc., Richmond, WA) ambulatory blood pressure device with a mercury sphygmomanometer (three times in supine, sitting, and standing positions). Diastolic blood pressure measurements were accurately recorded by the SpaceLabs device in all three positions (grade A); however, systolic blood pressure measurements were not (grade C or less). The higher the systolic blood pressure measured by a mercury

manometer, the greater the difference in measurements. Systolic blood pressure measurements were underestimated when mercury measurements exceeded 160 mmHg.

The Takeda TM-2420 (A&D Medical Ltd., Tokyo, Japan) was tested in 28 subjects 75 yr and older *(28)*. Sequential arm measurements were used because simultaneous, same arm measurements were not possible. The TM-2420 overestimated mercury measurements by 13.9/7.5 ± 13.9/6.4 mmHg. Most patients reported sleep disturbances.

Intraarterial blood pressure measurements were compared to noninvasive measurements with a standard manometer and an ambulatory oscillometric device (ABPM-630, Nippon Kohrin Co., Komaki, Japan) *(29)*. The systolic blood pressure was lower and the diastolic blood pressure higher with both noninvasive devices compared to intraarterial measurements in the nine subjects. The mean difference was –13.6/+4.2 mmHg for the manometer and –13.4/+5.4 mmHg for the oscillometric device.

Reproducibility

Long-term reproducibility of ambulatory blood pressure was assessed in 26 patients over a period of 4–12 mo using a Novacor Diasys Integra (Novacor, Rueil-Malmaison, France), which uses an ausculatory method preferentially and oscillometric method if ausculatory attainment fails *(30)*. The 24-h, daytime, and nighttime diastolic blood pressure and daytime average systolic blood pressure were not significantly different on repeat measurement. However, the 24-h and nighttime systolic blood pressure was higher on the second visit. The nighttime measurements showed poorer reproducibility than the daytime and 24-h periods.

Another study of 130 nonhypertensive subjects aged 55–79 yr performed clinic (three measurements) and ambulatory blood pressure on two occasions with an Accutracker II and an activity monitor *(31)*. After 5 yr, both clinic and systolic ambulatory blood pressure increased and 62% of study participants with a blood pressure of 130–139/85–89 mmHg became hypertensive. Increasing age predicted the increase in blood pressure.

Using the SpaceLabs device, the Systolic Hypertension in Europe Trial (Sys-Eur) assessed repeatability of office and ambulatory blood pressure in 141 patients with isolated systolic hypertension after a median of 33 d *(32)*. The median difference for clinic blood pressure consistency was 9/4.5 mmHg, whereas the median difference for 24-h ambulatory blood pressure was 5.4/3.5 mmHg.

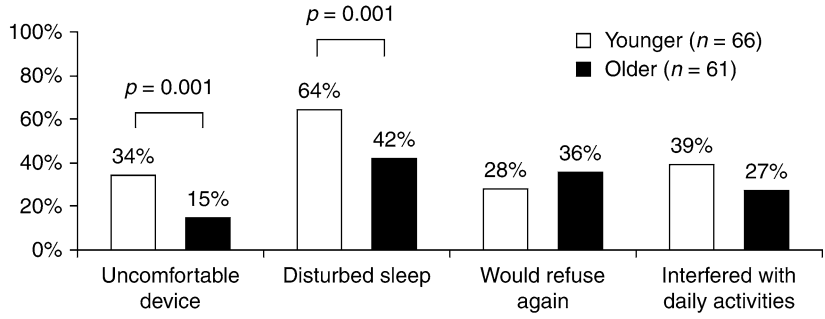

Fig. 3. Tolerability of ambulatory blood pressure in older and younger patients. Disturbed sleep was the most common complaint associated with ambulatory blood pressure monitoring. It was voiced more commonly among younger patients ($p = 0.001$). (Adapted from ref. *33*.)

Tolerability

It might be predicted that older patients may not tolerate ambulatory blood pressure monitoring. However, a study of 127 patients who underwent a 24-h recording with a SpaceLabs 90207 device and completed a questionnaire on removal of the equipment found that younger patients (<65 yr) were more likely to report the device as uncomfortable or interfering with sleep *(33)*. As shown in Fig. 3, elderly subjects were just as likely to state that they did not want to undergo the procedure again as younger participants. This has been reported in other studies, as have sleep disturbances in elderly patients *(34–36)*.

Normality (Reference Values)

One hundred and two healthy, untreated, elderly patients (65–83 yr) underwent ambulatory blood pressure monitoring with a SpaceLabs 90207 device to establish reference values for older persons *(36)*. Sleep period was determined by diary entries. The mean 24-h, daytime, and nighttime blood pressure was 133/81, 136/84, and 122/71 mmHg, and 95th percentile was 156/95 mmHg, 159/98, and 148/87, respectively. The average nocturnal decline in blood pressure was 15/14 mmHg. The prevalence on nondipping was 14%. Sleep disturbances because of the monitor occurred in 14% of patients.

Two hundred and forty-eight residents of Monza, Italy, were selected randomly and studied by recording clinic, home, and ambulatory blood pressure *(37)*. The population was 65–74 yr and included normotensives and hypertensives, treated and untreated. Ambulatory blood pressure

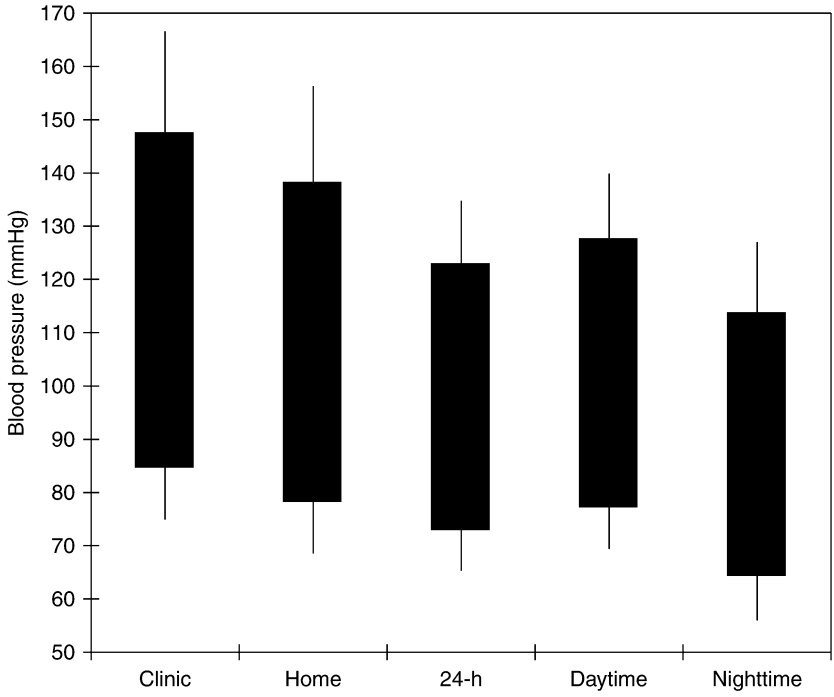

Fig. 4. Clinic, home, and ambulatory blood pressure among 248 participants from Monza, Italy, aged 65–74 yr. Clinic blood pressure measurements are higher than home blood pressure or ambulatory measurements. (Adapted from data from ref. *37*.)

was measured with a SpaceLabs 90207 device. Clinic measurements were higher than home or ambulatory blood pressure (Fig. 4). Sleep periods were not determined by diary reports. Home measurements were less than clinic measurements ($p < 0.01$). The 24-h mean blood pressure was less than clinic ($p < 0.01$) or home ($p < 0.01$) blood pressure. There was no clinically significant difference between men and women. The upper limits of normal blood pressure were 133/82 mmHg for home blood pressure and 120/76 mmHg for 24-h ambulatory blood pressure.

To establish reference values of 24-h ambulatory blood pressure, 1060 men from Uppsala, Sweden, underwent two office sphygmomanometer measurements and ambulatory blood pressure monitoring with an Accutracker II *(38)*. Sleep periods were not determined by diary entries. Using office blood pressure, only 25% of the population was normotensive and 27% of the hypertensive patients treated. The 95th percentile of

Table 2
Gender-Specific Normal Reference Values of 24-h, Daytime, and Nighttime Ambulatory Blood Pressure in Older Patients

Blood pressure	*Men*	*Women*
24-h Systolic (mmHg)	98–145	100–154
24-h Diastolic (mmHg)	62–93	62–89
Daytime systolic (mmHg)	102–154	103–158
Daytime diastolic (mmHg)	64–99	64–91
Nighttime systolic (mmHg)	84–133	85–143
Nighttime diastolic (mmHg)	53–82	51–85

Adapted from ref. *39*.

ambulatory blood pressure among the 685 untreated study participants was 162/88 mmHg for the 24-h blood pressure and 142/80 mmHg for normotensives. Regression analysis computed that a 24-h ambulatory blood pressure of 130/78 mmHg corresponded to an office measurement of 140/90 mmHg.

Another study examined 502 randomly selected subjects aged 64–87 yr from Lieto, Finland *(39)*. Nursing home residents were excluded. Blinded mercury manometer measurements were performed at the time of application of a Novacor Diasys Integra device. There were 211 normotensive and untreated hypertensive patients among the study participants. Ambulatory systolic blood pressure increased 0.4 mmHg per year of age, whereas ambulatory diastolic blood pressure decreased 0.2 mmHg per year of age. Women had higher mean ambulatory systolic blood pressure levels than men. The decline in nocturnal blood pressure (using diary entries) was 15/13% in normotensives and 14/13% in treated hypertensives. Using the normotensive and untreated hypertensives, the gender-specific ambulatory blood pressure values are displayed in Table 2.

White-Coat Hypertension

White-coat effect refers to the alerting response that a patient experiences in the medical setting *(40)*. All patients with white-coat hypertension have a white-coat effect. Even patients with sustained hypertension can have a white-coat effect. Thus, white-coat effect refers to a measure of blood pressure change *(41)*. One common definition is clinic blood pressure minus a daytime ambulatory blood pressure. The white-coat effect tends to be more pronounced for systolic than diastolic blood pressure. It tends to be greater with severe hypertension, women, and the elderly than younger individuals *(42)*. White-coat or office hypertension

refers to a measured blood pressure level. Specifically, an elevated clinic blood pressure with a normal ambulatory home blood pressure is white-coat hypertension. The implication for clinicians is that excess pharmaceutical treatment may ensue with its attendant risks *(43,44)*. For this reason, investigators have advocated the routine use of ambulatory blood pressure monitoring in elderly hypertensive patients *(29)*.

Using a SpaceLabs 5200 monitor, 81 untreated elderly patients with isolated systolic hypertension and 39 elderly normotensives were compared to determine the incidence of white-coat hypertension *(45)*. Data from the normotensive group defined the 90th percentile for the daytime systolic blood pressure. Using this definition, 35 (42%) of the hypertensives had white-coat hypertension. Blood pressure variability was not greater in this group compared to the sustained hypertensives or the normotensives.

Ten elderly subjects with isolated systolic hypertension were compared to 11 elderly normotensive controls to determine the relationship between office blood pressures measured in triplicate with a random zero sphygmomanometer and 24-h ambulatory blood pressure measured with an Accutracker II *(46)*. This procedure was repeated three additional times 1 wk apart. White-coat effect was greater among hypertensives (24/10 mmHg) compared to normotensives (0.4/8 mmHg) at the first visit. The individual reproducibility of clinic minus ambulatory blood pressure was 7.2/7.3 mmHg among normotensives and 13.1/6.7 for hypertensives. The mean white coat effect across all clinic visits was 7/8 mmHg for normotensives and 26/9 mmHg for isolated systolic hypertensives. Other researchers have questioned the limited reproducibility of white coat effect *(47)*.

One hundred and eight ambulatory elderly subjects (65–95 yr) had clinic blood pressure measured supine three times on 2 d and underwent 24-h ambulatory blood pressure with a SpaceLabs 90207 monitor *(48)*. White-coat effect was greater among the young elderly than the old elderly ($\geq$80 yr), especially the older females.

In a study that examined echocardiographic indices in 67 elderly patients 60 yr and older, white-coat hypertension was defined as a 24-h ambulatory systolic blood pressure of less than 140 mmHg and an office systolic blood pressure greater than 160 mmHg *(49)*. White-coat hypertensives ($n = 17$) had greater left ventricular mass index than the 16 normotensive patients ($p = 0.012$) and a lower left ventricular mass index than the untreated true hypertensive patients ($n = 34$). Patients with white-coat hypertension also had a moderately increased left atrial

dimension in association with a predilection for disturbed diastolic function. Systolic function was similar among all three groups. These findings suggest that white-coat hypertension in older individuals may not be innocent.

Not all studies have been concordant with the previously described findings. In one study, there was no difference in left ventricular index comparing 22 older white-coat hypertensives with 20 age-matched normotensives *(50)*. Left ventricular voltage scores for hypertrophy were similar among nine sustained and nine white-coat hypertensives *(51)*. There was no difference in left ventricular mass index among 28 definite hypertensives and 9 white-coat normotensives *(52)*. A case–control study of 33 normotensives, 29 white-coat hypertensives, and 87 hypertensives reported no difference in fraction shortening among all three groups *(53)*. The other echocardiographic parameters were similar when comparing normotensives and white-coat hypertensives. However, greater left atrial and left ventricular dimensions, interventricular and posterior wall thicknesses, and left ventricular mass index were greater in sustained hypertensives than normotensives or white-coat hypertensives.

White-coat normotension or reverse white-coat hypertension is defined as a normal clinic blood pressure and elevated daytime ambulatory blood pressure. The Second Australian National Blood Pressure Study performed ambulatory blood pressure as a substudy in 713 patients aged 65–83 yr *(54)*. Daytime ambulatory blood pressure was greater than clinic blood pressure for systolic blood pressure in 21% of patients and for diastolic blood pressure in 45% of patients. Although it was not reported in this study, another study reported that this phenomenon was associated with a similar left ventricular mass and carotid wall thickness as sustained hypertensives *(55)*.

Postprandial Hypotension

Postprandial hypotension is a well-recognized phenomenon that occurs with increasing age *(56)*. It is associated with increased blood pressure variability *(57)*. The morning surge in blood pressure is related to postprandial hypotension after breakfast. The cause is controversial, but has been attributed to (1) increased splanchnic blood flow causing a decrease in venous return to the heart, (2) increased vasoactive gastrointestinal peptides, and (3) insulin-related vasodilatation. In the presence of blunted receptor baroreceptor sensitivity, postprandial hypotension occurs.

A cohort of 53 healthy elderly men and women without hypertension or hypotension underwent ambulatory blood pressure monitoring with an Accutracker II twice 1 wk apart *(58)*. The evening meal was used for the primary analysis. Blood pressure was examined for 90 min before the meal and 120 min after the meal. The greatest decline in blood pressure of 7/8 mmHg was between 61 and 120 min after eating. Heart rate increased maximally by 4 beats/min between 31 and 90 min. Furthermore, when other meals were studied, there was no difference in the degree of postprandial blood pressure decline with breakfast and lunch compared to supper.

In a substudy of the Syst-Eur Trial, ambulatory blood pressure monitoring was used to evaluate postprandial hypotension in 530 patients between the ages of 60 and 100 yr *(24)*. Postprandial change was determined by subtracting the average blood pressure 2 h after the main meal from the 2 h before the main meal. A decrease in systolic or diastolic blood pressure was observed in 67.6 or 71.3% of patients, respectively. The average decline in blood pressure was 6.6/5.4 mmHg without any change in heart rate. A postprandial decrease of 16 mmHg in systolic blood pressure was observed in 24.1% of the cohort, whereas a decrease of 12 mmHg in diastolic blood pressure was seen in 24.5%. A subgroup of 147 patients underwent repeat testing, and individual reproducibility was poor. The median difference in postprandial change was 9.3/7.2 mmHg.

A study of 120 elderly patients (45 with falls without syncope and 75 with syncope) and 36 controls were studied with a SpaceLabs 90207 monitor in short-stay geriatric medicine ward in which meals were at scheduled times *(35)*. The goal was to examine postprandial hypotension. The patients' mean age was 80 yr. Postprandial blood pressure change was the difference between average systolic blood pressure 2 h before and 2 h after the meal. For the entire group, the average change was 5.3, 3.4, and 2.6 mmHg for breakfast, lunch, and supper (not significantly different), respectively. Compared with controls (1.8 mmHg), the group with syncope (4.5 mmHg) and falls (3.8 mmHg) experienced a significantly greater drop in blood pressure ($p = 0.015$). When examining the groups for the meal with the greatest postprandial drop in systolic blood pressure, the average maximal change was 13.4, 12.4, and 8.9 mmHg for the syncope, fall, and control groups ($p < 0.05$). Postprandial hypotension was defined as a change in systolic blood pressure 20 mmHg or greater, which was greater in the syncope (27%) and fall (18%) groups compared to the control group (8.5%, $p < 0.05$).

Postprandial hypotension was most likely to occur with breakfast, which correlated positively with the preprandial systolic blood pressure.

Nonpharmacological Interventions

There are limited data on nonpharmacological trials in the elderly *(59)*. In aggregate, data document that nonpharmacological therapy can decrease the need for drug therapy. Many of the trials are not blinded, well controlled, or adequately powered. However, national guidelines and one large trial report a benefit for elderly patients *(3,60,61)*.

Exercise

Using ambulatory blood pressure monitoring, sedentary elderly male patients were compared with elderly endurance runners *(62)*. Supporting enhanced parasympathetic tone, 24-h ambulatory blood pressure, heart rate, and blood pressure variability were lower among the athletic patients. Among 24 elderly hypertensives undergoing 45 min of low-intensity exercise, blood pressure decreased and persisted 22 h postexercise as assessed by ambulatory blood pressure monitoring *(63)*.

To assess the effect of endurance exercise training on 24-h ambulatory blood pressure (SpaceLabs 90207), 21 elderly men and women (61–77 yr) were randomly assigned to a control or an exercise group *(64)*. Exercise was performed on a treadmill and stair-climbers three times per week for 25 min initially and then progressed to 45 min to achieve 85% of their maximum heart rate. Maximal oxygen uptake increased by 14% in the training group. Weight decreased 2.2 kg in the exercise group and increased 0.7 kg in the control group. The weight change from baseline was not significant for each intervention or from each other. From baseline, 24-h blood pressure significantly decreased 7.9/3.6 mmHg in the exercise group and increased 0.8/3.3 mmHg in the control group.

Sodium

A double-blind, randomized, placebo-controlled, crossover trial was conducted in 17 white older hypertensive subjects who discontinued antihypertensive medications for 4 wk *(65)*. Dietitians advised patients on a daily sodium intake of 80–100 mmol over the 14 wk of investigation. After a 4-wk placebo run-in period, subjects received 80 mmol sodium chloride or placebo for 5 wk and subsequently were crossed over to the alternative strategy. Twenty-four-hour ambulatory blood pressure was performed after each of the treatment periods. Supine clinic systolic blood pressure was 8 mmHg higher in the high-sodium

group ($p < 0.05$). However, there was no difference in the mean 24-h ambulatory systolic or diastolic blood pressure for low- vs high-sodium treatment groups despite increased urinary sodium excretion and lower peripheral renin activity and plasma aldosterone in the high-sodium group.

Potassium

In a double-blind, randomized, placebo-controlled, crossover trial, 18 hypertensive elderly patients stopped all medication during a 4-wk placebo run-in period *(66)*. Flavored potassium chloride (20 mmol three times daily) or flavored placebo for 4 wk was given and then subjects were crossed over to the alternative treatment. At the end of each treatment period, ambulatory blood pressure was performed. Compared to the placebo period, the clinic blood pressure during potassium supplementation was significantly decreased (–10/–6 mmHg). However, only systolic blood pressure was significantly decreased by 24-h ambulatory blood pressure during potassium treatment (–6/–2 mmHg). Urinary potassium but not urinary sodium excretion increased.

Twenty nursing home patients with hypertension had ambulatory blood pressure performed before and after the introduction of low-sodium, high-potassium salt, consisting of 57% NaCl, 28% KCl, 12% $MgSO_4$, and 2% L-lysine HCl *(67)*. This special mineral salt was substituted for table and cooking salt for 6 mo. Forty-five percent of the subjects had a reduction in their daytime and nighttime blood pressure.

Calcium

Nine hospitalized elderly patients were given a diet for 4 wk, which included 500 mg calcium, 2 g sodium, and 3 g potassium *(68)*. In a crossover design, subjects were treated with 1 g elemental calcium in the form of oyster shell electrolyte for 8 wk with a washout period of 4 wk. Twenty-four hour ambulatory blood pressure was performed every 4 wk. The mean change in blood pressure was –13.6/–5 mmHg in the calcium treatment period and –1.5/+1.0 mmHg in the control period ($p < 0.005$ for systolic and $p < 0.05$ for diastolic blood pressure). Ionized calcium increased and parathyroid hormone levels declined. Both urinary sodium and calcium excretion increased.

Ascorbate (Vitamin C)

A double-blind, crossover study examined the effect of vitamin C 250 mg twice daily or placebo *(69)*. Each treatment phase lasted 3 mo. Clinic and 24-h ambulatory blood pressure was measured at baseline

and at the end of each treatment period. Plasma ascorbate levels increased from 49 to 85 μmol/L, but clinic blood pressure did not decrease. However, daytime ambulatory systolic blood pressure was lowered by –3.7 mmHg among the 17 hypertensive subjects, but not among the 23 normotensive subjects. There was no decline in diastolic blood pressure.

Coffee

To assess the effect of caffeine on blood pressure, 22 normotensive and 26 hypertensive subjects were randomized to a caffeine-free diet or 300 mg per day of caffeine for 2 wk after a 2-wk caffeine-free diet *(70)*. The mean age of the study population was 72 yr (range 54 to 89 yr), and all were nonsmokers. Twenty-four-hour ambulatory blood pressure was performed at the end of each 2-wk period. Blood pressure was increased significantly in the hypertensive subjects receiving caffeine (+4.8/+3.0 mmHg), but not in the normotensive group.

Pharmacological Treatment

There are many examples of studies in the elderly that have attempted to examine various pharmaceutical interventions with ambulatory blood pressure monitoring *(71–79)*. These studies in aggregate show the advantages of ambulatory blood pressure monitoring to define the duration of action and the effectiveness of drugs.

Target Organ Involvement

Heart

Left ventricular hypertrophy, whether diagnosed by electrocardiographically or echocardiographically, is the most potent cardiovascular risk factor *(80)*. Left ventricular mass increases with aging.

In the Syst-Eur Trial, 311 men and 497 women were studied to assess the relationship of ambulatory blood pressure and electrocardiographic left ventricular hypertrophy as measured by a Sokolow-Lyon voltage index score 35 mm or greater *(81)*. Clinic, 24-h, daytime, and nighttime systolic blood pressure correlated with the index better than diastolic blood pressure. Twenty-four-hour ambulatory pulse pressure enhanced the diagnostic precision compared to conventional measurements.

Ambulatory blood pressure and echocardiography were performed in 490 ambulatory Finnish subjects aged over 64 yr, of which 42% were normotensive *(82)*. The prevalence of echocardiographic left ventricular hypertrophy was 22%. Ambulatory systolic (but not diastolic) blood

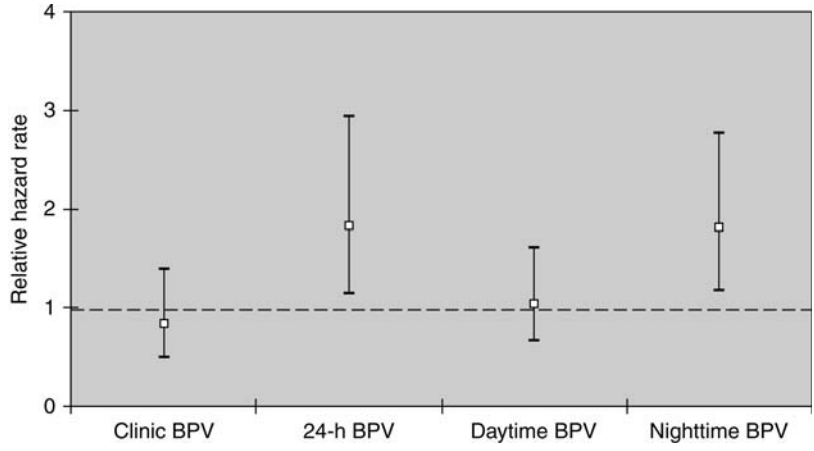

Fig. 5. Relative hazard rates of fatal and nonfatal sroke with 5 mmHg increase in systolic blood pressure variability among placebo-treated hypertensives. Twenty-four-hour and nighttime blood pressure variability was predictive of fatal and nonfatal stroke. BPV = blood pressure variability. (Adapted from ref. *21*.)

pressure, gender, body mass index, and age were significantly and independently associated with left ventricular mass. Daytime, but not nighttime, systolic blood pressure was a predictor of left ventricular mass.

Multiple other investigators have reported a relationship between ambulatory blood pressure and cardiac target organ damage *(83,84)*.

Brain

The Syst-Eur Trial examined whether systolic blood pressure variability was a risk factor for stroke using baseline clinic and 24-h ambulatory blood pressure *(21)*. Blood pressure variability was calculated as the within-subject standard deviation of systolic blood pressure among 744 study participants. Ambulatory blood pressure variability was correlated with age and the level of systolic blood pressure. There was greater daytime and nighttime variability among women. Treatment did not affect blood pressure variability after adjustment for the level of systolic blood pressure. In the placebo group, 24-h and nighttime systolic blood pressure variability increased the risk of fatal and nonfatal stroke ($p < 0.01$), but not cardiovascular mortality or cardiac events (Fig. 5). The stroke risk increased by 80% for each 5-mmHg increase in nighttime systolic blood pressure variability.

Lacunae are small (<1 cm), deep infarcts owing to occlusion of small penetrating arteries. Lacunae do not necessarily result in a clinical stroke. Periventricular white matter lesions on magnetic resonance

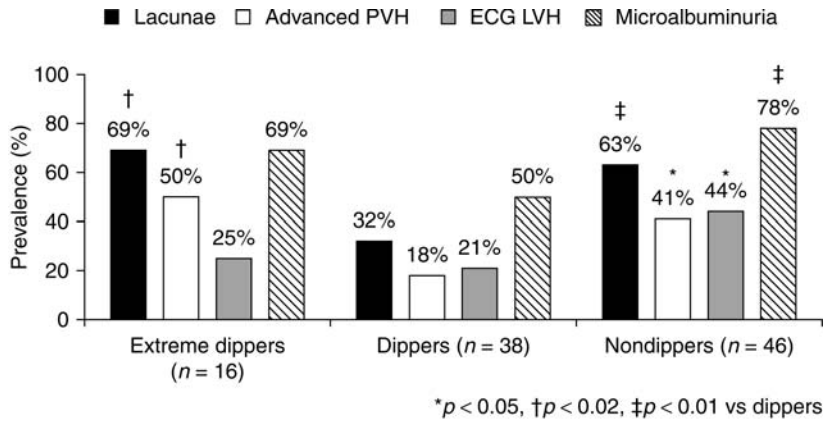

Fig. 6. Silent target organ damage of elderly patients with sustained hypertension. The nocturnal fall in systolic blood pressure (SBP) was calculated as (awake SBP – asleep SBP)/awake SBP. Extreme dippers were defined as ≥20% reduction in nocturnal SBP and nondippers as <10% reduction in SBP. Advanced PVH = Grades III and IV periventricular hyperintensity; ECG LVH = electrocardiographic left ventricular hypertrophy. (Adapted from ref. *86*.)

imaging or diffuse subcortical hypodensity (leukoariosis) on computed tomographic brain scans is seen in the elderly and may also be the result of small vessel disease. Healthy elderly subjects (n = 73) without neurological, cardiovascular (except untreated hypertension), respiratory, or endocrine disease underwent ambulatory blood pressure monitoring (ABPM-630) and magnetic resonance imaging *(85)*. Lacunae were present in 34 subjects (47%). The number of lacunae weakly correlated with age and the severity of periventricular hyperintensity. Twenty-four-hour, awake, and sleep blood pressure strongly correlated with the lacunes, whereas 24-h and sleep blood pressure correlated with the severity of periventricular hyperintensity. The correlation of sleep blood pressure with magnetic resonance imaging abnormalities was slightly higher than 24-h or awake blood pressure.

In a follow-up study, 100 healthy elderly hypertensive patients were studied using magnetic resonance imaging, ambulatory blood pressure (ABPM-630), urine albumin excretion rate, and electrocardiography *(86)*. Extreme dippers were just as likely as nondippers to have lacunae and advanced periventricular hyperintensity as nondippers (Fig. 6). However, cardiac and renal target organ damage occurred most commonly among nondippers.

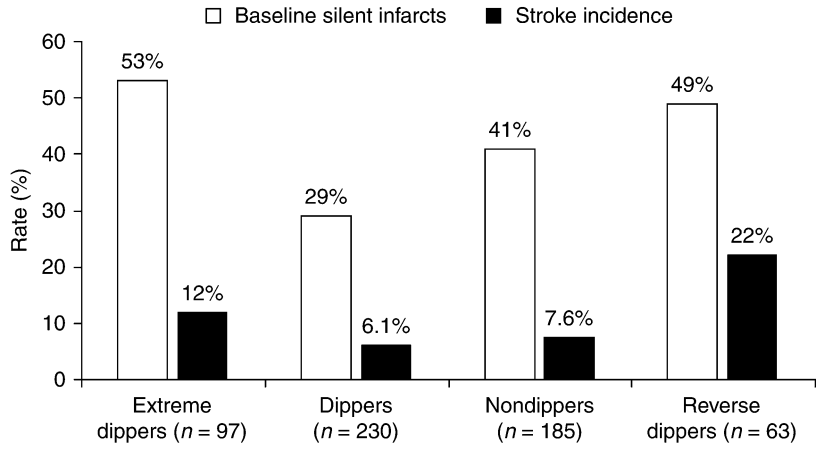

Fig. 7. Prevalence of silent cerebral infarctions and stroke incidence according to dipping pattern. Fatal and nonfatal stroke incidence was highest among reverse dippers (22%, $p = 0.0001$ vs dippers) and extreme dippers (12%, $p = 0.055$ vs dippers). (Adapted from ref. *87*.)

The same investigators studied 575 older hypertensives with ambulatory blood pressure to determine whether the blood pressure dipping pattern influenced stroke prognosis *(87)*. Sustained hypertension was defined as an average clinic blood pressure 140/90 mmHg or higher and a 24-h ambulatory blood pressure 130/80 mmHg or higher. Sleep blood pressure was determined according to diary records. Average follow-up was 41 mo. Extreme dipping was present if the systolic blood pressure dropped 20% or more than awake blood pressure. Reverse dipping was defined as a drop in systolic blood pressure less than 0% and nondipping as 0% to less than 10%. The following rates of dipping patterns were observed: 11% reverse dipping (n = 63), 32% nondipping (n = 185), 40% dippers (n = 230), and 17% extreme dipping (n = 97). Among the 361 patients that underwent magnetic resonance imaging, dippers had the lowest rate (29%) of multiple silent cerebral infarcts. The prevalence for reverse dippers, nondippers, and extreme dippers was 49% ($p = 0.03$ vs dippers), 41%, and 53% ($p = 0.01$ vs dippers), respectively. Fatal and nonfatal stroke incidence (Fig. 7) was highest among reverse dippers (22%, p = 0.0001 vs dippers) and extreme dippers (12%, $p = 0.055$ vs dippers). Among the seven hemorrhagic strokes that occurred, 29% was seen in the reverse dipper group (p = 0.04). Cardiovascular mortality was highest among reverse dippers.

From the results of the previous study, it appeared that the nadir of sleep blood pressure was the key factor for the 54 strokes that occurred in the follow-up period *(87)*. However, only seven strokes happened during sleep. A subsequent analysis of 519 elderly hypertensive subjects that underwent both ambulatory blood pressure and magnetic resonance imaging examined the morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease *(88)*. Morning surge in blood pressure was defined as the difference between the average of morning systolic blood pressures within 2 h of awakening and the three lowest systolic blood pressures during sleep. Using a partition value of greater than 55 mmHg, 53 patients (10.2%) were identified with an excess morning surge of blood pressure. This group had a higher prevalence of silent cerebral infarcts (70 vs 48%, $p < 0.01$), multiple silent cerebral infarcts (57 vs 33%, $p < 0.001$), and clinical strokes (19 vs 7.3%, $p < 0.01$). Most of the strokes in this group occurred between 6 AM and noon. Their analysis suggests that the morning surge in systolic blood pressure is more important than the nadir of nocturnal blood pressure.

Smaller brain volume and greater ventricular volume characterize brain atrophy that is considered to be a part of the normal aging process. In a study of 155 normotensive, healthy subjects aged 55–80 yr, ambulatory blood pressure (Accutracker II) and magnetic resonance imaging was performed *(89)*. Older age was associated with increased ventricular volume and reduced total brain volume. Men had a larger lateral and third ventricle than women. Increased systolic blood pressure variability during sleep was associated with a smaller total brain volume, and greater systolic blood pressure variability during waking and sleep predicted increased size of third and lateral ventricle. The coupling of higher systolic blood pressure with increased systolic blood pressure variability magnified the reduction in brain volume.

Kidney

To assess the relationship of urinary albumin excretion with both clinic and ambulatory blood pressure, 64 untreated elderly hypertensives underwent clinic and 24-h ambulatory blood pressure measurements and a 24-h urine collection for measurement of the urinary albumin *(90)*. Urinary albumin excretion correlated with clinic systolic blood pressure ($r = 0.33$, $p = 0.01$) and with 24-h ambulatory systolic ($r = 0.48$, $p < 0.001$) and diastolic ($r = 0.32$, $p = 0.01$) blood pressure.

Prognosis

In a longitudinal population-based study that began in Uppsala, Sweden, in 1970, 872 men aged 70 yr underwent ambulatory blood pressure (Accutracker II) in 1991–1995 and were followed for 9.5 yr *(91)*. Although both office and 24-h systolic blood pressure were predictive of the 172 cardiovascular events, 24-h pulse pressure and daytime systolic blood pressure variability were independent predictors when adjusted for cardiovascular risk factors. Even though nighttime ambulatory blood pressure was not predictive of cardiovascular morbidity, a night:day systolic ratio greater than 0.9 was a significant predictor.

The Syst-Eur Trial examined 808 study participants 60 yr and older to compare office blood pressure and ambulatory blood pressure to determine overall prognosis *(92)*. Office measurements were 21.9/1.9 mmHg higher than daytime ambulatory measurements on entry. Median follow-up was 4.4 yr. The adjusted relative hazard rates were significant for fatal and nonfatal cardiovascular events and strokes using 24-h and daytime systolic ambulatory blood pressure. For each 10-mmHg increment in daytime blood pressure, there was a 20% increase in cardiovascular risk for the group. Nighttime blood pressure was significantly associated with total mortality, cardiovascular mortality, and fatal and nonfatal cardiovascular events. Furthermore, the 24-h systolic blood pressure and the ratio of night-to-day systolic blood pressure were independently associated with the incidence of cardiovascular events. Thus, ambulatory systolic blood pressure was superior to conventional measurements for predicting risk.

In another substudy of the Syst-Eur trial, 295 placebo-treated patients were assessed by office (six measurements) and ambulatory blood pressure at baseline and office measurements only at 6 mo *(93)*. Over this time period, there was a significant decline in office blood pressure from 173/86 to 163/85 mmHg. The relationship between baseline ambulatory blood pressure and follow-up casual blood pressure was very poor; normal ambulatory blood pressure did not predict normal 6-mo casual blood pressure. Ambulatory systolic blood pressure, however, did predict cardiovascular events after a median follow-up period of 7.5 yr.

CONCLUSIONS

Ambulatory blood pressure has provided insight into the relationship between blood pressure and hypertension-related vascular disease and target organ damage in older patients. Prognosis has been refined. Our understanding of orthostatic hypotension and white-coat hypertension

expanded. Efficacy of nonpharmacological therapy and pharmacological therapy has been confirmed with ambulatory blood pressure.

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14 Ambulatory Blood Pressure in Children and Adolescents

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CONTENTS

INTRODUCTION

The prevalence of hypertension in children is increasing, possibly because of the increasing epidemic of obesity, poor dietary habits, and sedentary lifestyles in childhood. In fact, of all chronic diseases in childhood, only obesity (28%), asthma (7%), and attention deficit disorder

From: *Clinical Hypertension and Vascular Disease: Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics*
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(Year)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90

Fig. 1. Blood pressure levels for boys by age and height percentile.

(5%) have a higher prevalence than hypertension (3–5%). Hypertension in childhood is a precursor for the development of hypertension in early adulthood *(1)*. Although the etiology of hypertension in early childhood is more commonly secondary than in adult patients, in most cases of hypertension, particularly in later childhood and adolescence, the etiology is primary or essential hypertension *(2)*. The hypertension manifest in childhood may not be benign, as previously thought, as end-organ damage is now frequently detected in hypertensive children *(3–5)*.

Blood pressure (BP) measurement in children should now be a routine practice after the recent recommendations from the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents that encourages evaluation of BP in all children starting at 3 yr of age *(1)* and even before age 3 yr in patients with other chronic medical conditions such as a history of prematurity or renal or cardiac disease. The Working Group has also published revised normative BP data in children and adolescents *(1)*. In this fourth iteration of the guidelines, some new data and recommendations are available. The new tables (*see* Fig. 1) present for the first time the 50th percentile for age, gender, and height so that the clinician can understand what truly normal BP in children should be. The 99th percentile is also provided for assessment of more severe hypertension. The report also documents for the first time the presence of hypertensive end-organ damage in children particularly manifested primarily by changes in left ventricular mass. The guidelines also stage hypertension for the first time using stages similar to those published in the Seventh Joint National Committee Report (Fig. 2). Prehypertension is defined as age, gender, and height specific 90th percentile to the 95th percentile. Because in adolescence the 90th percentile is greater than 120/80 mmHg, the lower boundary for prehypertension in the adult, 120/80 mmHg become the lower limit in adolescents as well. Stage 1 is from the 95th percentile to the 99th plus 5 mmHg. The 5 mmHg were added to the 99th percentile because of the large variability of BP and to provide a broader stage of approx 12 mmHg as opposed to 20 mmHg in adults. The report further provides the

	SBP or DBP Percentile
Normal	<90th
Prehypertension	90th to <95th or if BP exceeds 120/80 even if below 90th percentile up to <95th percentile
Stage 1 hypertension	95th percentile to the 99th percentile plus 5 mmHg
Stage 2 hypertension	>99th percentile plus 5 mmHg

Fig. 2. Classification of hypertension in children and adolescents with measurement frequency and therapy recommendations.

Table 1
Indications for Antihypertensive Drug Therapy

Stage 1 hypertension
Symptomatic hypertension
Secondary hypertension
Hypertensive target-organ damate
Diabetes (types 1 and 2)
Persistent hypertension despite nonpharmacologic measures (therapeutic lifestyles changes [TLC])
Stage 2 hyptertension

most comprehensive guidelines to date for the evaluation of the hypertensive child and recommendations for which children require antihypertensive therapy (Table 1). The evaluation includes not only the diagnosis of hypertension, but the evaluation of the etiology of hypertension, comorbidities such as insulin resistance, obesity, and hyperlipidemia; and the presence of end-organ damage. Because cardiovascular mortal and morbid events are rare in the pediatric age group, this determination is done through more subclinical assessment such as echocardiographic evidence of cardiac hypertrophy or dysfunction, microalbuminuria (MA), and vascular changes such as a thickened carotid intimal-medial thickness or abnormalities in vascular compliance.

Thus, with increasing prevalence and vigilance for BP elevation in children, the management of hypertension in this population gains importance. Most pediatricians feel a degree of reluctance in starting lifelong therapy with a "blood pressure pill" in the young ones, particularly with lack of data on long-term effects of such medications. This reluctance combined with difficulty in obtaining accurate BPs in

children and the complex set of normative values previously noted makes management of hypertension in children a daunting task, even more so than in adults. Therefore, one wants to have as much confidence as possible in the proper diagnosis of hypertension. Thus, ambulatory blood pressure monitor (ABPM) use in children has found import. This includes not only the issue of white-coat hypertension (WCH), which has a prevalence in children similar to that seen in adults, but also determining the circadian pattern of BP elevation *(6)*.

CASUAL BLOOD PRESSURE MEASUREMENT

The standard method of BP measurement by auscultatory sphygmomanometer or by automated oscillometric arm-cuff devices can be used for casual BP (CBP) measurement (CBPM). One must remember that oscillometric monitors measure the mean arterial pressure by the point of maximum oscillations in the vessel and calculate by proprietary formulas systolic blood pressure (SBP) and diastolic blood pressure (DBP). There are many differences in the values obtained by the two techniques. In fact, the Working Group, recognizing that oscillometric monitoring is the most prevalent form of BP measurement in children because of its ease of use and excellent interobserver variability, have stated that any child with a BP greater than the 90th percentile should have the BP level confirmed by auscultatory measurement. Recent studies suggest that CBP by oscillometric monitor should be measured four times at each BP measurement session with an average of the last three measurements closer in value to auscultatory measurements, the standard used in the Working Group normative data. The first value is often quite higher because of the technical accommodation effect *(7)*. Factors that improve the accuracy of CBPM include frequent calibration of the instruments, several BP measurements on a single clinic visit with repeat measurements over several weeks in the clinic, and use of the correct cuff size according to the arm circumference and measurement of the BP by trained personnel. In the future, automated auscultatory devices may combine the ease and convenience of oscillometric devices, with a result that would be comparable to the technique used to develop the normative data.

However, BP is not constant and is a continuous physiological measurement that varies considerably with circadian rhythm and environmental factors. CBPM has been found often to be unreliable for assessment of hypertension in children, and the reliability may not be improved by multiple BP readings on a single occasion. Adding evaluation by ABPM

can give multiple measurements under various physiological states and provide a temporal pattern of BP for the individual patient over 24 h or longer (*see* Fig. 3A). The use of ABPM in a child helps to address the duration and timing of the hypertension and its relation to activities, stressors, or medications. Various patterns of BP in children can be identified by ABPM (Fig. 3), e.g., the early morning surge in BP, masked hypertension, WCH, dipping and nondipping patterns, and nocturnal hypertension. These patterns, to be discussed in detail later, are not possible with CBPM. BPs can also be measured at home by the parents using automated devices with correct cuff sizes but are not as accurate as ABPM *(8)*. Frequent monitoring at home may also be useful in evaluation of WCH, but may not an ideal method to detect nocturnal hypertension. Further, reliability of reporting of home BP has been a valid concern, but technological advances now affordably allow the use of monitors that objectively download the data and can transmit them to the physician. This advancement may make home BP monitoring a staple of our BP monitoring program.

AMBULATORY BLOOD PRESSURE MONITORING IN CHILDREN

An ever-increasing number of academic centers who care for children with hypertension in the United States, Europe, and around the world offer ABPM. There are several advantages and disadvantages to ABPM in children (Table 2). This chapter is focused on the indications and techniques of ABPM in children *(9–13)*.

METHODOLOGY OF AMBULATORY BLOOD PRESSURE MONITORING IN CHILDREN

Types of Monitors

Most popular monitors for use in children are fully automated, oscillometric arm-cuff devices. The auscultatory monitors are less popular in the pediatric age group because of higher rates of noise interference. The oscillometric monitors calculate the SBPs and DBPs after measuring the mean BP based on an algorithm. The monitors are lightweight, reasonably small, and can be worn without significant inconvenience even by children as young as 2 yr of age. In children, initial inflation to 160–180 mmHg is not well tolerated, and hence the subsequent inflations are programmed to be 20 mmHg higher than the previously measured SBP, thereby decreasing the discomfort. The monitors can be programmed to

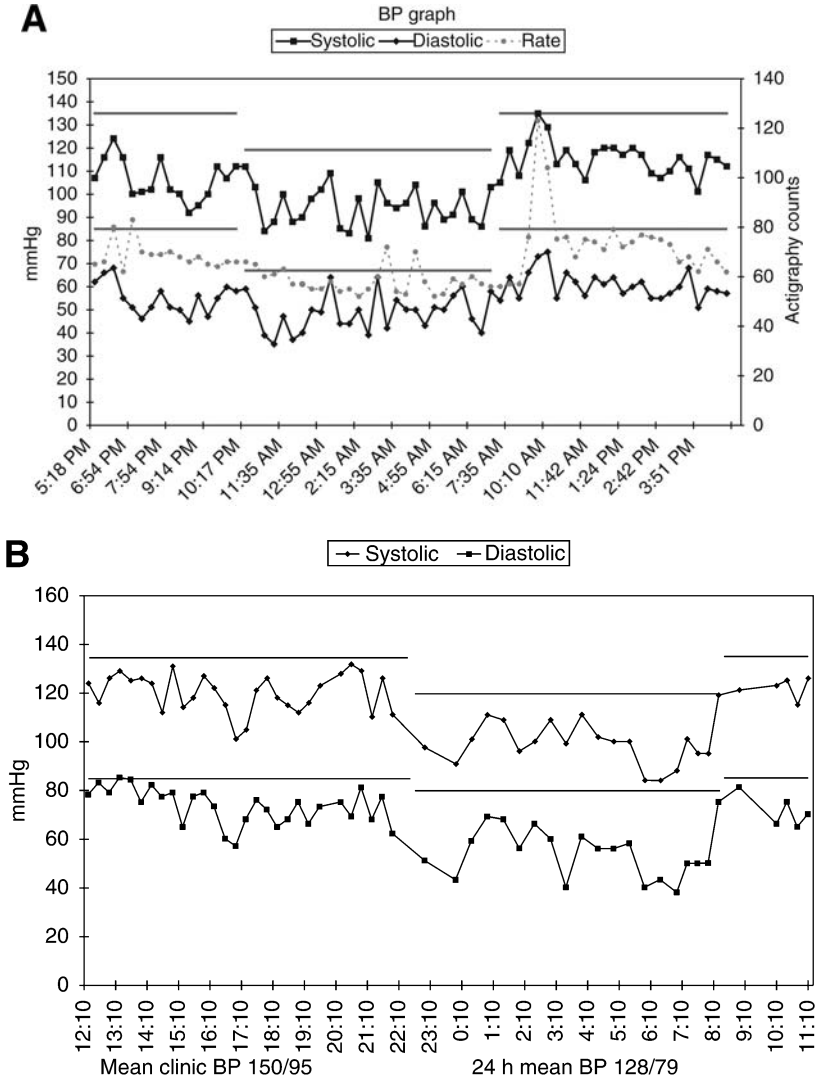

Fig. 3. *(Continued)*

measure BP at set intervals and to deflate in increments of 4, 6, or 8 mmHg (the "bleed step"). A bleed step less than 8 mmHg is not well tolerated in children. The accuracy of ABPM is increased with a position sensor or an actigraph, which is a device worn on the wrist that measures motion in three planes *(14,15)*. It allows for accurate interpretation of data by objectively determining the actual sleep week periods as well

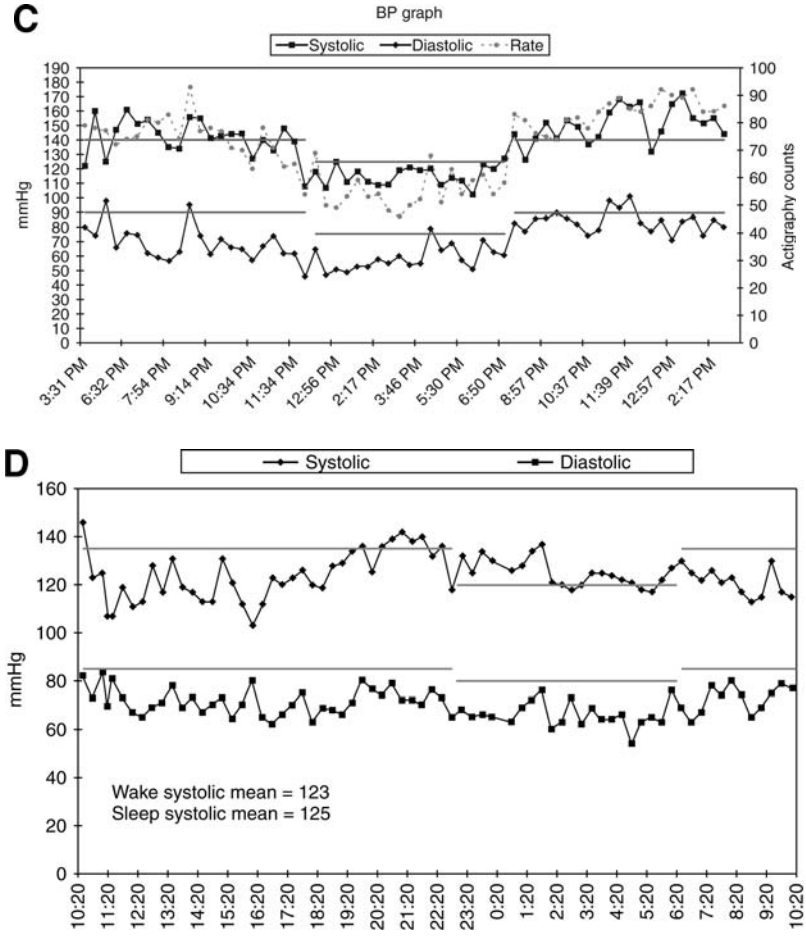

Fig. 3. *(Continued)*

as the periods of physical activity, as children can have marked variability in their activity pattern in comparison to the adults. The monitors are remarkably well tolerated in children and have been used on an ambulatory basis in children as young as 2 yr.

Training Requirements

A health care professional who is well versed in the techniques of BP monitoring in children can be further trained in the technique of ABPM placement and care of the device. However, the analysis and interpretation of the data obtained from ABPM requires a complete

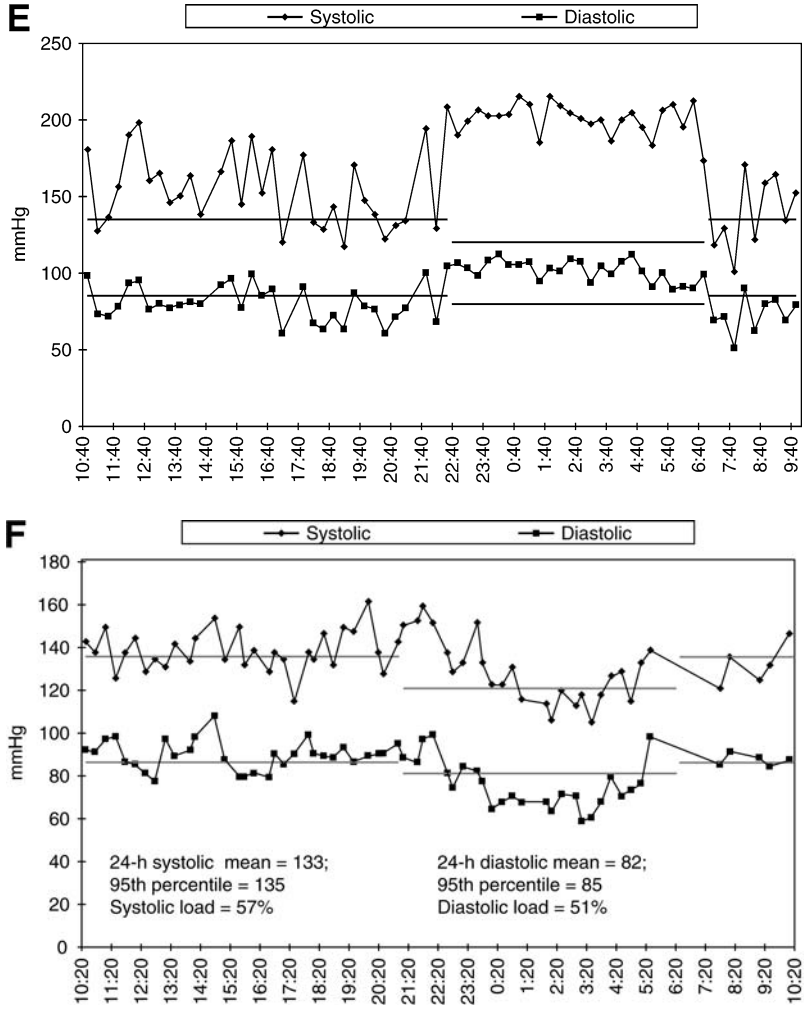

Fig. 3. (A) Chronograph of the ambulatory blood pressure monitoring in a normotensive child. Note the simultaneous actigraphy recording of the heart rate. **(B)** Chronograph of ambulatory blood pressure recordings in a hypertensive child with white-coat hypertension. **(C)** Chronograph of ambulatory blood pressure recordings in a hypertensive child with a dipping pattern. **(D)** Chronograph of ambulatory blood pressure recordings in a hypertensive child with a nondipping pattern. **(E)** Chronograph of ambulatory blood pressure recordings in a hypertensive child with nocturnal (sleep) hypertension. **(F)** Chronograph of ambulatory blood pressure recordings in a hypertensive child with a high-amplitude pattern.

Table 2
ABPM Advantages and Disadvantages in Children

Advantages
Large numbers of BP readings obtained over 24 h
Measurement of BP without influence of heath care setting
Measurement of nocturnal (sleep) BP values
Aid in decision making in presence of borderline or episodic hypertension
Determine risk for end organ damage
Detect efficacy or side effects of antihypertensive medications
High reproducibility with reliable measurements without observer bias
Disadvantages
Child has to be cooperative; therefore limited use in developmentally delayed
Expensive equipment
Time consuming
Detailed instructions to family and patients required
Requires staff training
Requires equipment calibrations and maintenance
Less reliable in presence of arrhythmias
Errors can occur with vigorous activity or exercise
Reimbursement does not cover expense of procedure
No specific pediatric indications for ABPM

understanding of BP patterns. The physician needs to be trained in the technique of ABPM and the computerized analysis of the ABPM data.

Placing the Monitor

Appropriate cuff size is determined and the monitor is standardized against a mercury sphygmomanometer using a Y-piece connector before each monitoring period to ensure the monitor is working properly. A child's activity can be a stress for the monitor itself, and this step, while cumbersome, prevents a child from experiencing a full monitoring period only to have no or inaccurate data recorded.

The cuff is placed on the nondominant arm to minimize interference in measurement because of movement and not to inhibit the child's activity. During the day, the monitor is placed in a pouch and placed on a shoulder strap or a waist belt. During the night the pouch is placed under a pillow. Removal of the device is discouraged except for a quick shower in between reads. The patient and family both need to be trained on the aim and use of the monitor and how to turn the monitor on and off.

Written instructions along with a diary card are given to the family. The child is asked to continue normal activities during the day and to keep the diary. The child is advised against intense exercise such as football and asked to remove the monitor during that activity if it must be done. The child and family are given a contact person for any problems related to the monitoring. They are also advised to call if the child develops pain or discoloration of the skin distal to the cuff. The parent and the patient are encouraged to check the diary or for a young child to fill out the diary of events during the monitoring, but the provided data may not be reliable and hence an actigraph may be of benefit. The family is instructed to maintain a diary regarding the child's physical activity, emotional states, symptoms and medication, meals, sleep (including naps), and wake times. It is interesting that school lunch periods are often associated with some of the highest readings of the day and nap time with BP values similar to nighttime sleep.

Potential Problems With Monitoring

The ABPM is recommended to be worn on a normal weekday rather than over a weekend because the school- or work-related BP recordings can be higher than home BPs *(16)*. However, there are special considerations. If one is trying to assess masked or stress-related hypertension, wearing the monitor for 48 h with 1 d of monitoring in school and the other on a weekend is a very helpful strategy. If one is assessing the effect of an intervention by serial monitorings, it is important to ensure that the monitoring is done on days with similar activities, e.g., both school or both weekend days. The monitor periodically sounds an alarm during the day while the child is at school, and the child needs to be warned about it. Thus, wearing a monitor at school can be embarrassing to a child. In addition, a letter informing the school nurse or teachers of the monitoring is usually required. The monitors can disturb sleep (<25% of patients) but is usually well tolerated by the children *(17)*. Very rarely, contact dermatitis and mechanical trauma with petechiae, edema, ecchymoses, phlebitis, abrasions, and acute neuralgia have been reported with monitors. Measurement errors can occur with ABPM because of excessive movement by the child, slippage of the cuff from the upper arm, and any other occurrences that preclude BP measurement. In very young children, the measurement errors can be higher compared to the those in older children because of the inability of a young child to hold his or her arm still during inflation and deflation of the BP cuff. Similar problems may occur in a developmentally

delayed child who may either refuse to wear or remove the monitor. Monitors should not be placed on children with bleeding disorders or those with arrhythmias.

Validation of Monitors

It is imperative that the monitors selected are validated according to international protocols such as those set by the Advancement of Medical Instrumentation (AamI) or by the British Hypertension Society (BHS) *(18,19)*. These validation protocols, however, have not required inclusion of children. Further, frequent calibration of the devices is required. The monitors are further standardized against a mercury manometer prior to placement on subject and at the end of the monitoring. This validation protocol can be set to acquire three sets of measurements and calculate the mean DBP and SBP and compare it to the mercury manometer. There should be a difference of no more than ±5 mmHg in the systolic and diastolic BPs between the two devices. Available monitors for use in children have an average validation score.

RELIABILITY OF AMBULATORY BLOOD PRESSURE MONITORING

Compared to the mercury sphygmomanometers, the oscillometric ABPM devices have been found to be accurate in recording data in children *(20)*. The systolic measurements by ABPM were 4 mmHg higher and diastolic measurements were virtually identical to the measurements obtained by mercury sphygmomanometers. This difference in systolic BP measurement was thought to be related to the bleed step of 8 mmHg used during ABPM. The higher SBP and sometimes DBP measurements on ABPM compared to the CBPM measurements in children may also be related to a higher physical activity levels seen in children.

There continues to be a lack of standardization for ABPM methodology and the BP thresholds used for children for ABPM. Although the definition of normal and hypertensive ABPM measurements in children have not been established for different pediatric patient populations in the United States, end-organ damage in the form of left ventricular hypertrophy has been correlated to elevated BP on the ABPM in children where it did not correlate well to CBP *(21)*. Treatment-induced decrease in BP as measured by ABPM has been found to correlated better with a decrease in left ventricular hypertrophy than as measured by CBPM. In the adult population, the ABPM has been found to have superior ability to predict hypertension-related complications than the CBPM *(22)*.

Acquiring the Data

The monitoring is usually done over a 24-h period. In certain patient populations such as those with kidney disease, a longer monitoring over 48 h may be more appropriate. The monitor is cycled to measure BP every 20 min around the clock. The bleed step on the monitors should be set at 8 mmHg. When the cuff starts to inflate, an acoustic signal is set off and the child is instructed to stop walking and relax his or her arm until the recording is complete. This acoustic signal can be turned off during the night when the child is asleep. When an error occurs during measurement, a different acoustic tone is set off that prompts the patient to check and adjust the equipment. The monitor repeats a measurement in 3 min. The BP measurement is not displayed so that the child does not know the value, thus avoiding subject biofeedback. Many monitors have an event button that can allow patients to start a measurement recording if they are experiencing symptoms.

NORMATIVE DATA

There are few data available for normal ambulatory BP values in children. The best data come from central Europe *(23)* from a little over 1000 children. When the distribution was found to be skewed, the data were reanalyzed by the skewness (L), median (M), the coefficient of variation (S) (LMS) method to be able to calculate standard deviation scores (*see* Figs. 4–6). As sophisticated as these data are, they are derived from a relatively small population of German patients. Thus, new efforts to generate more normal data are in progress by the International Pediatric Hypertension Association (IPHA) with more than 5000 patients from countries including Germany, Spain, United States, and England. Virtually all of the normative data have been generated with the Space Labs monitors. Further, the German technique eliminates 25% of the data by presuming day to be from 8 AM to 8 PM and night from 12 to 6 AM. This method provides some certainty for the separation of these time periods, but a better set of norms based on actual sleep and wake times including all data would be desirable. A study of younger children is also available with ABPM measurements based on gender, height, and age *(25)*.

Interpretation and Reporting of Data

Once the monitor is returned by the parents of the child, the data from the monitor are downloaded into a computer for analysis. The ABPM

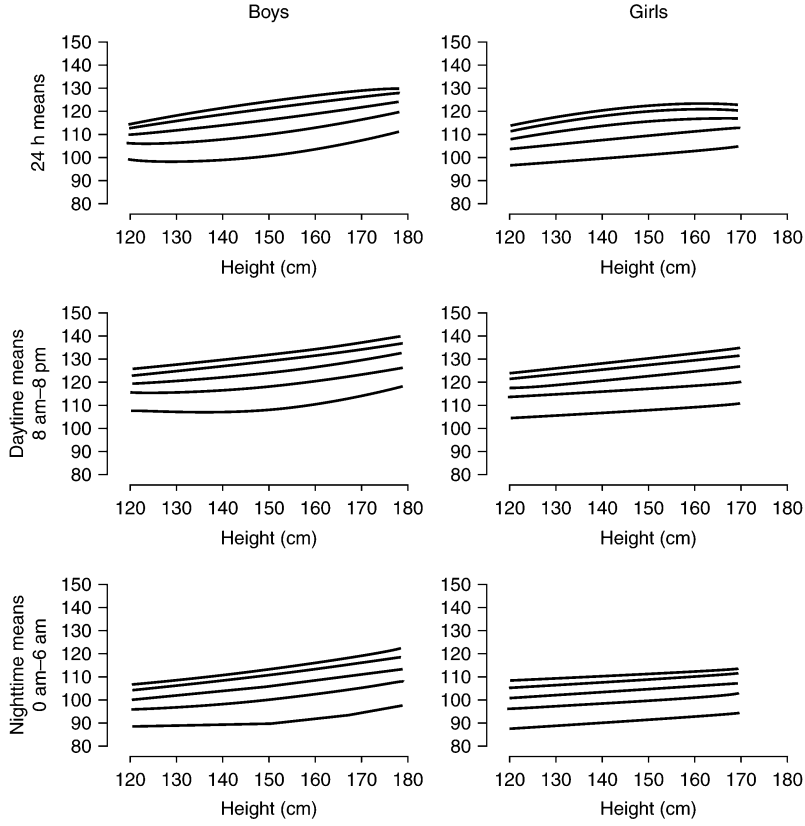

Fig. 4. Normative ambulatory blood pressure values in children. (From ref. *24*.)

has customized software for downloading, analyzing, and reporting the data. The physician evaluates the measurements obtained, edits the data, and generates the report. The individual BP measurements are synchronized according to the rest–activity cycle of the child. The values from first 2 h of monitoring are frequently discarded because there appears to be a period of adjustment in the first 2 h of monitoring when the BPs are higher. Measurement errors during monitoring are automatically edited by the device but stored in the memory. The BP measurements are further edited according to set criteria for removal of the outliers such as physiologically impossible BP values. The mean values for 24-h, daytime, and nocturnal (sleep) SBP, DBP, mean arterial pressure (MAP), and heart rate are computed. These data can also be analyzed by cosinor or Fourier analyses, but these techniques are rarely of value on a clinical basis.

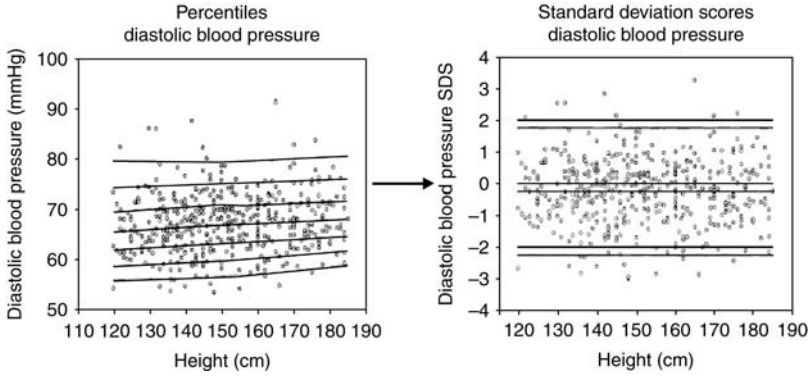

Fig. 5. Transformation for raw blood pressure data to standard deviation scores by use of the LMS method of Green and Cole *(25)*.

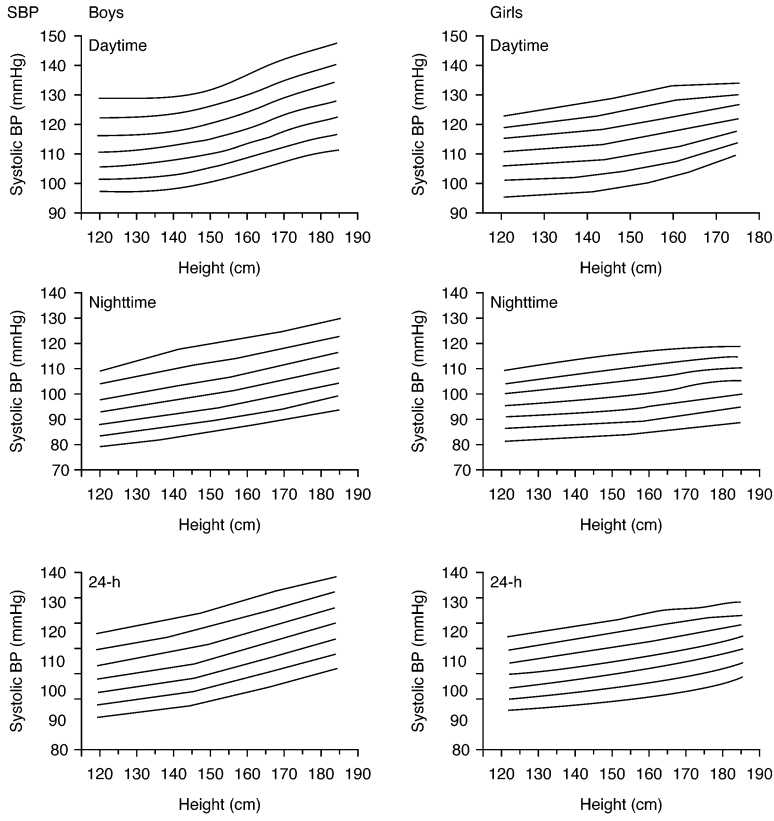

Fig. 6. *(Continued)*

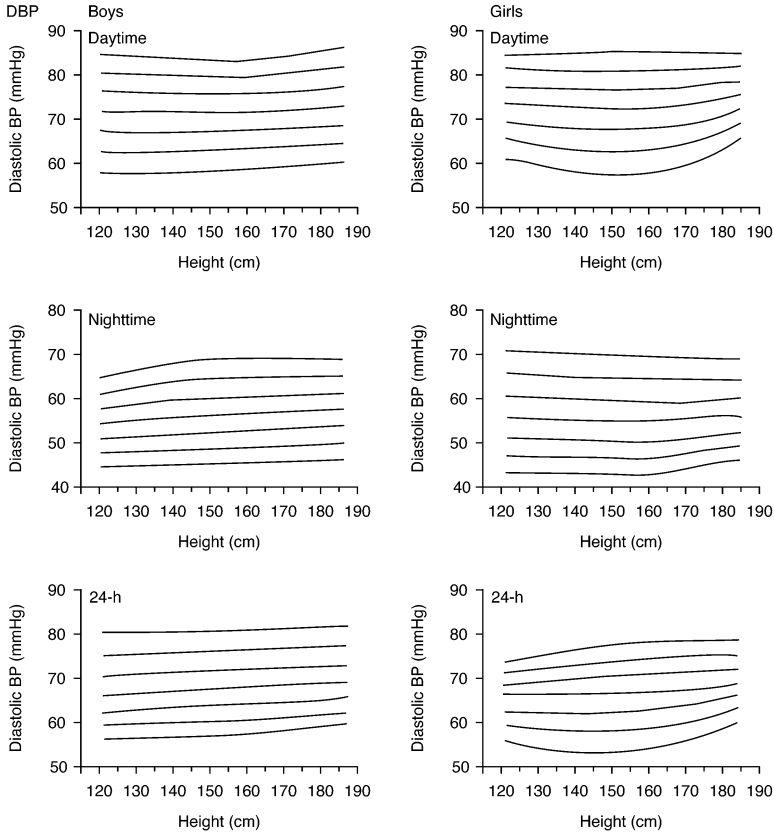

Fig. 6. LMS transformed normative ambulatory blood pressure data in children.

Mean SBP normally falls by 10% between wake and sleep periods. Someone whose BP falls by 10–20% is considered to have a dipping pattern (Fig. 3C). Patients with a less than 10% fall in BP during sleep are considered have a nondipping pattern (Fig. 3D). This pattern has a strong correlation to end-organ damage in adults and early suggestions are that it may be so in children as well *(3)*. Elderly adults with a dipping of more than 20–30%, i.e., superdippers, have an association with neurological sequelae, but this has not been observed in children.

In interpreting this plethora of data, it is not clear if the average of BP values over a given time period is of the most value or perhaps the sum of the peaks of BP values is superior. The "BP load" is defined as the percentage of BP exceeding the upper limit of normal for a given time period. Because this is a binary determination and does not really

reflect the magnitude of the excess over the upper limit, the BP index has come into common usage in pediatrics. It takes the BP averaged over a given time period and factors it by the 95th percentile for height and gender for that time period. For example, a child with a 24-h mean SBP of 124 mmHg with a 24-h 95th percentile of 115 would have a BP index of 1.08 or 8% above normal. This has been found to have a strong correlation to end-organ damage in children *(21)*.

As opposed to adults, the systolic and sometimes diastolic ABPM values in children have been found to be higher than CBPM measurements *(23,26)* and is likely related to the increased physical activity of the child *(20)*. Thus, the BP thresholds used for CBPM cannot be used for ABPM.

INFORMATION OBTAINED FROM AMBULATORY BLOOD PRESSURE MONITORING

Circadian Blood Pressure Pattern

In nonhypertensive and hypertensive children, the BP drops during sleep and peaks in the early hours of the morning during the waking period, a chronobiological pattern similar to that of adults *(26,27)*. There is an increase in BP from the sleep to the wake state, which may be related to hormonal, hematological, and nervous system changes. In hypertensive children there is a similar diurnal pattern that is, however, shifted upward *(27)*. The circadian nature of the BP can be evaluated by cosinor analysis of the data with determination of the mesor, amplitude, and the acrophase. In adults, the early morning surge in BP along with an increased heart rate, sympathetic outflow and receptor expression, and increased coagulability have been found to precipitate cardiovascular events. The concept of chronotherapy for hypertension has evolved from this finding. In addition, lack of nocturnal dipping in BP can be evaluated *(27)*. A blunted response of nocturnal dipping has been demonstrated in normotensive African-American adolescents *(28)*. Nonhypertensive African-American children have been found to have a higher mesor BP than white children *(29)*. Stress induced subtle changes in the circadian pattern can also be detected by ABPM in normotensive children *(30)*.

Magnitude of Blood Pressure Fluctuation

The magnitude and the speed of BP fluctuations have been found to have clinical relevance in adults. In hypertensive patients there is a steeper slope of BP rise than normotensive subjects, possibly increasing

the shear force on the blood vessels *(31)*. In children, however, the variability in BP is mostly a result of physical activity level, and about 49% of the variability in the BP in an individual child has been determined to be related to physical activity *(32)*. However, children after renal transplantation do not display the same variability for the same activity level, suggesting altered control of BP *(32)*. Normotensive adolescents have been found to have higher BPs on ABPM during periods of activity or stress *(20)*. The children who had a greater degree of activity level had greater variance in their circadian pattern of BP than children who were "hypoactive" *(20)*. Some borderline hypertensive adolescent children have an "amplitude hypertension" with wide fluctuations in their BPs, with peaks and troughs that negate each other and yield a normal mean BP (Fig. 3F) *(33,34)*. These children can spend a large part of the day in the hypertensive range with an increased BP load, resulting in increased risk for end-organ damage even though their mean BPs are normal *(35)*.

Blood Pressure During Various Disease Conditions and Physiological States

The ABPM can detect the change in BP in the same patient under various dynamic conditions. CBPM may not be appropriate or helpful in these settings to give a true picture of the pattern of BP or the change in BP in a child. The ABPM can help evaluate the effects on BP during fluid shifts in renal patients before, during, and after dialysis *(36,37)*. Altered circadian BP pattern has been seen in children with renal transplantation *(38,39)*. In children with diabetes, poor glycemic control has been shown to correlate with decrease in nocturnal dipping of BP *(40)*. Thus, ABPM should be indicated in disease states where altered circadian rhythms are known to occur.

Index of Total Load Exerted on Arterial Walls

The BP excess can be determined by calculating the BP load. The BP load is the percentage of values above a constant threshold (*see* Fig. 3). A BP load of greater than 25% is considered abnormal because this value is two standard deviations greater than the mean BP load in normotensive children *(20)*. A BP load greater than 40 has been associated with end-organ damage in adults, with a similar value of more than 60% associated with end-organ damage in children. The hyperbaric index examines the area under the curve between the measured pressure and the upper limit of normal over a given time period. It has not found any clinical utility in pediatrics as yet.

Table 3
End Organ Damage Associated With ABP in Children

Essential hypertension
Obesity/metabolic syndrome
Chronic kidney disease
Vesicoureteral reflex
Renal cystic diseases
Transplant
Dialysis

END-ORGAN DAMAGE

The purpose for measuring BP at all is to determine the risk for end-organ damage or events. The ABPM has proved superior to CBPM in virtually every adult or pediatric study in which it has been studied in predicting this risk. End-organ damage related to ABPM results has been found in pediatrics in several conditions (Table 3).

Numerous studies have shown that ABPM is superior to CBPM in its ability to predict hypertension induced end-organ damage and fatal and nonfatal cardiovascular events in adults and has been well enumerated in this volume *(41–43)*. In particular, ABPM is helpful in patients with kidney disease where abnormal BP patterns are prevalent. One of the authors (RJP) has reviewed this data in a recent publication of the National Kidney Foundation *(44)* and concluded from the data that ABPM facilitates the diagnosis of WCH even in patients with chronic kidney disease (CKD). The level of BP and abnormal patterns by ABPM show a high correlation with end-organ damage. In CKD, ABPM is associated with alterations in the circadian patterns of BP; the most common of these rhythm abnormalities is sleep-associated hypertension and a nondipping BP pattern. Abnormal ambulatory patterns have been shown to be related to varying degrees of abnormal protein excretion and to be related to cardiovascular damage and events. Abnormal ambulatory patterns have been related to more rapid progression of kidney disease in both native kidneys and transplanted kidneys. Because of these abnormal patterns, the correlation between CBP and ABP is poor, as is the relationship of CBP to end-organ damage. The diagnosis of nocturnal hypertension in CKD patients could affect the requirement for antihypertensive therapy.

Patterns in hypertensive patients such as nondipping have been found to have three times as many events as hypertensive dippers *(45)*.

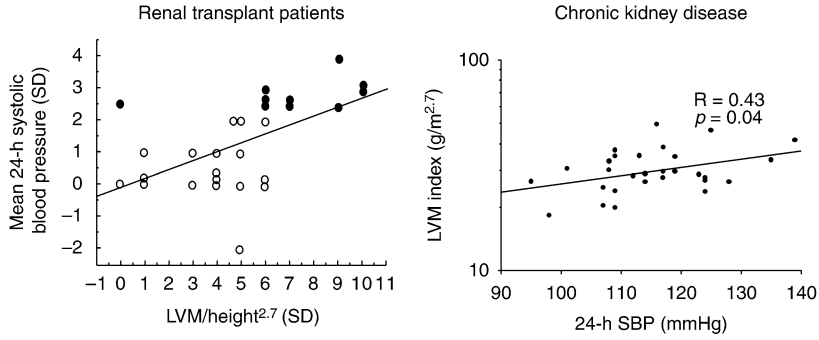

Fig. 7. Hypertension and left ventricular hypertrophy in children with chronic kidney disease. **(Left)** Left ventricular mass (LVM) indexed for height ($g/m^{2.7}$) vs mean 24-h systolic blood pressure. The regression line is shown. Values are expressed as SD. Symbols are open circles for normotensive patients and solid circles for hypertensive patients. The line was drawn for all data points ($n = 28$; $p = 0.02$; $r = 0.55$). **(Right)** Twenty-one percent of 29 children with glomerular filtration rate = 25–75 mL/min/1.73 m^2 had ambulatory blood pressure monitoring and echo and were hypertensive. There was no relationship between LVM and office blood pressure *(37)*.

Often patients will have a decrease in BP compared to CBP when the ABPM is used. When the BP falls to normal for both mean BP and BP load, the patient can be said to have WCH, a pattern found to have significantly less end-organ disease and less cerebrovascular and coronary events *(46)*. However, sometimes a profound drop in BP is seen with ABPM but the patient remains hypertensive on ABPM. This is termed the white-coat effect, and its magnitude has not been shown to have prognostic value.

In children, left ventricular hypertrophy was seen to correlate with the degree of high BP on ABPM *(3,21,47)*. Lower rates of creatinine clearance has been found to correlate to higher SBPs and DBPs during the night on ABPM in otherwise normotensive African-American children *(48)*. After renal transplantation, the degree of left ventricular hypertrophy in children was found to correlate significantly with ABPM but not with the CBPM *(49)*. In addition, ABP values have been shown to have a close correlation to vascular damage as manifested by abnormal carotid intima-medial thicknesses by ultrasound determination in children with essential hypertension, renal transplants, and CKD *(50)*. Mitsnefes has also shown in a body of work the closer correlation of ABP index to this end-organ damage without association with CBP (Fig. 7). He also showed a close correlation of SBP load to carotid

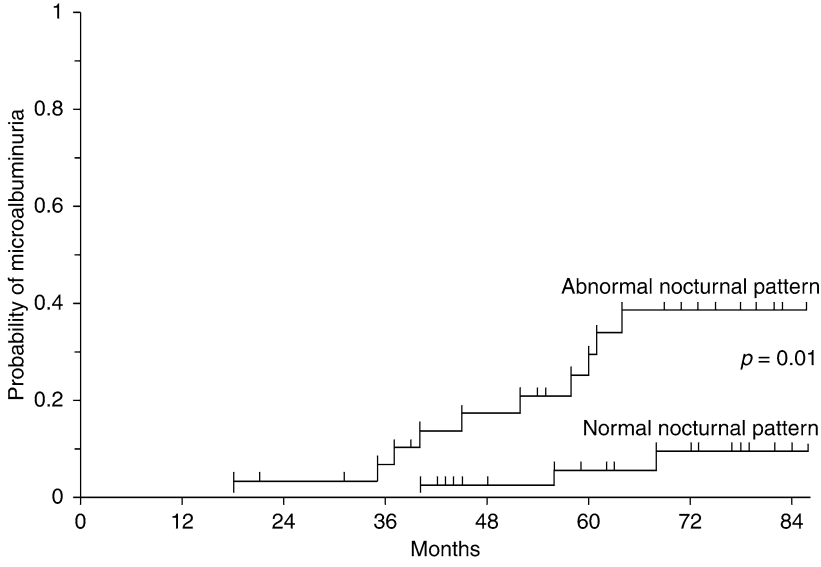

Fig. 8. Ambulatory blood pressure monitoring predicts microalbuminuria in patients with type 1 diabetes mellitus. Kaplan-Meier curves showing probability of microalbuminuria (MA) according to the pattern of daytime and nighttime systolic blood pressure. The probability of MA differed significantly between the two groups (p <0.01) by log-rank test; chi-square 6.217 with 1 df. The risk of MA was 70% lower in the subjects with a normal pattern than in those with an abnormal nocturnal pattern. (From ref. *51*.)

distensibility and stiffness. Newer covariates such as hyperlipidemia, vasculitis, obesity, and abnormal calcium/phosphorus balance are now also being identified to have a role in abnormal echocardiographic, vascular, and renal damage. Further, Wuhl and Schaefer have shown the close correlation of ABP to end-organ damage in the ESCAPE trial as well as the improvement in echocardiographic, cIMT, and proteinuria with improved ABP values in CKD patients treated with ramipril. Most importantly, there is now evidence that in some chronic disease, such as type 1 diabetes, an abnormal pattern of ABPM such as nondipping or sleep-related elevations *(51)* may be the first sign of incipient diabetic nephropathy as manifested by microalbuminuria (Fig. 8).

INDICATIONS FOR AMBULATORY BLOOD PRESSURE MONITORING IN CHILDREN

Figure 9 displays a schematic of the diagnosis of hypertension by CBP or ABP criteria.

	CBP	ABPM	Prevalence of CBP classification confirmed by ABP
'True' HTN	HTN	HTN	80%
'True' NTN	NTN	NTN	93–99%
WCH	HTN	NTN	20%
Masked HTN	NTN	HTN	~8–10%

Fig. 9. Classification of blood pressure as casual or ambulatory in children. CBP, casual blood pressure; ABPM, ambulatory blood pressure monitoring; NTN, normotension; HTN, hypertension; WCH, white-coat hypertension.

The finding of a persistently elevated CBP may be confirmed by ABP in approx 80% of cases leading to a diagnosis of true hypertension. However, in approx 20% of cases the ABPM will reveal a normal BP by both mean values and BP load values, confirming the diagnosis of WCH. The finding of a normal casual BP does not usually lead one to require that ABPM be performed; however, when the clinical history is inconsistent (e.g., a child who constantly complains of symptoms at school but not at home or in the doctor's office) the diagnosis of masked hypertension must be entertained. This may occur in up to 8% of normotensive children and is now the focus of studies in adults by Pickering et al. These patterns will now be discussed in more detail.

Diagnosis of Hypertension Including Masked Hypertension

In children the ABPM helps determine the presence of hypertension, especially when borderline BP elevations are found in the clinic. In addition, some children have episodic hypertension, when at certain clinic visits their BPs are completely within normal limits for age, gender, and height and at others they are found to be hypertensive. In addition, some children may have completely normal values on CBPM but demonstrate hypertension on ABPM when they are more active or in stressful states *(52–54)*, thus indicating masked hypertension (Fig. 10). Children on stimulant medications for attention-deficit hyperactivity disorder or on

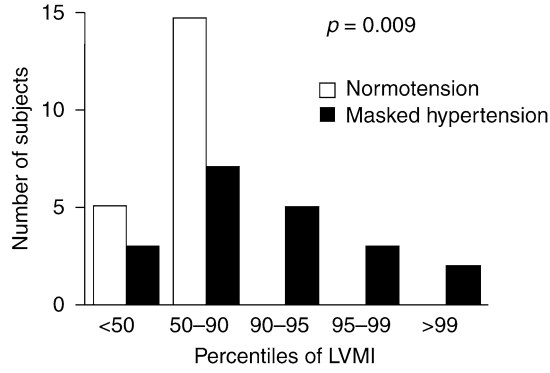

Fig. 10. Masked hypertension. Distribution of left ventricular mass index in 20 patients with masked hypertension and 20 matched normotensive controls. Cases and controls were matched for gender, age, and body weight. LVMI, left ventricular mass indexed to height to the power 2.7. (From ref. *54*.)

chronic steroid therapy may become hypertensive and evaluation by an ABPM on-and-off medication can help determine whether the hypertension is iatrogenic or not. In fact, a study by Samuels et al. *(55)* and data from the US Food and Drug Administration safety watch program have led to a recent "black box" warning about hypertension caused by stimulant medications.

The ABPM may be able to detect BP elevations at younger age in certain races or in those children with a positive family history of hypertension. In boys of African-American race, higher nocturnal BP has been detected by ABPM as compared to in white children and African-American girls *(56)*. Children of parents with hypertension have been found to have higher diastolic BPs at school *(57)* and have higher BPs values than children with a negative family history of hypertension *(58)*.

Detection of Phenomenon of WCH

Children, like adults, may demonstrate elevated BPs on CBPM and have completely normal recordings at home or at school; this phenomenon has been labeled WCH. Evaluation by ABPM can be invaluable in this condition because it prevents mislabeling a child with hypertension and avoids initiation of a drug on long-term basis *(59)*. In addition, the diagnosis of hypertension has social implications, such as clearing an athlete for competitive sports, employment and insurability, emotional stigmata, and financial burden. These children, however, need to

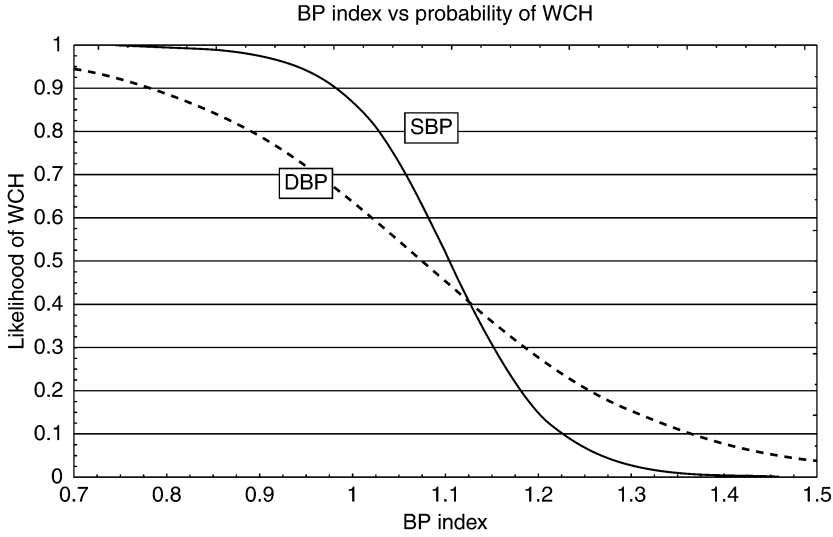

Fig. 11. Severity of hypertension and the likelihood of diagnosing white-coat hypertension. (From ref. *59*.)

be monitored periodically by ABPM because they may be at increased risk for developing sustained hypertension in the future. Our studies have also shown (Fig. 11) that the likelihood of WCH decreases with increasing severity of elevated BP. For example, those patients with a BP index of 1.0 (at the 95th percentile) have an almost 80% likelihood of having WCH, whereas someone with a BP index of 1.2 has a low likelihood of WCH. What is the import of WCH? In our practice, we feel the patient does not have true hypertension at this point in time and does not require the extensive and expensive evaluation recommended by the Fourth Working Group. Conversely, we do believe that WCH patients are an at-risk population and adult data as well as emerging but as yet unpublished data in children from end-organ damage evaluation suggest that WCH is an intermediate stage in the development of hypertension. It is a condition where aggressive therapeutic lifestyle changes or perhaps, in light of the TROPHY study *(60)*, early pharmacological intervention may prevent frank hypertension from developing.

Dipping, Nondipping, and Nocturnal Hypertension

Normally the mean SBP or DBP falls or "dips" by 10% during the sleeping hours (Fig. 3C). Patients whose BP fails to fall by this amount are termed "nondippers" (Fig. 3D). This phenomenon has been reported

Table 4
Approach to Evaluation of White Coat Hypertension and the Severity of Hypertension Using ABPM in Children

Classification	*Clinic BP*	*Mean Amb SBP*	*SBP load*
Normal BP	<95th	<95th	<25%
White coat	>95th	<95th	<25%
Stage 1 HTN	>95th	<95th	25–50%
Stage 2	>95th	>95th	25–50%
Stage 3	>95th	>95th	>50%

Table modified from ref. *62*.

as a night-to-day ratio of BP or a percentage fall in mean BP. Nondippers have been demonstrated to have a higher incidence of cardiovascular morbidity in adults, such as target organ damage and renal insufficiency. Children with conditions such as CKD, diabetes mellitus, Cushing's syndrome, glycogen storage disease, mineralocorticoid excess, high renin levels, congestive heart failure, cardiac transplantation, autonomic neuropathy, pheochromocytoma, congenital central hypoventilation syndrome, and obstructive sleep apnea may demonstrate higher nocturnal BP readings or a nondipping pattern. A blunted nocturnal dipping pattern has been demonstrated in the normal African-American adolescent male population *(61)*. Extreme nighttime dipping in BP with antihypertensive therapy has been correlated to advanced cerebrovascular disease and ischemic optic neuropathy in the elderly population. No such correlations have been seen in children, but extreme dipping of BP during therapy should be avoided in children as well. Belsha has demonstrated in children the association of left ventricular hypertrophy with nocturnal elevations of BP.

A schema for the diagnosis of hypertension and WCH using CBP and ABPM data is presented in Table 4. It is of importance to note that the prevalence of end-organ damage increases with each increasing stage of hypertension.

Guide to Monitoring of Antihypertensive Therapy and Detection of Refractory Hypertension

Response to antihypertensive therapy and detection of refractory hypertension can be evaluated reliably with several measurements obtained over various physiological states of a child during 24 h. The ABPM is superior in determining the adequacy of BP control with therapy than CBPM as a longer period of evaluation is more representative of the drug effect than a single measurement at the office when there a peak

levels of antihypertensive drug in the system *(63)*. In addition, hypotension because of medication may also be detected on an ABPM. The goal of medical management of hypertension is to obtain a smooth reduction in the BP over time; this can be assessed by evaluation of the trough:peak ratio, morning:evening ratio, and smoothness index of BP by ABPM. In children with refractory hypertension who are hypertensive on CBPM despite multiple antihypertensive drugs, an ABPM can help determine whether they are truly hypertensive in a nonclinical setting and thus avoid unnecessary titration of their medications if they are normotensive or well controlled outside the health care facility. Thus, use of ABPM can prevent more intensive drug treatment and lead to fewer side effects.

Application as a Clinical Research Tool

Other than clinical use, ABPM has been helpful in monitoring drug-efficacy trials. Several factors make ABPM a useful monitoring tool in research, including the ability to examine BP changes over the entire dosing interval, allow for calculation of trough-to-peak ratio as an arithmetic index of 24-h BP control, the higher degree of reproducibility of ABPM compared to CBPM, the ability to reduce sample size of study population because of the increased number of readings obtained by ABPM, the better predictive ability of ABPM of clinical cardiovascular outcomes in the adult population compared to CPBM, and finally, the ability to exclude patients with WCH from drug trials.

SUMMARY

In children, ABPM use is safe and effective and can be performed with minimal discomfort to the child. The ABPM is superior to CBPM in many ways. Perhaps its greatest use is the determination of WCH in children, preventing unnecessary therapy in a growing, physically active child. Perhaps as important is the determination of patterns such as nocturnal hypertension. Overall, the association of ABP parameters with end-organ damage is also extremely valuable. Larger studies are required to define the normal and hypertensive ABPM threshold measurements in different age groups in children and in various ethnicities in the United States.

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15 Ambulatory Blood Pressure During Pregnancy

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CONTENTS

INTRODUCTION

Hypertensive disorders in pregnancy represent a major cause of maternal and perinatal morbidity and mortality. Hypertension affects approx 10% of all pregnancies and is the second leading cause of

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maternal death in the United States *(1,2)*. The diagnosis of hypertension in pregnancy has relied on the use of conventional in-office blood pressure (BP) screening measurements during prenatal visits. This method of BP assessment has come under scrutiny because of poor measurement techniques, observer error, and the possibility of white-coat hypertension, leading to misdiagnoses. Thus, out-of-office BP measurements using both self- (home) and ambulatory BP monitoring (ABPM) recently have been viewed as superior methods for detecting true hypertension. In fact, in the nonpregnant patient, ABPM has become a clinical standard for diagnosing and managing hypertension *(3)*.

Preeclampsia, a pregnancy-specific disease, is defined as hypertension after 20 wk of gestation accompanied by proteinuria *(4,5)*. Some of the more severe clinical manifestations of preeclampsia include renal insufficiency, hemolysis, pulmonary edema, cerebral hemorrhage, hepatic dysfunction, seizures, intrauterine growth restriction, oligohydramnios, abruptio placentae, and intrauterine fetal death *(1,2)*. Because of these risks, an elevation of BP in the obstetrician's office creates substantial concern and leads to more intensive evaluation during the course of the pregnancy. The development of pregnancy hypertension often results in referral to maternal–fetal medicine specialists for consultation and follow-up. Management decisions with regard to use of pharmacological agents and even preterm delivery because of complications related to hypertension require a thorough understanding of the normal cardiovascular physiology in pregnancy as well as maternal and fetal effects of hypertension.

The use of ambulatory and home BP monitoring in pregnancy is a promising method of managing patients with hypertension in pregnancy *(6)*. This chapter discusses the benefits of out-of-office BP monitoring compared to conventional BP assessment and summarizes the available literature on ambulatory and home BP monitoring in pregnancy.

CLASSIFICATION OF HYPERTENSIVE DISORDERS IN PREGNANCY

The most important consideration in the classification of hypertension during pregnancy is differentiation of those hypertensive disorders that antedate pregnancy from pregnancy-related hypertension, or preeclampsia. Much of the difficulty in interpreting results of various studies on hypertension in pregnancy comes from the inconsistency in terminology used to describe pregnancy-related hypertension around the

world. The National Institutes of Health working group on hypertension has prepared a system of nomenclature that defines the following categories of hypertension in pregnancy: chronic hypertension, preeclampsia/eclampsia, preeclampsia superimposed on chronic hypertension, and gestational hypertension *(1)*.

Chronic hypertension is defined as BP ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic, which is present either prior to pregnancy or before the 20th week of gestation. Hypertension that is diagnosed during pregnancy and does not resolve by the 84th postpartum day is also classified as chronic hypertension *(1,4)*. Although several causes of chronic hypertension exist, the most common diagnosis in women of childbearing age is essential vascular hypertension. Similar to the case in the nonpregnant patient, chronic hypertension in pregnancy is classified as mild, moderate, and severe, depending on the absolute level of blood pressure or the presence of end-organ damage. Pregnant patients with chronic hypertension may be treated with various pharmacotherapy; the most commonly used drugs include β-blockers (e.g., labetalol), α_2-agonists, (e.g., α-methyldopa), and calcium antagonists (e.g., amlodipine).

Preeclampsia, as previously stated, is a syndrome peculiar to pregnancy and is associated with reduced organ perfusion secondary to vasospasm, endothelial injury, and activation of the coagulation cascade with platelet consumption *(1,4,5)*. Preeclampsia is diagnosed when hypertension (≥140/90 mmHg or 30 mmHg systolic/15 mmHg diastolic above first trimester BP) develops after the 20th week of gestation and is accompanied by proteinuria of at least 0.3 g in a 24-h specimen. The hypertension must be persistent (two measurements taken 6 h apart). Edema, once a part of the diagnosis of preeclampsia, is no longer considered a marker for preeclampsia because of the difficulty in differentiating pathological edema from benign edema frequently encountered among pregnant patients.

Although the etiology of preeclampsia remains obscure, typical pathophysiological changes, including generalized arteriolar constriction and an imbalance in prostaglandin metabolism, have been recognized. The severity of preeclampsia is further classified based on clinical symptoms and laboratory values. The clinical manifestations of severe preeclampsia are outlined in Table 1.

Eclampsia is the occurrence of seizures, not attributable to any other cause, in a patient with preeclampsia. Eclamptic convulsions, while rare, are life threatening for both the patient and her fetus. Uterine

Table 1
Clinical Manifestations of Severe Preeclampsia

Blood pressure >160 mmHg systolic or >110 mmHg diastolic
Proteinuria >5 g/24 h (normal <300 mg/24 h)
Elevated serum creatinine
Grand mal seizures (eclampsia)
Pulmonary edema
Oliguria (<500 mL/24 h)
Microangiopathic hemolysis
Thrombocytopenia
Hepatocellular dysfunction (elevated transaminases)
Intrauterine growth restriction or oligohydramnios
Symptoms suggesting end-organ involvement (headache, visual disturbances, epigastric, or right upper quadrant pain)

activity is often increased during such convulsions. In addition, fetal heart rate changes including bradycardia, decelerations, and decreased fetal heart rate variability have been reported *(5)*.

Preeclampsia superimposed on chronic hypertension is a clinical entity that worsens the prognosis for both mother and fetus and warrants closer monitoring for its development during pregnancy. Patients with chronic hypertension are at increased risk for developing preeclampsia during the pregnancy *(7,8)*, and differentiation between worsening chronic hypertension vs the development of preeclampsia should be made. Factors that may help in distinguishing these two entities are (1) new-onset proteinuria in women with hypertension and no proteinuria prior to 20-wk gestation, (2) a sudden increase in proteinuria, (3) a sudden worsening of BP in a previously well-controlled, compliant patient, and (4) abnormal laboratory values known to be associated with preeclampsia, especially low platelet count or elevated transaminases *(4,5)*. Patients with chronic hypertension are generally followed closely with baseline 24-h urine protein measurements as well as liver and renal function assessment in the first trimester.

Gestational hypertension is classified as hypertension detected after 20-wk gestation in the absence of proteinuria or other laboratory signs or symptoms of preeclampsia. This term is limited only to those patients who do not develop preeclampsia by the time of delivery and whose BP returns to normal postpartum. If the hypertension persists for more than 6 wk beyond the pregnancy, the diagnosis of chronic hypertension is given. Patients with gestational hypertension warrant close observation for the development of preeclampsia, but medical treatment or early

Table 2
Hemodynamic Alterations During Pregnancy

Parameter	*Early pregnancy*[a]	*Late pregnancy*[b]
Mean arterial pressure	Decreased	Maintained or increased
Plasma volume	Increased	Maintained
Red cell volume	Increased	Increased
Heart rate	Increased	Increased
Cardiac output	Increased	Decreased
Stroke volume	Increased	Decreased
Systemic vascular resistance	Increased	Maintained

[a]Less than 20 wk gestation.
[b]More than 30 wk gestation.

delivery are generally not indicated. Patients with white-coat hypertension often fit into this classification, and the use of BP monitoring outside the office is important in the clinical management of the patient.

NORMAL BLOOD PRESSURE CHANGES DURING PREGNANCY

Several hemodynamic alterations take place during the course of a normal pregnancy (Table 2). Plasma volume increases progressively, starting as early as 6-wk gestation, and usually reaches a maximum volume of 45–50% above baseline in the mid-third trimester. Cardiac output also increases by 30–50% as a result of both increased stroke volume and heart rate *(4)*.

Arterial blood pressure usually decreases in the first and early second trimester because of progesterone-related smooth muscle relaxation and decreased peripheral vascular resistance. The brachial artery pressure is highest when the patient is in the sitting position and lowest when the patient is lying on her side. Wide variations in the values of BP may be noted, depending on the position of the pregnant patient. Uterine size and compression of the vena cava can cause alterations in BP as pregnancy progresses. For this reason, consistency must be used while measuring BP conventionally at each office visit, and it has been recommended that BP be routinely checked when the patient is seated after several minutes of rest *(1,5)*.

Because of the normal changes in BP during pregnancy, there is some controversy as to the use of first and early second trimester BP measurements in diagnosing chronic hypertension. Many women present for initial prenatal care at this point in the pregnancy, and while

their BP measurements are considered normal (<140/90 mmHg), their baseline prepregnant BP values could actually be much higher.

CONVENTIONAL BLOOD PRESSURE ASSESSMENT

There have been many criticisms of conventional BP measurement in diagnosing and managing the hypertensive patient. Although the mercury column sphygmomanometer is still considered the most accurate clinical instrument for blood pressure measurement, both equipment and observer error have been implicated in providing inaccurate BP measurements. Improper cuff size, for example, is a common reason for discrepancies noted with conventional BP assessment. A standard cuff and bladder size should be used on patients with a mid-bicep arm circumference <32 cm, whereas a large cuff is more appropriate for patients with an arm circumference ≥33 cm.

Observer error and bias are additional problems that may be encountered with conventional BP assessment. Error may occur as a result of fatigue, poor memory, decreased visual or auditory acuity, and poor interpretation of Korotkoff sounds *(9)*, Observer bias often results from the tendency to "normalize" BP *(10)* as well as the practice of rounding off measurements to the nearest 5 or 10 mmHg *(11)*.

An additional limitation of conventional BP measurement in pregnancy is the controversy of whether to use Korotkoff phase IV (muffling of sounds) vs phase V (disappearance of sounds) to record diastolic blood pressure. In the past, phase IV was accepted as more reproducible and a better estimate of diastolic pressure *(12,13)*. However, more recent data support the use of Korotkoff phase V in pregnancy *(14)*. The Report of the National High Blood Pressure Education Program Working Program on High Blood Pressure in Pregnancy recommends the use of phase I and V for determining systolic and diastolic pressures, respectively *(1)*.

AMBULATORY BLOOD PRESSURE MONITORING IN PREGNANCY

Ambulatory blood pressure monitoring (ABPM) allows multiple recordings of BP in an out-of-office environment, thus providing a better estimate of actual BP levels and variability. In addition, ABPM records BP changes in response to physical and mental activity, which is not achieved by office BP monitoring. These benefits are well documented in the nonpregnant patient, and the growing body of international literature over the past decade indicates a heightened interest in ABPM among pregnant patients as well.

Several studies have been published on the patterns of ABPM in normal pregnancy (Table 3). Marguiles et al. were among the first to describe the 24-h BP profile in 11 normotensive pregnant women in the third trimester *(15)*. Although these women were hospitalized during the monitoring session, they described a similar pattern of 24-h BP to that of nonpregnant patients, as well as a significant difference between awake and sleep BPs.

Since then, two larger studies have further evaluated the ambulatory BP patterns in healthy normotensive women. Halligan et al. studied ABPM in 106 primigravid white women at three time points during the pregnancy (9–16, 18–24, and 33–40 wk) and 6 wk postpartum *(16)*. The quality of this study was strengthened by (1) a high compliance rate (>90% of the patients studied had at least four monitoring sessions), (2) a very homogeneous patient population, and (3) evaluation at 6 wk postpartum serving as a form of control group. The results showed no difference in systolic BP between 9 and 33 wk, but a significant rise from 33 to 40 wk. There was a decrease in diastolic BP between 18 and 24 wk, and a significant increase from 33 to 40 wk. Postpartum BPs were significantly higher than first trimester readings.

Contard et al. *(17)* performed ABPM on 48 patients at three points during the pregnancy (3, 6, and 9 mo). This group of patients was less homogeneous than the group studied by Halligan et al. Additional limitations of the study included: (1) there was no nonpregnant control group; and (2) the monitor used by some of the study patients had not been validated in pregnancy. Still, their results showed that BPs were lowest in the first trimester with significant increases in 24-h diastolic BP, daytime diastolic BP, and nighttime systolic and diastolic BP between the second and third trimesters. All patients demonstrated a significant decrease in sleeping BPs when compared with awake BPs.

Ferguson et al. published a cross-sectional study of ABPM in 150 women at different gestational ages *(18)*. The women were equally divided so that 50 had ABPM between 18 and 24 wk, 50 between 30 and 32 wk, and 50 between 36 and 38 wk. Using a nonpregnant control group for comparison, the study patients had a significantly higher ambulatory BPs at 36- to 38-wk gestation as compared with the other two groups.

In a paired observational study in 2001, Walker et al. assessed 24-h ABPM in 100 normotensive women who worked outside the home late in pregnancy *(19)*. The objective of the study was to determine whether significant changes in BP occurred while the patients were working

Table 3
Patterns of Ambulatory Blood Pressure Monitoring in Normal Pregnancy

Author (ref.)	*Year*	*No. of subjects*	*Study type*	*TM monitored*	*Control*	*Results*
Marquiles et al. *(14)*	1989	11	Cross-sectional	3rd	Yes	Pattern similar to nonpregnant pts; awake BP> sleep BP
Contard et al. *(16)*	1993	48	Longitudinal	1st, 2nd, and 3rd	No	↑ SBP and DBP between 2nd and 3rd TM
Halligan et al. *(15)*	1993	106	Longitudinal	1st, 2nd, and 3rd	Yes	↑ SBP after 33 wk GA and ↓ DBP b/w 18–24 wk GA
Ferguson et al. *(17)*	1994	150	Cross-sectional	2nd or 3rd	Yes	↑ BP at 36–38 wk GA compared to earlier in pregnancy

	Walker et al. *(19)*	2001	100	Cross-sectional	3rd	Yes	Higher BPs during work days compared with non-work days
	Hermida et al. *(20)*	2004	234	Longitudinal	1st, 2nd, and 3rd	Yes	No difference in mean values in nulliparas compared with multiparas

TM, trimester; SBP, systolic blood pressure; DBP, diastolic blood pressure; GA, gestational age; b/w, between.

compared with values obtained at home. The results of this study demonstrated significantly higher systolic and diastolic BP on work days compared with non-work days, independent of parity. The study demonstrated the practical use of ABPM in pregnancy, especially in assessing maternal BP responses to work.

More recently, Hermida et al. reported ABPM on 234 women to evaluate the circadian pattern in nulliparous gravidas compared to multiparas, which demonstrated no significant difference between the two groups at any stage of the pregnancy *(20)*.

With regard to patient satisfaction with the devices used in APBM in pregnancy, Walker et al. evaluated the acceptability of the SpaceLabs 90207 ambulatory blood pressure monitor in 2004 *(21)*. In this study, patients participating in research projects involving ABPM completed a questionnaire regarding the comfort and acceptability of wearing the monitor as well as any sleep disturbances they attributed to the monitor. Overall, the results showed a low rate of inconvenience with regard to noise and weight of the monitor, but there was a high rate (28%) of sleep disturbance, which was associated with noncompliance.

AMBULATORY BLOOD PRESSURE MONITORING AS A PREDICTOR OF PERINATAL OUTCOME

As a screening tool for preeclampsia, few researchers have studied the predictive value of ABPM. In the British literature, two papers have been published addressing this issue. Kyle et al. studied 162 nulliparous women with no other risk factors for preeclampsia by performing ABPM at two points in the pregnancy (18- and 28-wk gestation). Patients were followed until delivery to determine which ones developed preeclampsia *(22)*. They obtained adequate results on 127 women and showed that awake and mean arterial pressures were significantly higher at 18 wk in those patients who eventually developed preeclampsia compared with those who did not. However, the difference between the two groups was clinically insignificant (mean difference ranging between 2.3 and 6.9 mmHg).

The sensitivity in predicting preeclampsia for a mean 24-h arterial pressure of ≥85 mmHg at 28-wk gestation was 65% with a positive predictive value of 31%. One limitation of this study was the high incidence of preeclampsia in the study group (13%), perhaps a result of their nontraditional definition of preeclampsia (diastolic BP ≥ 25 mmHg above baseline).

A larger study by Higgins et al. evaluated ABPM in 1102 nulliparous women *(23)*. The definitions of preeclampsia and gestational hypertension were much more stringent than in the previously cited study, resulting in a smaller percentage of patients with these diagnoses (2.1 and 5.8%, respectively). Again, both hypertensive groups had significantly higher ambulatory BPs than the normotensive group, but the differences were too small to be considered clinically significant. In this study, the best predictor of preeclampsia was 24-h mean diastolic BP ≥ 71 mmHg, which had a sensitivity of only 22% and a positive predictive value of 15%. Their conclusion was that second trimester ABPM was not a clinically useful modality in predicting preeclampsia in a healthy primigravid population. Bellomo et al. *(24)* reported on a prospective cohort study in pregnant women with office hypertension using ambulatory monitoring to rule out a significant white-coat effect. Women with 24-h ambulatory blood pressures less than 125/74 mmHg but with office pressures >140/90 mmHg were classified as having white-coat hypertension. Patients with white-coat hypertension had a significantly lower risk of developing preeclampsia than women with elevated ambulatory BP or true hypertension (7.1 vs 61.7%). In addition, the authors showed a higher cesarean rate, lower birthweight, and longer hospital stay for both mothers and neonates in the true hypertensive group compared to the normotensives and white-coat hypertensive groups.

Although this study was quite an important contribution to the maternal–fetal medicine literature, it does have certain limitations. For example, the 24-h BP monitoring was performed on just one fixed occasion during the pregnancy (at 35 wk gestation), and the patients were admitted to the hospital for the entire recording period. By admitting patients to the hospital where physical and mental activities are substantially reduced compared with home and work environments, these ambulatory BP values were unlikely to represent accurate BPs for most of the patients. In addition, 75% of the patients with hypertension in the study were started on antihypertensive therapy in the third trimester. As it is not routine practice to medically treat gestational hypertension or preeclampsia in the United States, results of a similarly designed study here could have quite different outcomes. Finally, self- (or home) BP monitoring was not performed in the Italian study. This is of relevance because self-monitoring is far easier to accomplish in clinical practice than ambulatory BP monitoring for a variety of reasons and is less costly *(25)*.

More recently, Hermida et al. described various circadian patterns of ambulatory pulse pressure in 2523 patients *(26)*. In this large prospective

cohort study, BP was sampled for 48 h every 4 wk throughout pregnancy and pulse pressure was analyzed and compared to those who had uncomplicated deliveries to those who developed pregnancy-related hypertension. A significantly higher 24-h mean pulse pressure was noted in the group of patients who developed both gestational hypertension and preeclampsia when compared to those who had uncomplicated pregnancies. This difference was even greater in the third trimester than the second trimester.

A few studies evaluating the association between ambulatory BP and fetal growth have been published since 1996. Churchill and coworkers studied 209 healthy nulliparous pregnant women by monitoring ambulatory BP at three different points during pregnancy *(27)*. The results of this study showed a continuous inverse relationship between fetal growth and maternal BP. A 5-mmHg increase in mean 24-h diastolic BP at 28-wk gestation was associated with a 68-g decrease in birthweight. A similar elevation of diastolic BP at 36 wk corresponded to a 76-g decrease in birthweight. These findings were independent of confounding variables such as maternal cigarette smoking, age, alcohol intake, and preterm delivery. Peek et al. *(28)* and Halligan et al. *(29)* found similar results in their studies, indicating that elevated ambulatory BPs correlated better with small-for-gestational-age infants than conventional BP assessment.

Benedetto et al. *(30)* evaluated a two-stage screening protocol for detecting preeclampsia and fetal growth restriction using ABPM and uterine Doppler ultrasound. The study population consisted of 180 pregnant women with at least one risk factor for preeclampsia. Each patient underwent uterine artery Doppler ultrasound and ABPM between 20 and 24 wk gestation, and patients were followed until delivery. The rates of preeclampsia, gestational hypertension, and fetal growth restriction were assessed. Thirty-three (18%) patients developed preeclampsia with or without fetal growth restriction, and 20 (11%) developed fetal growth restriction alone. When both the uterine artery Doppler studies and ABPM results were abnormal, the sensitivity to predict preeclampsia was only 58% with a positive predictive value of 63%. Both sensitivity and positive predictive value (PPV) were less in detecting fetal growth restriction without preeclampsia (30 and 20%, respectively).

In 2004, Tranquilli et al. *(31)* performed ABPM on 334 patients at 20-wk gestation and found that women who later developed fetal growth restriction or gestational hypertension showed a higher mean diastolic BP than those with normal outcomes. They concluded that

ABPM was a reliable predictor of idiopathic fetal growth restriction and gestational hypertension. A summary of the literature on ABPM and pregnancy outcome is presented in Table 4.

AMBULATORY BLOOD PRESSURE MONITORING IN PREGNANT PATIENTS WITH CHRONIC HYPERTENSION

Patients with chronic hypertension who become pregnant are at increased risk for developing preeclampsia compared to those women without hypertension prior to the pregnancy. The American College of Obstetrics and Gynecology (ACOG) Technical Bulletin on Hypertension in Pregnancy reports a risk ratio for the development of preeclampsia of 10:1 in women with hypertension antedating the pregnancy *(2)*. This risk ratio represents the data from various studies evaluating the incidence of preeclampsia in these women, which ranges from 25 to 50% *(7,8)*.

Studies of ABPM in pregnant women with preexisting hypertension have been more promising in the detection of preeclampsia and poor perinatal outcome than studies in healthy normotensive women. Halligan et al. used a linear regression model to identify a significant correlation between day and night, systolic and diastolic BP, and 24-h urine protein levels *(29)*. A similar correlation was not detected using office or obstetric day unit BPs. Peek et al. *(28)* noted that a systolic BP cutoff of 140 mmHg on ABPM had a strong correlation with preterm delivery (RR 2.14, p = 0.025), small-for-gestational-age infants (RR 2.22, $p = 0.02$), and admission to the neonatal special care nursery (RR 2.67, $p = 0.014$).

Although there was a correlation between elevated ambulatory systolic BP and proteinuria, this did not reach statistical significance (RR 1.68, p = 0.068). A stronger correlation was made for elevated ambulatory diastolic BPs >90 mmHg and proteinuria (RR 1.82, $p = 0.03$). These data suggest that there is a promising role for ABPM in women with chronic hypertension or other significant risk factors in predicting worsening of disease and development of superimposed preeclampsia with its inherent perinatal morbidity.

A recent study by Brown et al. evaluated 241 women with a diagnosis of chronic essential hypertension in early pregnancy *(32)*. Because only 86 of these patients had the diagnosis confirmed by ABPM or home BP monitoring prior to the pregnancy, the remaining 155 underwent 24-h ABPM early in the pregnancy. Their results showed a prevalence

Table 4
Summary of Reported Literature on Ambulatory Blood Pressure Monitoring as a Predictor of Pregnancy Outcome

Author (ref.)	*No. of subjects*	*TM monitored*	*Primary outcome*	*Results*
Kyle et al. *(18)*	145	2nd and 3rd	Preeclampsia	Using MAP ≥85 mmHg: sens = 65%, PPV = 31%
Higgins et al. *(19)*	1048	2nd	Preeclampsia	Using mean DBP >71 mmHg: sens = 22%, PPV = 15%
Bellomo et al. *(20)*	148	3rd	Preeclampsia	Elevated ABPM had sens = 87.5% and PPV = 77.7%
Churchill et al. *(22)*	209	2nd and 3rd	Fetal growth restriction	Continuous inverse relation to ABP and fetal growth
Peek et al. *(23)*	109	2nd or 3rd	Proteinuria	Using mean SBP >140 mmHg: sens = 41.2%, spec = 76%
Halligan et al. *(24)*	48	3rd	Proteinuria	Better correlation b/w 24-h SBP and DBP (day + night) and proteinuria compared with clinic BP
Benedetto et al. *(25)*	180	2nd	Preeclampsia; fetal growth restriction	Using abnormal uterine artery Doppler and ABPM: sens = 93%, PPV = 63%

(Continued)

Table 4 ***(Continued)***

Author (ref.)	*No. of subjects*	*TM monitored*	*Primary outcome*	*Results*
Tranquilli et al. *(26)*	334	2nd	Gestational hypertension; fetal growth restriction	Higher mean diastolic BP at 20 wk in patients developing fetal growth restriction or hypertension

MAP, mean arterial pressure; TM, trimester; SBP, systolic blood pressure; DBP, diastolic blood pressure; sens, sensitivity; PPV, positive predictive value; ABPM, ambulatory blood pressure monitoring; b/w, between.

of white-coat hypertension in this group of 32%, with a low prevalence of development of preeclampsia (8%). This study demonstrated the clinical utility of ABPM in distinguishing patients with white-coat hypertension from those with pregnancy-related hypertension that may have an impact on their pregnancy outcome.

AMBULATORY BLOOD PRESSURE MONITORING IN PREGNANT WOMEN WITH TYPE 1 DIABETES

Pregnant patients with type 1 diabetes have an increased incidence of developing preeclampsia, which has been reported to be as high as 20% compared to the baseline population of 6–7% *(34,35)*. Flores et al. reported on the ability of ABPM to predict the development of preeclampsia in such a high-risk population *(35)*. They studied 22 normotensive diabetic women and 10 normal controls by monitoring 24-h BP in all three trimesters of pregnancy. Despite their small numbers, the authors showed that the incidence of preeclampsia was fourfold greater in the diabetic women vs controls. The diabetics had a higher mean 24-h diastolic BP in the third trimester than controls, and those who developed preeclampsia had higher BP profiles in all three trimesters. The best predictor of preeclampsia in this study was the nighttime systolic BP of >105 mmHg in the second trimester (85% sensitivity, 92% specificity).

Although there are many other medical and pregnancy conditions that increase a woman's risk for developing preeclampsia, including

systemic lupus erythematosis, renal disease, and multifetal gestation, there is scant literature evaluating the use of ABPM in the management of such pregnancies.

Overall, ABPM has become a clinically useful modality in blood pressure assessment. In the nonpregnant patient, it is currently a standard practice in the diagnosis and management of hypertension *(3)*. The growing body of literature on ABPM in pregnancy indicates heightened interest in this area. Several ABPM devices have been validated in pregnancy *(36)*. Still, the role of ABPM in managing pregnant patients with hypertension and predicting perinatal outcome has yet to be determined in a well-controlled, prospective manner. Although there is no effective prevention or treatment of preeclampsia, the value of predicting it through early assessment of maternal ambulatory BP measurement may be in the clinical management and follow-up of appropriate patients.

HOME (SELF-) BLOOD PRESSURE MONITORING IN PREGNANCY

Automated self-monitoring BP devices are currently commercially available and provide an inexpensive and noninvasive method of BP assessment outside the office. They provide a more realistic estimation of true blood pressure and are especially useful in rural areas where frequent visits to a medical facility are difficult. Although the use of these devices has been well established in the nonpregnant population, there has been less widespread use of home BP monitoring in pregnancy. Unlike ABPM, there is a paucity of literature on the subject of home or self-BP assessment in pregnancy. In a study by Naef et al. *(37)*, a small number of patients with chronic hypertension were prospectively evaluated by recording their blood pressure at home four times a day using an electronic transtelephonic BP monitor (VasoPlex home BP monitor, American Medical Systems). The patients participated in the study for an average of 12.2 ± 5.8 wk at gestational ages that ranged from 23 to 42 wk. None of the patients had difficulty using the home monitor, and most found the device helpful in managing their hypertension and avoiding unnecessary visits to their care provider. Their data also showed that mean arterial pressure and heart rate were significantly higher in the office than at home. Although limited by its small sample size, this study represents one of the few published papers addressing home or self-BP monitoring in pregnancy.

In 1997, Gupta et al. evaluated the accuracy of the Omron HEM 705 CP oscillometric home BP device in pregnancy and preeclampsia *(38)*. After testing the device according to the British Hypertension Society

protocol in 85 women with a wide variety of blood pressures and 43 women with preeclampsia, they found that the device did reach a B grading for the pregnant population. However, in the preeclamptic population, the device did not reach acceptable accuracy criteria, receiving a grade C for systolic BP and a grade D for diastolic BP. In addition, the device failed to meet the criteria for Association for the Advancement of Medical Instrumentation (AAMI) in both the pregnant and preeclamptic populations.

This study emphasized the importance of separate device validation specifically in pregnancy and preeclampsia. It also suggests that perhaps validation guidelines should be reevaluated for pregnant patients. Because hemodynamic changes occur in preeclampsia such as systemic vasospasm and reduced circulatory volume (Table 2), the issue of device validation in these patients can become quite complicated. To date, very few studies have been performed to validate home BP monitors in pregnancy. Although several ambulatory monitors have been validated in pregnancy, only one device has been validated in patients with preeclampsia *(36)*.

Given the high prevalence of white-coat hypertension in pregnancy *(28)* and the limitations of conventional sphygmomanometry, as discussed earlier, the use of home (self-) BP monitoring in pregnancy has been studied and found to improve the identification of patients at risk for perinatal complications *(24)*. With regard to comparing home BP with ABPM, Brown et al. reported a prospective comparison of the automated Omron HEM 705 CP with ABPM in pregnancy *(39)*. Their conclusion after evaluating limits of agreement between BPs using each device was that home BP using this device was useful but could not reliably replace ABPM for managing hypertension in the pregnant patient.

CONCLUSION

Over the last decade, the importance of ambulatory and home BP monitoring in diagnosing and managing hypertensive patients has been increasingly established. In pregnancy, there is a growing interest in these forms of out-of-office BP assessment, as evidenced by numerous publications in the obstetric and hypertension literature. Out-of-office BP monitoring during pregnancy is much more common in Europe and Australia than in the United States. Based on the expanding body of literature demonstrating the clinical utility of out-of-office BP monitoring in pregnancy, it appears likely that ABPM and home BP monitoring will become a more standard diagnostic method in the management of pregnant patients with various types of hypertension.

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16 Ambulatory Blood Pressure in Patients With Chronic Kidney Disease

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CONTENTS

INTRODUCTION

Chronic kidney disease (CKD) is a growing health care problem. The current prevalence of CKD in the adult US population is estimated to be 11% *(1)*, and this prevalence is likely to grow as most of the cases of CKD occur in the setting of diabetes, hypertension (HTN), and aging, all conditions of increasing prevalence in modern societies. As a result, the incidence of adults with end-stage renal disease (ESRD) has

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also consistently increased *(2)*. CKD and ESRD patients have a significant rate of morbidity and mortality *(2)*, resulting in high utilization of health care resources.

HTN is highly prevalent in CKD, where it is estimated that up to 80% of patients have elevated blood pressure (BP) by the time they reach advanced stages of kidney disease (glomerular filtration rate < 15 mL/min) *(3)*, and is the most important factor in the progression of most chronic renal diseases *(4)*. HTN is also highly prevalent in dialysis *(5)* and kidney transplant *(6)* patients. Furthermore, cardiovascular diseases (CVDs) are the major cause of death in any stage of renal impairment *(7)*. Therefore, HTN is a major cardiovascular risk factor during any stage of kidney disease.

Ambulatory blood pressure monitoring (ABPM) is an important tool in HTN research and clinical practice in view of its superior ability to detect target organ damage and to predict prognosis compared to office BP measurements *(8,9)*. Data in patients with kidney disease are still based primarily on exploratory cross-sectional studies, although the literature has been steadily growing, with well-designed prospective, hypothesis-driven studies. This chapter will review these relevant findings applicable to patients with CKD.

ABPM AS A TOOL TO IDENTIFY INCREASED RISK OF DEVELOPMENT OF KIDNEY DISEASE

A small increase in urinary albumin excretion may be the first sign of renal damage in diabetic and hypertensive patients *(10,11)*. Microalbuminuria is also associated with increased cardiovascular death *(12)*. In patients with essential HTN or diabetes mellitus (DM; type 1 and type 2), the presence of microalbuminuria is better correlated with ABPM parameters than office BP, although there is controversy about which BP, systolic or diastolic, better predicts risk *(13)*. Furthermore, nondipper patients with essential HTN have almost threefold higher albumin excretion rates (42 vs 17.5 mg/24 h; $p < 0.001$) than dipper hypertensive patients independent of office or daytime ambulatory BP *(14)*.

Kidney disease is a common complication of DM. Type 1 diabetic patients have a characteristic natural history in which the earliest sign of kidney disease, microalbuminuria, is accompanied by increased office BP *(15)*. A large body of literature has evaluated ABPM findings in such patients, primarily through cross-sectional studies *(16)*. In the few longitudinal studies available, it has been determined that in patients with

type 1 diabetes and normoalbuminuria, individuals who progressed to microalbuminuria over a 3.1-yr follow-up had a lower nocturnal diastolic BP drop than those who did not progress, further representing an increase in 24-h BP, which was noted by changes in follow-up ABPM, not in office BP *(17)*. A recent prospective study shed light on the course of events linking BP and albuminuria in type 1 DM *(18)*. In this study, 75 young patients with type 1 DM were followed prospectively for an average of 63 mo and underwent ABPM every 2 yr. The investigators noted an increase in nighttime BP in the group who developed microalbuminuria, and this increase in BP preceded the identification of albumin in the urine, raising a possible pathophysiological link between increased nighttime BP and albuminuria *(18)*. In a logistic regression model, a 5-mmHg rise in nighttime systolic BP resulted in a 44% increased risk of development of albuminuria on subsequent examinations. Office BP was unable to detect these differences, and daytime BP was less prominently changed. Last, individuals with a preserved diurnal BP rhythm (defined as night:day BP ratio ≤ 0.9) had a 70% lower likelihood of developing microalbuminuria (Fig. 1) *(18)*.

A series of studies has analyzed the relationship between diurnal BP and renal structural changes in DM. In a cross-sectional study of ABPM and renal structure in 41 adolescents and young adults with type 1 diabetes, Torbjornsdotter et al. showed that nocturnal mean BP correlated directly to basement membrane thickness, volume fraction of mesangial matrix, and foot process width *(19)*. A follow-up biopsy in patients who remained normolbuminuric and normotensive showed that nighttime systolic and mean arterial pressure at the time of the first biopsy predicted mesangial matrix and mesangial volume fraction per glomerulus, foot process width, and slit pore length on a second biopsy on average 6 yr later *(20)*.

Although the natural history of type 2 diabetes is less predictable than in type 1, microalbuminuria is also an early sign of renal damage in type 2 diabetes *(21)*. In these patients, 24-h BP level is a better predictor of increasing albuminuria than office BP in both normo- and microalbuminuric patients over an average follow-up of 4.6 yr *(22)*. However, no relationship was noted between changes in diurnal rhythm and progression of albuminuria in this group *(22)*.

Thus, ABPM is a better predictor of early renal damage than office BP in hypertensive and diabetic patients. In type 1 diabetic patients, circadian BP changes are associated with early kidney damage, and nighttime BP may be used to detect these individuals.

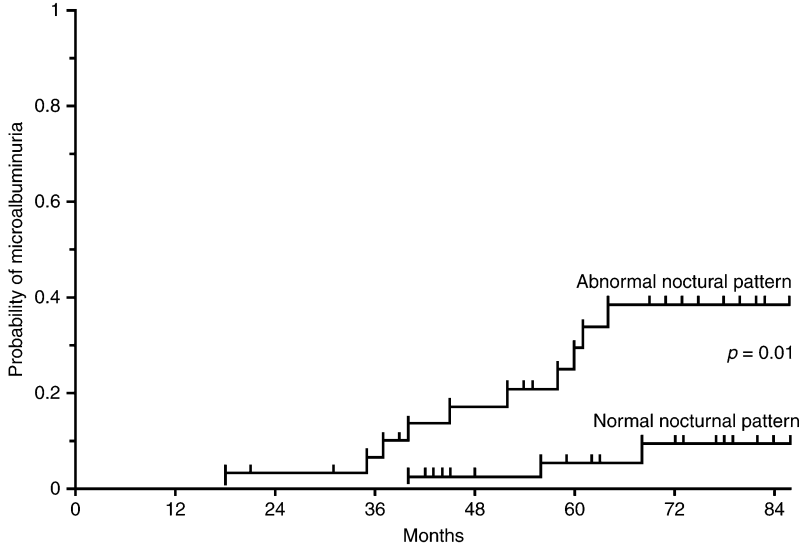

Fig. 1. Kaplan-Meier curves showing the probability of microalbuminuria according to the diurnal blood pressure pattern. (From ref. *18*.)

ABPM IN ESTABLISHED CHRONIC KIDNEY DISEASE (STAGES 1–4, PREDIALYSIS)

Chronic kidney disease and HTN commonly coexist. Approximately 75% of patients reaching stage 5 CKD (glomerular filtration rate < 15 mL/min) have BP levels more than 140/90 mmHg. CKD is currently classified according to the presence or absence of renal damage (by urinalysis or imaging studies) and the degree of renal function based on estimates of glomerular filtration rate (K-DOQI classification of the National Kidney Foundation). This classification is as follows:

1. Stage 0: at risk for kidney disease, normal kidneys and GFR >90 mL/min.
2. Stage 1: urine or imaging abnormalities with GFR >90 mL/min.
3. Stage 2: GFR 60–89 mL/min.
4. Stage 3: GFR 30–59 mL/min.
5. Stage 4: GFR 15–29 mL/min.
6. Stage 5: GFR >15 mL/min, dialysis or renal transplantation.

The following paragraphs refer to patients with stage 1–4 CKD.
One of the most consistent findings in these patients is the prevalence of abnormal diurnal BP profiles, with blunting of the nocturnal BP dip *(13,23,24)*. In a landmark study, Baumgart et al. showed uniformly

blunted circadian BP profiles in patients with various CKD not on dialysis, patients on hemodialysis (HD), and patients with a kidney transplant compared with controls matched for age, sex, office systolic BP, and presence/absence of antihypertensive drug therapy *(25)*. Average dipping during sleep (SBP%/DBP%) was 7%/11% in CKD patients (vs 18%/24% in controls), 4%/8% in HD patients (vs 14%/24% in controls), and 5%/9% in transplantation patients (vs 13%/18% in controls) *(25)*.

Evaluation of Kidney Disease Progression

HTN is a major risk factor for the progression of CKD of any etiology *(3)*. Because ABPM is a better predictor of target organ damage than office BP and diurnal BP changes may add to this prediction, one could speculate that ABPM could be a better predictor of CKD progression. However, surprisingly few data are available on this topic. In a relevant study, Timio et al. reported on 48 hypertensive patients with renal insufficiency (creatinine clearance < 60 mL/min), 28 of whom were nondippers, and compared the rate of decline in renal function between dippers and nondippers *(26)*. Nondippers lost renal function more rapidly than dippers during a 3-yr follow-up period (0.37 vs 0.27 mL/min/month; $p = 0.002$). Nondippers also had a greater increase in proteinuria at the end of follow-up than those with a normal BP rhythm (993 vs 691 mg/24 h; $p = 0.009$). Similarly, Farmer et al. retrospectively analyzed the role of circadian BP rhythms on the progression of diabetic nephropathy in 26 patients with type 1 or type 2 diabetes followed for a median of 6 yr *(27)*. The rate of decline of creatinine clearance was lower in dippers thannondippers (2.9 vs 7.9 mL/min/yr; $p < 0.05$) *(27)*. The role of ABPM in predicting the progression of IgA nephropathy was evaluated in 95 subjects followed for 36 mo *(28)*. They demonstrated an increase in serum creatinine in the group of 8 normotensive nondippers (1.2 vs 1.0 mg/dL at baseline; $p < 0.05$), whereas no increase was observed in the 28 normotensive dippers (0.95 vs 0.9 mg/dL at baseline). In addition, they showed a rise in serum creatinine (1.2 vs 1.0 mg/dL at baseline; $p < 0.05$) in 10 patients classified as white-coat hypertensives (office BP > 140/90 mmHg, daytime ambulatory BP < 135/85 mmHg), although this was much less pronounced than the increase observed in the 52 sustained hypertensive patients (1.4 vs 1.15 mg/dL at baseline; $p < 0.05$).

A recent study took an alternative approach to the relationship between diurnal BP rhythms and kidney damage. Wuhl et al. performed 24-h ABPM in 214 children with CKD and analyzed the data according to different methods of determination of BP variability: classic dipping/

nondipping (night:day ratio) and BP amplitudes employing Fourier analysis using either circadian (24-h) or ultradian (6-, 8-, or 12-h) periods. Ultradian (especially 8-h), but not circadian mean arterial pressure correlated well with level of renal function and baseline protein excretion rate *(29)*. On the other hand, absence of circadian rhythm using Fourier analysis resulted in faster loss of glomerular filtration rate (10.8 mL/min/yr compared with 4.9 mL/min/yr in those with preserved circadian rhythm. Neither classic dipper/nondipper classification nor ultradian rhythms resulted in better prediction of loss of renal function (Hadstein and Schaefer, personal communication).

Presently available studies indicate that ABPM is a marginally better predictor of kidney disease progression than office BP, primarily by assessing the white-coat effect and the dipping phenomenon. Unfortunately, the size and methodology of available studies do not allow us to draw definitive conclusions at this time. Ultradian rhythms may be better predictors of renal damage. Because there are no intervention data, the available literature cannot determine whether the abnormal BP profile is the cause or consequence of progressive renal disease.

Target-Organ Dysfunction, Morbidity, and Mortality

The presence of CKD is an independent risk factor for CVD *(7)*.With the deterioration of renal function, nontraditional risk factors are added to the highly prevalent traditional risk factors for CVD found in these patients *(30)*. Both HTN and left ventricular hypertrophy (LVH), a strong surrogate marker for cardiovascular events, increase in prevalence as renal function declines *(31)*.

As in essential HTN, ambulatory BP is better than office BP to predict left ventricular mass (LVM) index in nondiabetic patients with CKD *(32)*. In hypertensive patients with IgA nephropathy, LVM was significantly related to nighttime BP and "diurnal index" (percent BP decline at night), but there was no relationship with daytime BP *(33)*.

In normotensive patients with autosomal dominant polycystic kidney disease with normal renal function, LVM was higher compared to health control subjects. The increase in LVM index was related to ambulatory BP. The nocturnal decrease in BP was also attenuated in polycystic kidney disease patients, but it was not associated with the increased LVM *(34)*.

Despite recent attention to the interplay between CVD and CKD, few studies have addressed the role of ABPM in predicting LVH, and no study has tested ABPM variables as independent predictors of cardiovascular events in the earlier stages of CKD.

ABPM IN HEMODIALYSIS AND PERITONEAL DIALYSIS (CKD STAGE 5)

BP Profile

HD provides a unique scenario of BP variability, making ABPM a potentially valuable diagnostic tool. Fluid gain between HD session, represented by the increase in body weight, is removed by ultrafiltration, and the reduction in extracellular volume is usually accompanied by a fall in BP *(35,36)*. The characteristic intermittence of HD treatment and wide fluctuations of extracellular volume during and between HD sessions give BP a unique profile in HD patients. The analysis of interdialytic ABPM, performed for approx 44 h, shows that both awake and sleep BP increases between HD sessions *(37,38)* (Fig. 2) and that this is not influenced by HD shift assignment (morning or afternoon) *(38)*. Although interdialytic fluid retention plays a role in BP increase, most studies failed to find a correlation between interdialytic weight gain and interdialytic BP *(23,38)*. ABPM also shows that intradialytic BP trends influence interdialytic BP levels *(39)*. Most of the ABPM descriptive studies showed that the nondipping pattern is very frequent in HD patients; more than two-thirds of patients lack the normal diurnal BP rhythm *(24)*.

ABPM has been used to determine reasonable clinic BP references in HD patients, i.e., those BPs taken before (pre-HD BP) and after (post-HD BP) HD sessions that best predict interdialytic BP *(39–42)*. In a study of 70 HD patients, Agarwal and Lewis showed that predialysis BP was flawed by a measurement bias (overestimation of interdialytic BP by 13.5/3.8 mmHg) and that both pre- and post-HD pressures had wide limits of agreement with interdialytic BP *(40)*. These data raise concerns about the use of peri-dialysis BP levels, but also allow the clinician who does not have access to ABPM to make clinical decisions relating the prevalent clinic BP levels to the anticipated interdialytic BP. Indeed, Agarwal and Lewis *(40)* have published clinic BP thresholds that have an accuracy rate of about 80% to predict a diagnosis of HTN on ABPM ("hypertension" defined as 44-h interdialytic BP > 135/85 mmHg): best sensitivity and specificity are observed using pre-HD BP averages between 140–150 and 80–85 mmHg and post-HD BP averages between 130–140 and 70–80 mmHg *(40)*. Data from our group *(39)* and others *(41)* indicate that the best estimate of interdialytic BP lies around the average of pre-HD and post-HD BP levels.

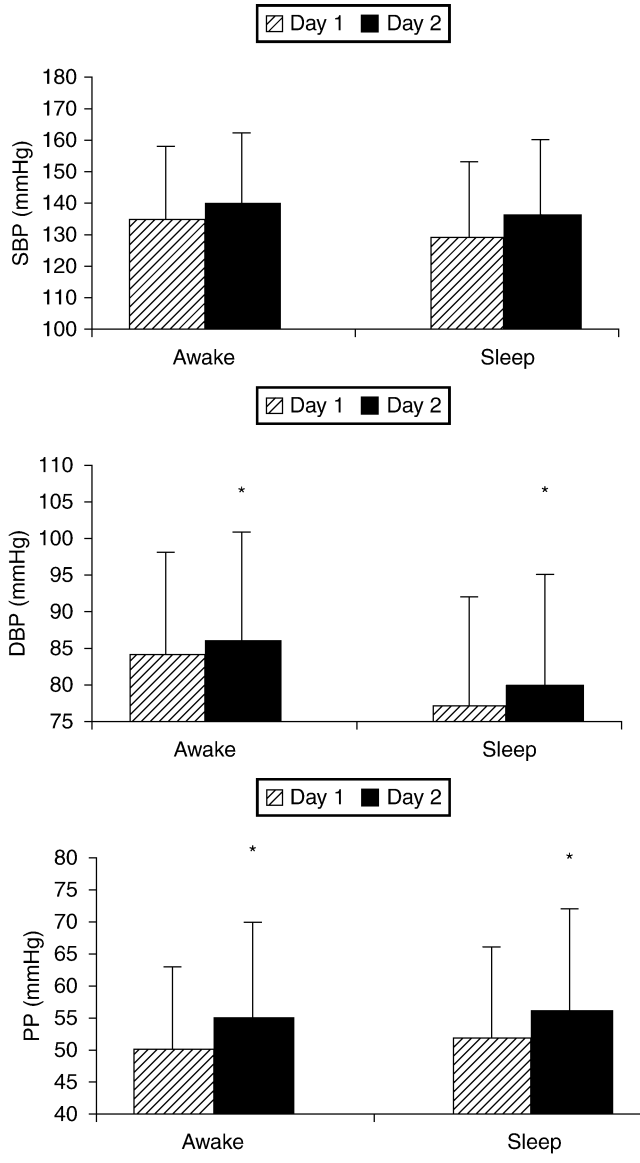

Fig. 2. Ambulatory blood pressure values on each interdialytic day during 44-h interdialytic monitoring in hemodialysis patients. SBP, systolic BP; DBP, diastolic BP; PP, pulse pressure. *$p < 0.05$. (From ref. *38*.)

ABPM provides a useful tool to evaluate the effects of antihypertensive drugs throughout the interdialytic period. Investigators have used this approach to show the efficacy of observed therapy with atenolol *(43)* or lisinopril *(44)* given three times weekly immediately following each HD session. The demonstration of the efficacy of this approach has been an important contribution to the management of HTN in HD subjects.

An application of ABPM of value in HD is the analysis of interdialytic symptoms. Many patients have problems with volume removal during dialysis because of inappropriate plasma refilling *(45)*, and their BP control and behavior may be better assessed by interdialytic BP *(46)*. In an important paper, Battle et al. showed that a substantial portion of HD patients have a delayed BP nadir occurring 4–6 h following HD *(46)*. Decisions about dialysis prescription and timing of antihypertensive drug administration can thereby be made more effectively after understanding the duration of BP control (or even low BP) after each dialysis session. Home BP monitoring is a valuable adjunct in this assessment, and we often use it in our practice.

Fluid removal in peritoneal dialysis methods is continuous, and patients do not have large fluctuations in BP related to extracellular volume changes. Therefore, standard methods can be used to assess BP in PD subjects, who are usually seen monthly in the ambulatory setting. ABPM descriptive studies showed a blunted decline in BP in peritoneal dialysis patients that is very similar to the profile of HD patients *(47,48)*. A recent study explored differences in BP profile according to peritoneal transport characteristics *(49)*. Although there was substantial difference in the prevalence of HTN and average BP levels (elevated in high and high-average transporters), there were no differences in the diurnal BP profile among groups.

ABPM and Target-Organ Dysfunction, Morbidity, and Mortality in Dialysis Patients

Several cross-sectional studies have studied the relationships between office BP, ambulatory BP, and LVH in dialysis patients. Two studies in patients undergoing long, slow HD showed no significant correlation between BP levels, office or ambulatory, and LVH *(50,51)*. Others have shown higher correlation coefficients between ambulatory BP and LVH than those linking office BP and LVH in conventional HD patients *(36,37,52–54)*, although others have not confirmed this observation *(55,56)*. Understanding these differences is not straightforward. Study design, echocardiographic methods, and

ABPM techniques were relatively similar among studies. It is possible that the use of a composite of many peridialysis readings (or home BP readings, for that matter) improves the consistency of the results in such a way that the correlations between LVH and office BP become indistinguishable from the more consistent and reproducible ABPM values *(55,56)*. Furthermore, because dipping is blunted, casual and ambulatory BPs tend to be more similar, and differences in prediction are minimized. One last possible factor is that echocardiographic determination of LVM depends on assumptions of cardiac symmetry that are not always present in HD and is dependent on the state of hydration of the patient, which inevitably fluctuates in HD subjects. Echocardiograms underestimate LVM at low LVM values and overestimate it at higher LVM values, a bias that is amplified in patients with higher end-diastolic volumes (a possible indicator of latent volume overload) *(57)*.

Another question that has been addressed by some investigators is whether the circadian BP rhythm matters in the evaluation of LVH in dialysis. Amar et al. did not observe any relationship between dipping status and echocardiographic LVH *(58)*, whereas other investigators have found that the degree of dipping correlates with LVM on univariate, but not multivariate analysis *(51)*, and that nocturnal systolic BP is the strongest predictor of posterior LV wall thickness, but not of other indices of LVH *(54)*. Wang et al. showed that nocturnal systolic BP load greater than 30% (percent of readings >125/80 during the night) was the only significant predictor of LVH in a group of peritoneal dialysis patients *(59)*. In the only available longitudinal study in dialysis, Covic et al. followed echocardiographic and ABPM changes over 12 mo and established that patients with a blunted circadian BP rhythm had progressive LV dilatation but no other markers of LV dysfunction on follow-up *(60)*. Overall, it remains uncertain whether ABPM adds to the evaluation of LVH or if these observations have any prognostic value to dialysis patients.

Arterial stiffness is a strong predictor of mortality in ESRD *(61)*. The relationship between ABPM and pulse wave velocity (a marker of arterial stiffness) was studied by Amar et al. in 42 HD patients *(58)*. Casual and ambulatory BP had similar correlations with pulse wave velocity. However, nondipper patients had significantly higher pulse wave velocity than patients with preserved diurnal rhythm (14.1 vs 11.5 m/s, $p = 0.03$).

Three studies have evaluated ABPM as a predictor of cardiovascular events among dialysis patients *(62–64)*. Amar et al. *(62)* followed 57 HD

patients for an average of 2.9 yr and used data from a baseline ABPM recording to predict future cardiovascular events. After adjustments for age, gender, and previous cardiovascular events, ambulatory pulse pressure and nocturnal systolic BP were the most relevant factors associated with cardiovascular events. However, because only 18 events (10 fatal and 8 nonfatal) occurred during follow-up, the Cox model was overfitted, and limited conclusions can be drawn. In a separate study with more events (36 in total) and appropriate model fitting, Liu et al. followed 80 HD patients for a mean period of 33 + 19.1 mo and found that the incidence of cardiovascular events and cardiovascular deaths was 3.5 and 9 times higher in patients who were nondippers during baseline ABPM than in dippers *(63)*. In the most robust of the studies, Tripepi et al. followed 168 nondiabetic HD patients who had not sustained a previous cardiovascular event, 49 of whom died during an average follow-up of 38 mo. Patients on the highest tertile of the night:day ratio (>1.01, i.e., reverse dippers) had an adjusted hazard ratio of 2.5 for total mortality and 4.3 for cardiovascular mortality *(64)*. Of relevance, BP (either daytime or nighttime) was not associated with increased mortality risk.

Outcome data relating ABPM to cardiovascular damage and mortality in dialysis are controversial. Only larger studies followed by intervention trials will settle this issue.

Technical Issues Specific to Dialysis Patients

Dialysis patients, and more specifically those on HD, have several features that may make BP measurement and ABPM difficult. These include the presence of arteriovenous grafts or fistulas, which alter blood flow in the extremities, the frequent changes in volume status represented by each dialysis session, and the fluctuation in BP throughout the period of 48–72 h separating one dialysis session and the next. Because of these shortcomings, it is important to have devices formally validated in these patients.

In one relevant study, Fagugli et al. monitored 44 patients during the interdialytic period with an ABPM device that is capable of simultaneous oscillometric and auscultatory measurements (A&D Takeda TM2421) to evaluate the relative accuracy of each technique in HD patients *(65)*. The oscillometric component of the device performed better based on several measures: standard deviations of both all BPs were lower (18.7 vs 20.4 mmHg for systolic; 10.9 vs 12.6 mmHg for

diastolic; both $p < 0.01$); coefficients of variation were also lower (14.6 vs 16.1% for systolic; 14.6 vs 17.7% for diastolic; both $p < 0.01$); and percentages of valid BP readings were higher (94 vs 72%; $p = 0.001$). The authors concluded that the oscillometric method was preferable in this group of patients. No other study has compared these two methods, but we have validated an oscillometric device in HD patients (SpaceLabs 90207) with favorable results *(66)*.

The effects of arteriovenous fistulas or grafts have not been systematically assessed. Nonetheless, in a validation protocol, we demonstrated that an oscillometric device performed equally well in patients with an arteriovenous graft/fistula as in patients with intact arms undergoing HD via a tunneled venous catheter *(66)*.

Fluctuations in volume status raise issues about the reproducibility of ABPM in HD patients. To address this question, we evaluated the reproducibility of ABPM compared with dialysis clinic BP in 21 HD patients evaluated on average 68 d apart *(67)*. As shown in Fig. 3, this study confirmed the wide BP variability in these patients. However, despite this shortcoming, ABPM had lower coefficients of variation and tighter limits of agreement than isolated clinic readings or a composite of readings from the week surrounding the monitoring period. We concluded that ABPM provides more reproducible BP values in HD patients. When unavailable, a composite of clinic readings are a suitable alternative (investigators have used averages of 1–4 wk), whereas isolated readings should not be used to make any management decisions *(68)*.

A last but important issue is the need to evaluate the entire interdialytic period and attendant BP fluctuations. This need is compromised by the fact that, in our experience, up to a third of patients are unable to complete a full 2-d monitoring period. Addressing this issue, Kyriazis et al. demonstrated that 3- and 4-h averages sampled from the daytime ABPM readings correlated well with the 24-h ABPM values (correlation coefficients between 0.8 and 0.91) *(69)*. These short period averages also correlated with LV mass comparably to ABPM and much better than isolated pre- or post-HD BP readings. Therefore, such an approach may be useful in some circumstances, although we would argue that this could be substituted by the less expensive use of home self-monitoring, which has been successfully employed in adults and children with ESRD *(70–72)*. Unfortunately, no studies have analyzed the prognostic value of home BP monitoring in CKD.

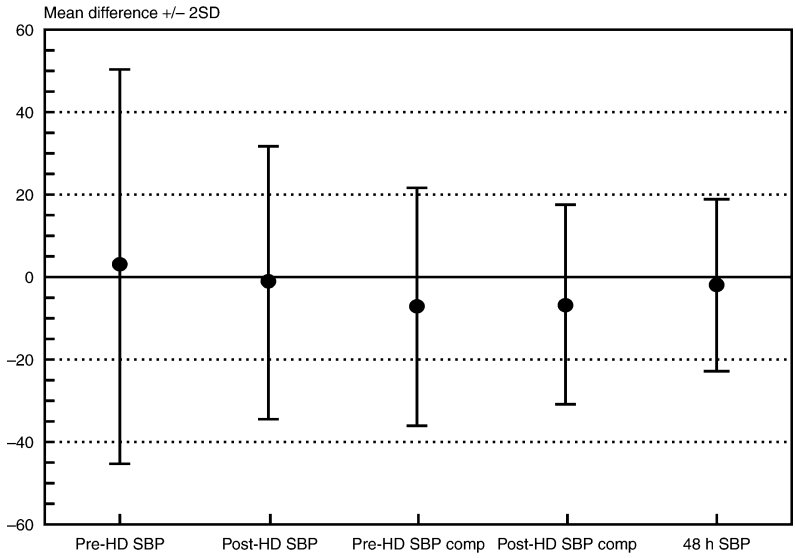

Fig. 3. Limits of agreement of systolic blood pressure measurements between two 44-h monitoring periods in hemodialysis patients. The lines and whiskers indicate the 95% limits of agreement (mean difference ± 2 SD). HD, hemodialysis; SBP, systolic blood pressure; comp, composite (average of five peri-dialysis readings surrounding each ambulatory blood pressure recording). (From ref. *67*.)

ABPM AFTER KIDNEY TRANSPLANTATION (CKD STAGE 5)

Up to 70% of transplant patients have HTN *(6)*. HTN is an independent risk factor for graft loss after renal transplantation after control for multiple covariates *(73)*, including baseline renal function *(74)*. Similar to other types of CKD, transplant patients have disparities between office and ambulatory BP *(75)*, especially in the presence of chronic allograft nephropathy *(76)*. The nondipping profile is often present in patients with a kidney transplant and occurs in all age groups *(75,77)*, although some have found a higher prevalence of normal dipping in patients with preserved renal function after 1 yr of transplantation (73%) compared to the early posttransplant period (27%) *(78)*.

To compare office and ambulatory BP values as predictors of renal outcomes after transplantation, Jacobi et al. followed 46 transplant patients (all from deceased donors) for 5 yr after two ABPM monitoring protocols at 6 and 18 mo posttransplant *(79)*. Ambulatory BP values,

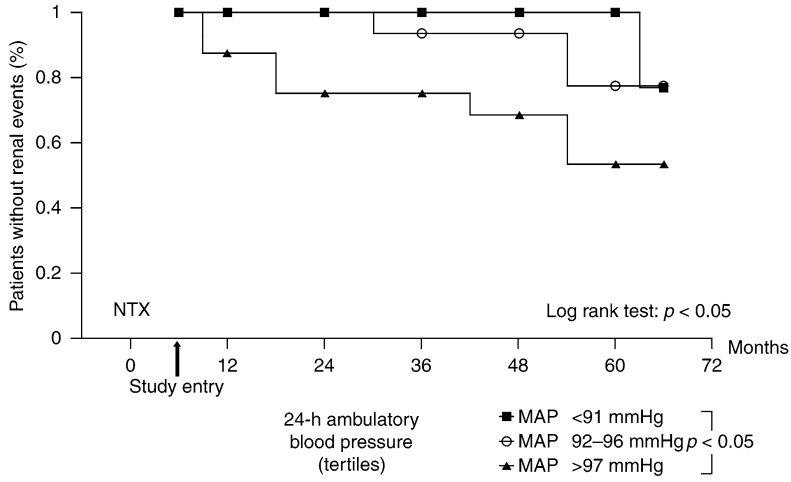

Fig. 4. Kaplan-Meier curve for patients without renal event stratified according to their 24-h ambulatory blood pressure and renal graft survival. NTX, transplantation; MAP, mean arterial pressure. (From ref. *79*.)

but not office BP, were positively correlated (r = 0.37 – 0.42) with serum creatinine values at 6 and 18 mo. When patients were stratified according to tertiles of diastolic BP, a significant difference was noted in serum creatinine levels for each tertile, and Kaplan-Meier curves for renal survival were significantly worse in the highest tertile of ambulatory BP (Fig. 4), even after adjustment for confounding variables. No such relationship was observed for office BP.

Haydar et al. evaluated the importance of the diurnal BP rhythm to predict renal dysfunction following transplantation in 177 kidney transplant recipients. In their analysis, the diurnal BP pattern (dipper, nondipper, or riser, for those whose BP increased during the nighttime) did not have any impact on measured serum creatinine levels *(80)*.

Prediction of target organ damage other than the allograft in renal transplant patients has been evaluated through LVH. In the most detailed report assessing sequential changes in ABPM and LVM over a 12-mo period, Ferreira et al. *(81)* demonstrated that LVM correlated better with ABPM than casual BP, and systolic BP load derived from ABPM was the only pressure component to predict LVM in a multiple regression model (although the model was overfitted). Other studies corroborate ABPM as a better correlate of LVH than clinic BP in transplantation *(82)*.

MECHANISTIC CONSIDERATIONS IN THE BLUNTED DIURNAL RHYTHM IN RENAL DISEASE

As previously discussed, nondipping is the prevailing BP profile in patients with CKD. The mechanisms responsible for abnormal circadian BP rhythms in CKD patients remain unclear. Possible mechanisms include volume overload *(13)*, autonomic dysfunction *(83)*, decreased physical activity *(84,85)*, sleep-disordered breathing *(86)*, or abnormalities in several hormonal and neuroendocrine mediators (catecholamines, renin, aldosterone, insulin, atrial natriuretic peptide, asymmetrical dimethylarginine, parathormone) *(23)*. Of these, the best documented factor affecting nighttime BP is the presence of sleep-disordered breathing, which is diagnosed in up to 70% of patients with stage 5 CKD *(87)*. Zoccali et al. showed that HD patients without episodes of nocturnal desaturation had a small decline in sleep BP (by 2.5%), whereas those with two or more desaturation episodes per hour had a reversal of the BP rhythm (sleep systolic BP increased by 3.9%) *(86)*. These observations are relevant because sleep-disordered breathing is associated with LVH in dialysis patients *(86,88)*. Although it is known that intensive dialysis corrects the sleep disorder *(87)*, there are no data linking correction of sleep apnea and normalization the BP profile in CKD, as has been demonstrated in patients without renal disease *(89,90)*. We are unaware of data on the impact of sleep-disordered breathing on BP in earlier stages of CKD.

The role of volume expansion also deserves mention *(13,77)*. In patients with essential HTN, a change from a high- to a low-sodium diet corrects nondipping in salt-sensitive subjects *(91,92)*. In addition, hydrochlorothiazide restores dipping in nondipper, but not in dipper hypertensive subjects *(93)*. Thus, it is possible that salt balance and salt sensitivity mediate dipping in hypertensive patients without renal disease. However, it is probable that this is not the case in advanced CKD, where multiple attempts to correlate interdialytic weight gain with degree of dipping have failed to show any significant correlation *(23,38)*. Furthermore, even patients on long-slow HD, who are characterized by excellent BP control *(51,94)* and less marked expansion of extracellular volume than patients on conventional HD *(95)*, are nondippers in 50–75% of cases *(96)*. Likewise, the transition from standard HD to short-daily HD leads to better BP control and decreased extracellular water, but no change in nocturnal dipping *(97)*.

A possible translation of ABPM to the care of hypertensive patients is the use of chronotherapy, where dosing schedules and/or drug delivery

Table 1
Applications of Ambulatory Blood Pressure Monitoring in Chronic Kidney Disease

Application	*Comment*
Evaluation of out-of-office BP	More accurate assessment of BP than office values. No outcome data available to justify use of ABPM as primary management tool.
Evaluation of nocturnal BP	Nondipping is the rule. Possible predictive value in patients with progressive renal failure. Limited reproducibility in ESRD.
Evaluation of interdialytic BP in hemodialysis patients	Most reproducible technique. May help define hypertension better.
Prediction of progression of renal disease	ABPM better than office BP in estimating rates of disease progression in chronic renal insufficiency and in renal transplantation.
Prediction of morbidity and mortality in renal disease LVH	ABPM better than office BP in chronic renal insufficiency. Inconclusive data in dialysis patients. Unclear role of nocturnal BP and nocturnal dip on prediction in renal patients.
Arterial stiffness	Nondippers have higher pulse wave velocity than dippers.
Mortality	Ambulatory pulse pressure and nocturnal systolic BP are strong predictors of mortality in small longitudinal study of hemodialysis patients.
Evaluation of therapeutic interventions	Evaluation of adequacy of therapy throughout the interdialytic period is possible and may allow for observed therapy thrice weekly in the dialysis unit with long-acting agents.

BP, blood pressure; ABPM, ambulatory blood pressure monitoring; ESRD, end-stage renal disease; LVH, left ventricular hypertrophy.

From ref. *24*.

systems are manipulated to mimic the normal circadian BP changes and to minimize the early morning BP rise. Indeed, nondipping can be improved or corrected in patients with CKD *(98)*. Unfortunately, there is no evidence to date that such an approach leads to better outcomes.

CONCLUSIONS

The applications of ABPM in clinical nephrology (patients at risk for developing kidney disease, CKD, HD, peritoneal dialysis, and kidney transplantation) are summarized in Table 1. ABPM allows better understanding of BP behavior, is more reproducible than office BP, and may be a better marker of renal and cardiovascular prognosis in CKD, although several issues remain unresolved, thereby limiting the extent of any recommendations for more extensive use of ABPM in the routine care of CKD patients.

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IV Ambulatory Blood Pressure Monitoring and Therapy

17 Chronobiology and Chronopharmacology of Hypertension

Importance of Timing of Dosing

Björn Lemmer, MD

Contents

INTRODUCTION

Heart rate was one of the earliest physiological functions reported not to be constant throughout the 24-h day (*see* refs. *1* and *2*). As early as at the beginning of the 17th century, daily variations in pulse rate, as well as a rapid increase on awakening, were described *(3)*. In the 18th and 19th centuries, general observations as well as detailed data on daily variations in pulse rate and pulse quality were reported *(4–13)*. The pulse of a healthy subject as determined in the late afternoon was even proposed as an easily available "metronome" to be used by musicians (Fig. 1) *(14)*. The metronome itself was not invented until 1816 by Mälzel.

The development of the pulse-watch by Floyer *(15)* and the introduction of a "third hand" into the clock to precisely measure the seconds made it possible to determine changes in the pulse rate *(16)*. It is of interest to note that the symptoms of office hypertension, or white-coat

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"What I found to be an appropriate timegiver for the tempo .... is the pulse at the hand of a healthy man."

"One should take the pulse of a merry and good tempered man ... as it is after lunch until evening and the tempo will be fine."

Fig. 1. From Johann Joachim Quantz, "Versuch einer Anweisung die Flöte traversière zu spielen" (*14*; translated by BL).

hypertension—nowadays of increasing medical importance *(17–20)*—was precisely described more than 300 yr ago independently by several authors (*21–23*; *see also* ref. *24*).

Hellwig proposed that the doctor sit down and talk to the patient for a while before examining the quality of the pulse once or several times *(22)*, a recommendation reflecting our modern guidelines for measuring the blood pressure. Soon thereafter Théophile de Bordeu, a professor at the University of Montpellier, named the same observation "le pouls du médicin" *(23)* (*see* Fig. 2).

In the 17th century, when watches showing minutes were not yet available, it was difficult to measure a patient's pulse rate exactly. To overcome this diagnostic deficiency, Sanctorius Sanctorius, professor of medicine at the University of Padua, invented in 1631 the "pulsilogium," with which he was able to record the pulse rate present at different stages of a disease or at different times of the day *(25)* (Fig. 3).

When plethysmographic devices became available (e.g., refs. *26–28*) it was also noted that blood pressures in healthy and in diseased persons were not the same throughout 24 h *(27,29–37)*. Zadek *(27)* was the first to present detailed data on daily variations (*Tagesschwankungen*) in blood pressure, with an increase in the afternoon and a drop at night. At the beginning of the 20th century different types of hypertension were verified by their different blood pressure profiles *(35–37)*.

Very early reports described the nightly occurrence of symptoms and/or the onset of angina pectoris attacks and myocardial infarction *(16,38)* (*see also* Chapter 11). In light of these observations it is not surprising that more than 200 yr ago, in 1796, Reil recommended that "the time of day of drug application and the dose must be in harmony with each other" *(7)*.

Joachim Targiri (1698)

"Most of all one has to have an experienced knowledge to study the pulse of the artery, the movement of which can be manifold increased, decreased, and disturbed by internal causes and external conditions. Even catching sight of the doctor and the doctor's stepping in may not be of minor importance,.....because this, indeed, can induce changes in the movement of the pulse."

Christoph Hellwig (1738)

"It is important to note that the patient's puls may change remarkably...most commenly this is caused by the advent of the doctor".

Théophile de Bordeu (1756)

"In order to estimate the quality of the pulse it is neccessary to feel the pulse several times; it is an exception that the presence of the doctor does not lead occasionally to some changes which may *elevate* or *increase* it: the practitioners never forget to keep in mind the pulse which they call the *pulse of the doctor*."

Fig. 2. Early reports on the symptoms of white-coat hypertension (*italics* in the original text) (all translations by BL).

CHRONOBIOLOGY OF THE CARDIOVASCULAR SYSTEM

In recent years numerous more sophisticated studies have provided convincing evidence for circadian rhythms in cardiovascular function both in healthy subjects and in patients suffering from cardiovascular disease (for review, *see* refs. *39–47*). Although the rhythms in heart rate and blood pressure are the best-known periodic functions in the cardiovascular system, other parameters have been shown to exhibit circadian variations as well, e.g., stroke volume, cardiac output, blood flow, peripheral resistance, parameters of electrocardiogram recordings, in the plasma concentrations of pressor hormones such as noradrenaline,

"In order to get good and rapid information I have invented a pulse measuring device (pulsilogium) with which I can precisely measure, observe and commemorate the beats and the rest of the arteries in comparison to those of earlier days."
"The pulsilogium tells us at what day and a what hour of the day the pulse of the patient varies from the natural state."

Fig. 3. Description of the "pulsilogium" by Sanctorius *(25*; translated by BL).

renin, angiotensin, and aldosterone, in atrial natriuretic hormone and plasma cAMP concentration (higher during the day than at night), in blood viscosity, aggregability and fibrinolytic activity, and so on. Also, the vasodilating system of nitric oxide (NO) is circadian phase-dependent, with higher excretion rates of NO during the daytime than at night; in addition, young females have higher values than age-matched males *(48)*, indicating a greater buffering capacity in blood pressure regulation in females. Figure 4 shows a simplified scheme of the physiological parameters involved in the regulation of the blood pressure.

In recent years the development of easy-to-use devices to continuously monitor blood pressure and heart rate in humans by ambulatory blood pressure monitoring (ABPM) devices demonstrated not only that the blood pressure levels in normotensive and hypertensive patients are clearly dependent on the time of day (Fig. 5), but also that drugs can affect the blood pressure rhythm differently, depending on the circadian time of drug dosing. There is no doubt about the usefulness of ABPM in assessing antihypertensive treatment and in testing for clinical relevance (*see* refs. *49,50*). In Fig. 6, a representative example is given of ABPM in a hypertensive patient in whom high drug dosing at night resulted in a "superdipping" profile (systolic/diastolic values of 65/30 mmHg) accompanied by angina attacks at late night hours (unpublished). This again demonstrates the usefulness of ABPM in controlling drug treatment *(51,52)*.

Moreover, different forms of hypertension can exhibit different circadian patterns: in normotension as well as in primary hypertension, there is in general a nightly drop in blood pressure; such patients are termed "dippers" (Fig. 5), whereas in secondary hypertension resulting from renal disease, gestation, Cushing's disease, diabetes mellitus, and so on,

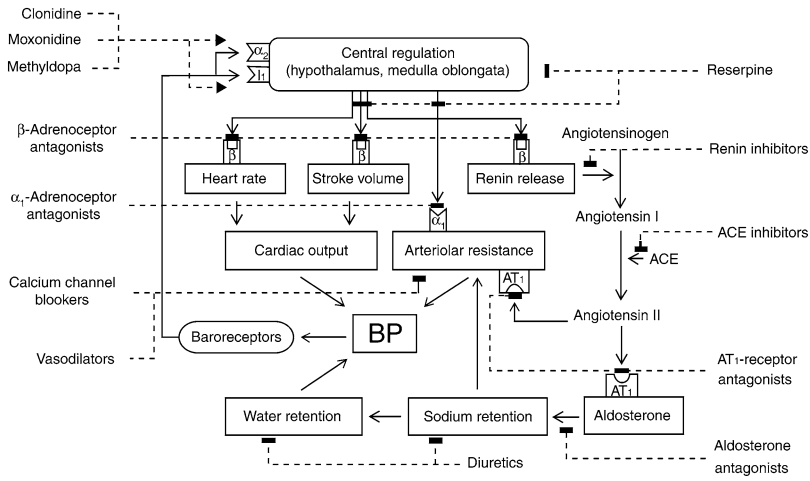

Fig. 4. Simplified scheme of the mechanisms involved in the regulation of blood pressure (BP) and the main target mechanisms by which drugs lower BP.

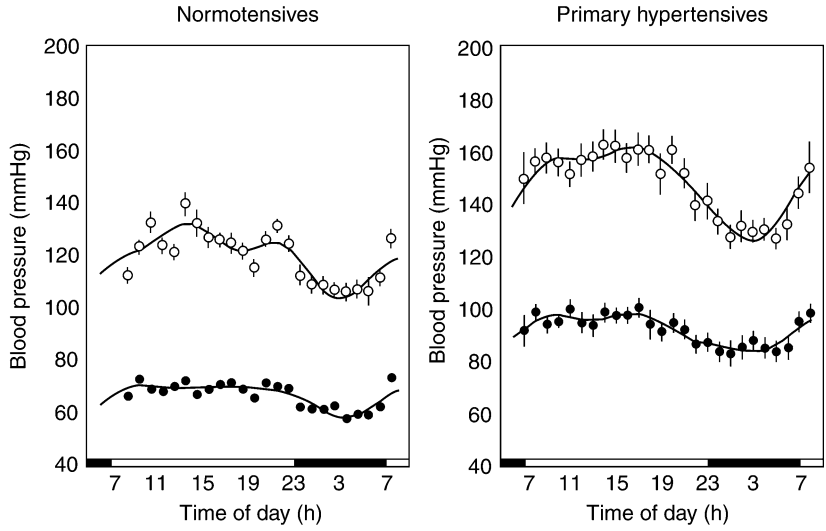

Fig. 5. Twenty-four-hour profiles of systolic and diastolic blood pressures in normotensives and in primary hypertensive patients as determined by ambulatory blood pressure recording; shown are mean hourly data ± SEM of 12–17 subjects *(59)*. Solid lines represent nonlinear fitting of partial Fourier series to the ABPM data *(108)*.

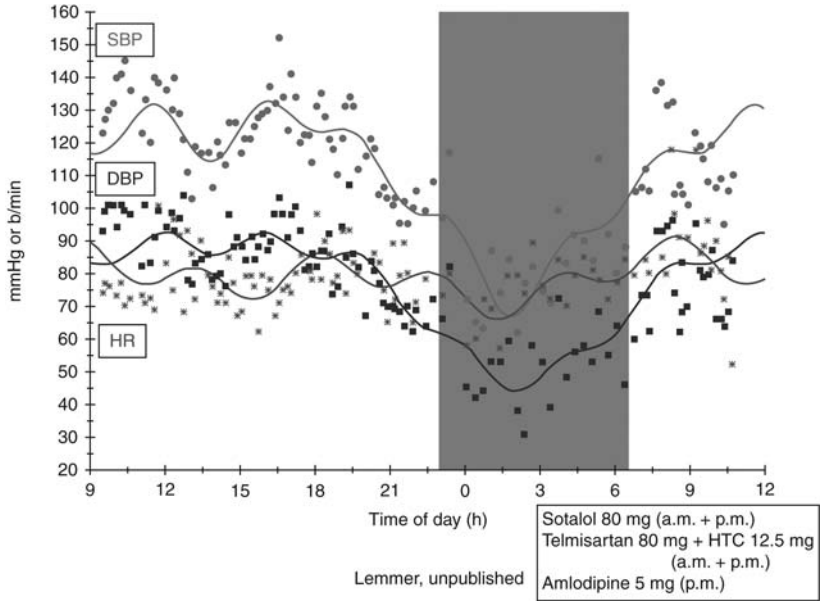

Fig. 6. ABPM profile in a hypertensive patient on high antihypertensive drug treatment at night leading to superdipping and angina attacks late at night; solid lines represent nonlinear fitting of partial Fourier series to the data *(52)*.

the rhythm in blood pressure is in about 70% of the cases abolished or even reversed, with the highest values at night; such patients are termed "nondippers" *(47,53–56)*. This is of particular interest because the loss of nocturnal blood pressure fall (nondipping) correlates with increased end-organ damage in cardiac, cerebral, vascular, and renal tissues; no doubt: nocturnal hypertension is a risk factor *(57)*.

CLINICAL CHRONOPHARMACOLOGY OF HYPERTENSION

Chronopharmacodynamics

Drug treament of hypertension includes various types of drugs such as diuretics, β- and α-adrenoceptor blocking drugs, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, AT1-receptor blockers, and others, which differ in their sites of action, as depicted in Fig. 4. Because the main steps in the mechanisms regulating the blood pressure (Fig. 4) are circadian phase dependent, it is not surprising to

note that antihypertensive drugs may display a circadian time dependency in their effects and/or their pharmacokinetics as well *(58–60)*.

Moreover, the different groups of antihypertensive drugs as well as the various compounds within one group of antihypertensives differ in pharmacokinetic half-life, galenic formulation, duration of drug effect, and, thus, in dosing interval. However, despite the great number of studies published in evaluating antihypertensive drug efficacy, the time of day of drug application was only rarely a specific point of investigation.

β-Adrenoceptor Blocking Drugs

Unfortunately, in hypertensive patients no crossover (morning vs evening) study with β-adrenoceptor antagonists has been published. From the studies performed without time-specified drug dosing, however, it is difficult to draw definite conclusions as to the importance of the circadian time of drug dosing for the antihypertensive drug efficacy. A resume of 20 "conventionally" performed studies *(61)* showed that β-adrenoceptor antagonists—β_1-selective, nonselective, or with intrinsic sympathomimetic activity—do not affect or reduce the rhythmic pattern in blood pressure. In general, however, there is a tendency for β-adrenoceptor antagonists to reduce daytime blood pressure levels and not to greatly affect nighttime values, being less/not effective in reducing the early morning rise in blood pressure *(47,61)*. Consistently, decreases in heart rate by β-adrenoceptor antagonists are more pronounced during daytime hours. Similarly, in healthy subjects a fourfold crossover study with propranolol showed a more pronounced decrease in heart rate and blood pressure during daytime hours than at night *(62)* (Table 1). Moreover, this study shows that the dose–response relationship can also be circadian phase dependent. Interestingly, the agent with partial agonist activity, pindolol, even increased heart rate at night *(63)*.

Thus, clinical data indicate that β-adrenoceptor-mediated regulation of blood pressure dominates during daytime hours and is of less or minor importance during the night and the early morning hours. This correlates well with the circadian rhythm in sympathetic tone, as indicated by the rhythm in plasma noradrenaline and cAMP *(48,64,65)*.

Calcium Channel Blockers

The effects of calcium channel blockers were also analyzed, mainly by visual inspection of the blood pressure profiles (for review, *see* ref. *47*). In primary hypertensives, t.i.d. dosing of nonretarded verapamil did not greatly change the blood pressure profile, being, however, less effective at night *(66)*. A single morning dose of a sustained-release

Table 1
Chronopharmacology of Propranolol After Oral Dosing of 80 mg of (±)-Propranolol in Four Healthy Subjects Applied in a Crossover Design at Four Different Circadian Times

	Time of (±)-propranolol (80 mg p.o.) application			
	8 AM	*2 PM*	*8 PM*	*2 AM*
Pharmacokinetics				
C_{max} (ng/mL)	38.6 ± 11.2	20.0 ± 6.5	26.2 ± 5.3	18.4 ± 4.4[a]
t_{max} (h)	2.5 ± 0.5	3.5 ± 0.5	3.0 ± 0.6	3.5 ± 1.0
AUC (ng/mL·h)	169 ± 47	106 ± 30	140 ± 23	92 ± 22
$t_{1/2}$ β (h)	3.3 ± 0.4	4.2 ± 0.5	4.9 ± 0.2	4.4 ± 0.6[b]
C_{max}/t_{max} (ng/mL/h)	17.9 ± 6.4	7.5 ± 3.9	10.6 ± 3.7	7.1 ± 2.4[a]
Hemodynamics (heart rate)				
E_{max} (b/min)	16.0 ± 2.4	11.7 ± 1.8	16.3 ± 1.5	15.3 ± 4.6
t_{max} (h)	2.3 ± 0.6	4.5 ± 1.0	6.5 ± 1.5	7.0 ± 1.0[a]

Shown are the pharmacokinetics of (–)-propranolol and the effects on heart rate (E_{max} = peak effect; t_{max} = time to peak effect) in comparison to the circadian control values. ANOVA: [a]$p < 0.05$; [b]$p < 0.01$.

Data from ref. *62*.

verapamil showed good 24-h blood pressure control *(67)*, whereas a sustained-release formulation of diltiazem was less effective at night *(68)*. Dihydropyridine derivatives, differing in pharmacokinetics, seem to reduce blood pressure to a varying degree during the day and night; drug formulation and dosing interval may play an additional role (*see* ref. *47*).

Twelve studies using a crossover design have been published *(69–79)* (Table 2). In essential hypertensives (dippers), amlodipine, sustained-release isradipine and lacidipine, nifedipine GITS, and nisoldipine ER and in normotensives immediate-release nifedipine did not differently affect the 24-h blood pressure profile after once-morning or once-evening dosing, with nitrendipine the profile remained either unaffected or slightly changed after evening dosing (Table 2). In primary hypertensive patients, twice-daily nifedipine also lowered the blood pressure throughout a 24-h period *(74)*. Most interestingly, the greatly disturbed blood pressure profile in secondary hypertensives (nondippers) because of renal failure was only normalized after evening but not after morning dosing of isradipine *(71)*, whereas amlodipine and nisoldipine

Table 2
Effects of Calcium Channel Blockers on 24-h Pattern in Blood Pressure[a]

	Dose		*Effect on 24-h blood pressure*				
Drug	*mg/d*	*Duration/dosing time*	*Patients* (n)	*Day*	*Night*	*24-h profile*	*Ref.*
Primary hypertension (dippers)							
Amlodipine	5	4 wk/	20				*69*
		AM		++	++	Preserved	
		PM		++	++	Preserved	
Amlodipine	5	3 wk/	12				*75*
		8 AM		+	+	Preserved	
		8 PM		+	+	Preserved	
Isradipine	5	4 wk/	18				*70*
		7 AM		++	++	Preserved	
		7 PM		++	++	Preserved	
Lacidipine	4	6 wk/	33				*78*
		Morning		++	+	Preserved	
		Evening		+	+–++	Preserved?	
Nifedipine GITS	30	1 or 2 wk/	10				*72*
		10 AM		++	++	Preserved	
		10 PM		++	++	Preserved	
Nisoldipine ER	20	4 wk/39					*79*
		7–9 AM		++	+(+)	Preserved	
		9–11 PM		++	++	Preserved	

(Continued)

Table 2 ***(Continued)***

Drug	*Dose*		*Effect on 24-h blood pressure*				
	mg/d	*Duration/dosing time*	*Patients* (n)	*Day*	*Night*	*24-h profile*	*Ref.*
Nitrendipine	20	4 wk/	41				*77*
		7 AM		+	+	Preserved	
		7 PM		+	+	Preserved	
Nitrendipine	10	3 d/	6				*76*
		6 AM		++	++	Preserved	
		6 PM		+	++	Changed	
Secondary hypertension (nondippers)							
Amlodipine	5	3 wk/	39				*73*
		8 AM		+	++	Normalized	
		8 PM		+	++	Normalized	
Isradipine	5	4 wk/	16				*71*
		8 AM		++	++	Not normalized	
		8 PM		+	+++	Normalized	
Nisoldipine ER	20	4 wk/	36				*79*
		7–9 AM		++	+++	Normalized	
		9–11 PM		++	+++	Normalized	
Normotension							
Nifedipine i.r.	10	Single dose/	12				*74*
		8 AM		+	++	Preserved	
		7 PM		+	+	Preserved	

[a]The table includes only data from crossover studies in essential (primary) and secondary hypertensives and in normotensives.

ER normalized the disturbed blood pressure profile in nondippers after both morning and evening dosing *(73,79)* (Table 2).

These studies clearly demonstrate that calcium channel blockers (1) lower the elevated blood pressure both in nondippers and in dippers without distorting the normal blood pressure profile of the latters or leading to superdipping and (2) are able to transform the nondipping behavior into a dipping one; evening dosing could be preferable.

ACE Inhibitors

Six crossover studies (morning vs evening dosing) with ACE inhibitors in essential hypertensive patients have been published (Table 3). They demonstrate that in dippers evening dosing of benazepril, enalapril, and perindopril resulted in a more pronounced nightly drop than morning dosing, shifting the blood pressure profile to a superdipping behavior *(80–82)*. Evening dosing of quinapril also resulted in a more pronounced effect than morning dosing; the BP pattern, however, was not greatly modified *(83)*. Ramipril had no obvious effect on the 24-h blood pressure profile after either dosing time *(84)*. In light of a reduced cardiac reserve of patients with hypertension at risk, a too pronounced nightly drop in BP (superdipping) after evening dosing might be a potential risk factor for the occurrence of ischemic events (*see* ref. *47*).

Diuretics and Other Antihypertensive Drugs

Antihypertensives of other classes have rarely been studied in relation to possible circadian variation. Once-daily morning dosing of the diuretics xipamide *(85)* and indapamide *(86)* reduced BP in essential hypertensives without changing the 24-h BP pattern. An interesting study was performed with diuretics in salt-sensitive hypertensive patients (dippers and nondippers): Uzu and Kimura *(87)* demonstrated that diuretics did not affect the circadian blood pressure profile in dippers but transformed the nondippers into dippers.

On twice-daily dosing the α-adrenoceptor antagonists indoramin *(88)* and prazosin *(89)* also did not change the BP profile. A single nightime dose of the α-adrenoceptor antagonist doxazosin reduced both systolic and diastolic BP throughout the day and night, but the greatest reduction occurred in the morning hours *(90)*. A recent study in dippers with a monotherapy of a retard formulation of doxazosin, doxazosin-GITS, showed a mild but significant lowering of the blood pressure throughout 24 h without disturbing the normal blood pressure profile *(91)*. Because α-adrenoceptor blockade more effectively reduced the peripheral

Table 3
Effects of ACE Inhibitors on 24-h Blood Pressure Pattern

	Dose		*Effect on 24-h blood pressure*				
Drug	*mg/d*	*Duration/dosing time*	*Patients* (n)	*Day*	*Night*	*24-h profile*	*Ref.*
Benazepril	10	Single dose/	10				*80*
		9 AM		+++	++	Preserved	
		9 PM		+	++	Changed	
Enalapril	10	Single dose/	10				*81*
		7 AM		++	+	Preserved	
		7 PM		++	+++	Changed	
Enalapril	10	3 wk/	10				*81*
		7 AM		++	+	Preserved	
		7 PM		+	++	Changed	
Perindopril	2	4 wk/	18				*82*
		9 AM		++	+	Preserved	
		9 PM		+	++	Changed	
Quinapril	20	4 wk/	18				*83*
		8 AM		++	+	Preserved	
		10 PM		++	++	Preserved	
Ramipril	2.5	4 wk/	33				*84*
		8 AM		+	(+)	Preserved	
		8 PM		(+)	+	Preserved	

The table includes only data from crossover studies in primary (essential) hypertensives with dipping behavior.

resistance during the early morning hours than at others times of the day *(92)*, these findings point to the importance of α-adrenoceptor mediated regulation of BP during the early morning hours. In addition, peak treatment effect after nigthtime dosing of doxazosin occcurred later than predicted from the drug's pharmacokinetics *(90)*, an observation that supports similar findings on circadian phase dependency in the dose–response relationship of nifedipine *(74)*, enalapril *(81)*, and propranolol *(62)*.

Chronopharmacokinetics

There is good evidence that the kinetics of cardiovascular active drugs may also be dependent on the time of day (for review, *see* refs. *39,102–105*). Our own studies have shown that cardiovascular active compounds such as propranolol (*see also* Table 1), oral nitrates, and the calcium channel blocker nifedipine showed higher peak drug concentrations [C_{max}] and/or a shorter time-to-peak concentration [t_{max}] after morning than evening oral drug dosing, at least when nonretarded formulations were used (Table 4). In the case of retard formulation of IS-5-MN and nifedipine, however, no circadian phase dependency in their pharmacokinetics was found (Table 4). There was also no circadian time dependency in the kinetics of sustained-release molsidomine *(106)* or in the kinetics of the hydrophilic β-blocker atenolol *(107)*.

Concerning the underlying mechanisms responsible for the chronokinetic behavior of these lipophilic compounds, a faster gastric emptying time in the morning *(108)* and—more important—higher gastrointestinal perfusion in the morning than in the evening are assumed to be involved *(109)*.

Duration of the Antihypertensive Effect

ABPM has also been widely used to evaluate the duration of drug action. In general, ABPM is performed for a single 24-h span. However, the restriction of ABPM to 24 h may cause potential pitfalls, as can be demonstrated from several studies *(110)*. *A* 4-wk treatment of hypertensive patients with the β_1-selective adrenoceptor blocking drug bisoprolol showed that the duration persisted up to 48 h after cessation of therapy *(111)*. Similarly, after chronic morning dosing of the β-adrenoceptor blocking drug atenolol, the BP-lowering effect was no longer observed 20–24 h after the last dose (Fig. 7). However, ABPM being continued for 48 h revealed that the reduction in BP was observed again on the next day off therapy *(112)* (Fig. 7).

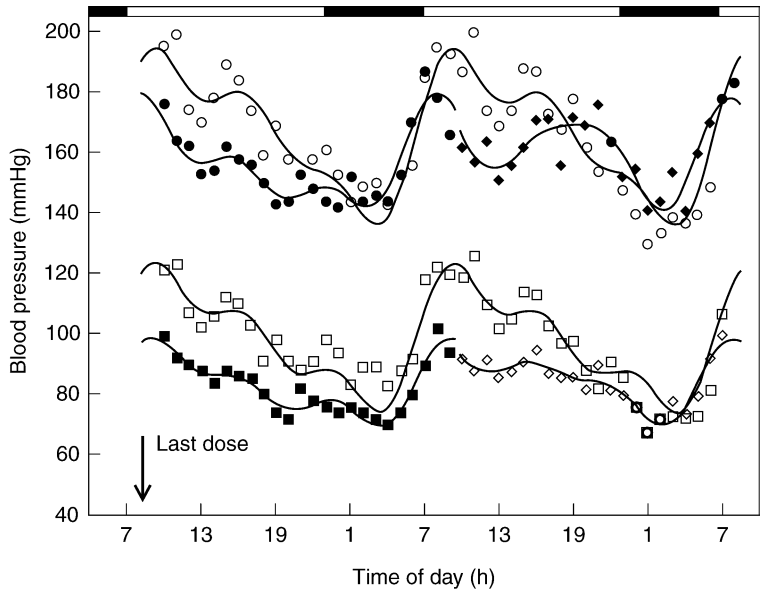

Fig. 7. Circadian blood pressure profile of hypertensive patients before (filled circles) and after once-a-day treatment with atenolol (100 mg/d) for 6 wk (open circles); 48-h ambulatory blood pressure data after last dose. Note the convergence of blood pressure data curves at night and separation again during day 2. Data from ref. *112* were submitted to a nonlinear rhythm analysis by ABPM-FIT *(51)* and redrawn accordingly *(60)*.

Similar findings were reported after 3-wk once-a-day morning or once-a-day evening administration of the ACE inhibitor enalapril when the BP profile was monitored for 48 h after the last dose *(81)* (Fig. 8). Conversely, the duration of the antihypertensive effect of a 3-wk treatment with a sustained-release preparation of diltiazem was restricted to about 18 h when the BP was monitored by ABPM for 48 h after the last dose *(68)*.

These data show that the conventional method to estimate the duration of an antihypertensive effect by the peak-to-trough ratio within 24 h can be misleading. The peak-to-trough ratio does not take into account the fact that regulatory mechanisms of blood pressure rhythm predominate at certain times of day and are of minor importance at other times (*see* refs. *45,58*). β-Adrenergic tone, for example, is higher during the daytime activity phase than at night; β-adrenoceptor blockers are therefore less active at night. Panza et al. *(92)* showed that the vascular tone is higher in the morning and decreases thereafter, leading

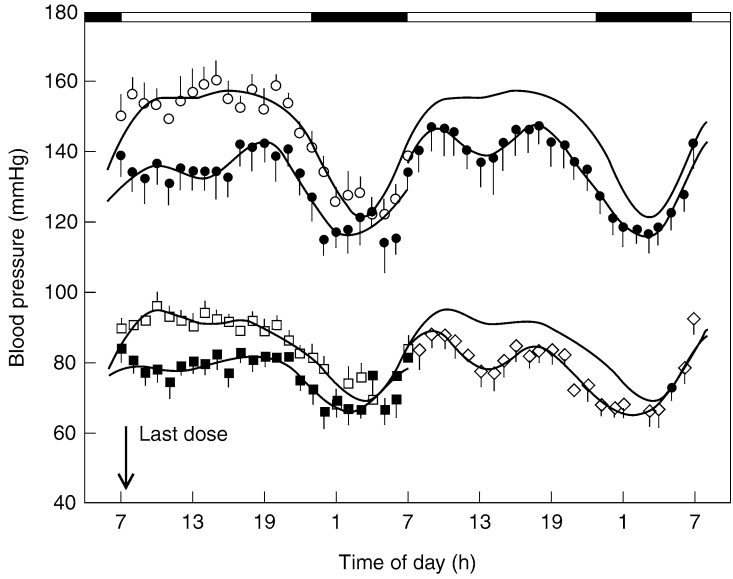

Fig. 8. Circadian blood pressure profile of hypertensive patients before (filled circles) and after once-a-day morning treatment with enalapril (10 mg/d) for 3 wk (open circles); 48-h ambulatory blood pressure data after last dose. Note that the antihypertensive effect reappears again on the second day off therapy. Solid lines represent nonlinear fitting of partial Fourier series to the ABPM data *(51)* (data from ref. *81*).

to a more pronounced reduction of the peripheral resistance by the α-adrenoceptor-blocking drug phentolamine in the morning than at other times of day. As a consequence, it may be worthwhile to not restrict ABPM to a 24-h period in order to avoid false-conclusions about the duration of action of an antihypertensive drug.

CONCLUSION

Various functions of the cardiovascular system, including blood pressure and heart rate, are well organized in time *(43,45,47,60)*. There is also good evidence that a disease is able to disturb, reverse, or even destroy a rhythmic pattern. In the rat the rhythms of systolic and diastolic blood pressures are mainly endogenous in nature, i.e., driven by an internal pacemaker *(113–115)*. In humans there are only indirect data supporting the involvement of an endogenous pacemaker in blood pressure rhythm and—even more evident—in heart rate rhythm as

Table 4
Pharmacokinetic Parameters of Cardiovascular Active Drugs Determined in Crossover Studies

		C_{max} (ng/mL)		t_{max} (h)		
Drug	*Dose (mg)/duration*	*Morning*	*Evening*	*Morning*	*Evening*	*Ref.*
Digoxin	0.5, sd	3.6[a]	1.8	1.2	3.2	*119*
Enalaprilat						
after Enalapril	10, sd	33.8	41.9	4.4	4.5	*81*
after Enalapril	10, 3 wk	46.7	53.5	3.5[a]	5.6	
IS-5-MN i.r.	60, sd	1605.0	1588.0	0.9[a]	2.1	*120,121*
IS-5-MN s.r.	60, sd	509.0	530.0	5.2	4.9	*74*
Molsidomine	8, sd	27.0	23.5	1.7	1.9	*106*
Nifedipine i.r.	10, sd	82.0[a]	45.7	0.4[a]	0.6	*74*
Nifedipine s.r.	2 × 20, 1 wk	48.5	50.1	2.3	2.8	*74,122*
Atenolol	50, sd	440.0	391.8	3.2	4.0	*123*
Oxprenolol[b]	80, sd	507.0	375.0	1.0	1.1	*124*
Propranolol[c]	80, sd	38.6[a]	26.2	2.5	3.0	*62*
Propranolol (±)	80, sd	68	60	2.3	2.7	*125*
Verapamil s.r.	360, 2 wk	389.0	386.0	7.2[a]	10.6	*126*
Verapamil	80, sd	59.4[a]	25.6	1.3	2.0	*127*

At least two dosing times (around 6–8 AM and 8 AM to 7 PM) were studied; in some studies up to six circadian times were included. Only the parameters C_{max} = peak drug concentration and t_{max} = time to C_{max} are given. sd, single dose; i.r., immediate-release preparation; s.r., sustained-release preparation.

[a] p morning vs evening at least <0.05.

[b] Significant difference in half-life.

[c] (±)-propranolol was given; kinetic data for (–)-propranolol.

derived from transmeridian flights *(116,117)* and from studies performed under unmasking conditions under constant routine *(118)*.

Moreover, it has been shown that different cardiovascular active compounds, such as propranolol, oral nitrates, and the calcium channel blockers nifedipine and verapamil, display higher peak drug concentrations (C_{max}) and/or a shorter time to peak concentration (t_{max}) after oral morning than evening drug dosing, at least when nonretarded formulations were used. In the case of a sustained-release formulation of IS-5-MN and nifedipine and of molsidomine, no circadian phase dependency in their pharmacokinetics were found (Table 4).

The cardiovascular active drugs mentioned are in general absorbed by passive diffusion; the underlying mechanisms responsible for their chronokinetics can be explained by a faster gastric emptying time in the morning *(108)* and—more important—by higher gastrointestinal perfusion in the morning *(109)*, resulting in higher C_{max} and/or shorter t_{max} in the morning than in the evening.

There is evidence that in hypertensive dippers, antihypertensive drugs should be given during early morning hours, whereas in nondippers it may be necessary to add an evening dose or even to administer a single evening dose in order not only to reduce high blood pressure, but also to normalize a disturbed 24-h blood pressure profile which (documented, however, only for two calcium channel blockers). Because the pharmacokinetics of cardiovascular active drugs can be circadian phase dependent as well, the galenic formulation and/or the indiginous half-life of a drug has to be considered in order to come to a final recommendation concerning the most appropriate dosing time within 24 h.

Recent studies clearly demonstrate that the effects as well as the kinetics of cardiovascular active drugs can be dependent on the circadian phase, i.e., time of day or circadian time of drug dosing. However, daily variation in the kinetics seems to be of minor importance to the degree of circadian-time-dependent effects of the compounds. Nevertheless, the data published in respect to time of day and the efficacy of cardiovascular active drugs clearly demonstrate that the dose–response relationship can be circadian phase dependent.

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18 Advances in Ambulatory Blood Pressure Monitoring for the Evaluation of Antihypertensive Therapy

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CONTENTS

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INTRODUCTION

Over the past decade there has been a marked increase in the utilization of 24-h ambulatory blood pressure (BP) monitoring to assess new drugs for hypertension, beginning with the first and second phases of drug development (studies that establish the range of doses in patients with hypertension), continuing to the fourth phase, in which the drugs approved for the marketplace are tested in comparison to other registered drugs or in a special population, such as the elderly or diabetic patient with hypertension.

Several specific attributes have made ambulatory monitoring of BP important in clinical trials involving the assessment of antihypertensive drug therapy *(1–4)*. Some of these benefits include removal of observer bias or error *(5)*, better short- and long-term BP reproducibility *(6,7)*, elimination of the white-coat effect during patient selection *(8,9)*, and the ability to assess the effects of therapy on diurnal and nocturnal BP variability *(10)*. Furthermore, recent data have demonstrated that ambulatory BP is a superior predictor of hemodynamic abnormalities in the hypertensive patient *(11)*, hypertensive target organ involvement *(12,13)*, and prognostic outcomes, including myocardial infarction, stroke, and other types of cardiovascular morbidity *(14–18)*.

In this chapter, an overview of the utility of ambulatory BP monitoring in clinical pharmacology research will be provided with several examples using data from randomized, controlled, or comparator trials. Furthermore, examples that show the utility of ambulatory monitoring for the assessment of treated patients in clinical practice will also be discussed.

IMPACT OF BLOOD PRESSURE VARIABILITY ON THE REPRODUCIBILITY OF OFFICE VS AMBULATORY BLOOD PRESSURE AS IT RELATES TO DRUG DEVELOPMENT

The typical reduction in systolic or diastolic BP observed in a clinical trial of an antihypertensive drug (generally in the range of 5 to 20%) must be viewed in light of the magnitude of the relatively large variability of office BP from one visit to the next (12–18%). Studies that have examined the repeatability of office and ambulatory BP in patients with hypertension have consistently demonstrated much less variance with ambulatory BP *(7,19)*. Many years ago, Conway et al. *(19)* recorded the diastolic BP of 75 hypertensive subjects on two occasions, 1 mo apart, while they were being administered a placebo.

Table 1
Reproducibility of Clinic and Ambulatory Blood Pressure Studies Separated by Up to 2 yr in Patients With Hypertension

Blood pressure measure	*Diastolic*	*Systolic*	R-*value*	*SDD CV*	R-*value*	*SDD CV*
Office	0.48	17.0	11.0	0.31	10.0	10.0
24-h mean	0.87[a]	9.8[a]	7.0	0.90[a]	4.7[a]	5.6
Awake	0.86[a]	10.7[a]	7.4	0.88[a]	5.8[a]	6.5
Sleep	0.92[a]	7.7	6.3	0.88[a]	5.2	7.1

R-value, correlation coefficient; SDD, standard deviation of the differences; CV, coefficient of variation.

[a]Significantly different from the office blood pressure correlation coefficients, SDD, and CV.

From ref. *7*.

With clinic measurements, the mean difference in diastolic BP was 1.7 mmHg and the standard deviation of this difference was 12.3 mmHg. In contrast, the daytime ambulatory BP fell by 0.9 mmHg and the standard deviation of the difference was halved to 6.3 mmHg. The implications of this marked reduction in BP variability with ambulatory BP recordings compared to the clinic pressure is that it will double the precision of a short-term trial and allow as much as a fourfold reduction in the number of patients required to achieve an accurate result.

Similarly, the long-term reproducibility of ambulatory BP is also superior to office BP *(7)*. In patients for whom there was nearly 2 yr between visits (hypertensives studied under the same therapeutic and environmental conditions on two different occasions), the standard deviation of the differences was significantly lower and the correlation coefficients significantly higher for ambulatory BP than for office BP (Table 1). The improved reproducibility of ambulatory over office BP continued to be present when the data were divided into awake and sleep periods. These data suggest that clinical trials involving ambulatory BP over long periods would also require smaller sample sizes than similarly designed trials in which the statistical power is based on the ability to show changes in a more highly variable clinic BP.

In contrast, there may be little advantage of ambulatory BP over clinic pressure in clinical trials when the measure of interest is a small block of time, such as 1 or 2 h. In an evaluation of a group of hypertensives using both noninvasive and intraarterial BP over 24 h, Mancia et al. *(20)*

showed that the standard deviation of the differences for 24-h mean BP values was similar for the two methodologies. However, despite the much larger number of BP values obtained in an intraarterial study, the hourly BP reproducibility was no different for the direct measurements than it was for noninvasive BP monitoring. Thus, unlike the larger blocks of time (e.g., 24 h, the awake period, or the sleep period), the reproducibility of hourly ambulatory BP data has not been shown to be superior to that of office BP measurements *(20)*. Hence, ambulatory BP recordings will not allow a reduction in sample sizes if the end point is for short periods of time. This increased variability in hourly BP levels is probably secondary to differences in the activities of patients monitored on two different days. Because controlling for hourly physical and mental activities is nearly impossible in free-ranging subjects, longer periods of time (e.g., 4 h) will remain statistically and practically appropriate for clinical trials involving ambulatory BP monitoring.

The benefits of ambulatory monitoring of the BP over clinic BP with regard to sample size requirements in clinical trials of the elderly may be substantially reduced, however. One report in elderly hypertensive patients with isolated systolic hypertension suggests that there would not be improvement in reproducibility for ambulatory BP over clinic BP measurements, as the between-subject variance was not much different for the two methods *(21)*. Staessen et al. reported that 60 subjects with isolated systolic hypertension would be required to detect a 10-mmHg difference in systolic BP between two treatments in a parallel design using clinic readings, whereas if ambulatory BP monitoring was used, the number would only fall to 54. In contrast, if a crossover design was used, the number of subjects needed to show the same systolic BP difference would be 18 and 14, respectively, for clinic vs ambulatory BP measurements.

AMBULATORY BLOOD PRESSURE FOR EVALUATING PATIENTS FOR CLINICAL TRIAL ENTRY

At the recruitment and enrollment phases of a clinical hypertension trial, current antihypertensive medication is discontinued, and baseline BPs and heart rates are obtained during a single-blind placebo period that generally lasts for 2–4 wk. Conventional inclusion criteria for these trials have been based on the seated clinic systolic or diastolic BPs at the end of the single-blind placebo period. In recent years, many protocols have also included ambulatory BP values as primary or secondary criteria for inclusion into the study. For example, it is not uncommon to

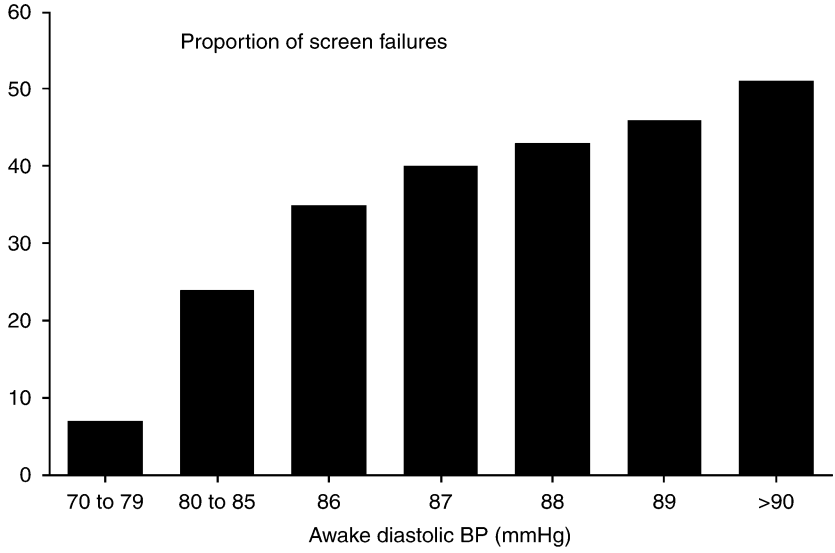

Fig. 1. Effects of patient recruitment using an office diastolic blood pressure >90 mmHg and various awake ambulatory diastolic blood pressures as the selection criteria in antihypertensive drug trials. (Modified from ref. *1*.)

require that the seated diastolic BP in the clinic exceed 90 or 95 mmHg and that the awake (or daytime) ambulatory BP exceed 85 or 90 mmHg. *(1)*. The impact of various awake ambulatory BP values for exclusion of patients during the screening process can be fairly dramatic when the requirement for the office diastolic BP is 90 mmHg or greater. An example of this is shown in an analysis from a multicenter US clinical trial (Fig. 1). In this study, a seated clinic diastolic BP of >95 and <115 mmHg was used as the criterion for entering and remaining in the single-blind portion of the trial. To progress into the double-blind randomized portion of the study, ambulatory BP values at certain thresholds were used. However, when using an ambulatory awake BP cutoff value of 85 mmHg, nearly 30% of the study group was excluded from randomization into the double-blind part of the trial. When 90 mmHg was the cutoff value for ambulatory diastolic pressure, more than 50% of the group was excluded from randomization.

The major reason for the high exclusion rate based on the ambulatory BP values compared to the office pressure is that a relatively high percentage of patients entering these trials experience a white-coat effect *(4,8,22)*. There has always been substantial controversy as to whether patients with white-coat hypertension should be included or

excluded from participation in clinical trials of antihypertensive drugs. The viewpoint of those favoring inclusion of white-coat hypertensive patients is that it is relevant to study their hemodynamic response to the new drug because it is likely that many patients with the white-coat syndrome will have therapy prescribed by physicians who base treatment decisions solely on office BP measurements. Although not an unreasonable concern, a number of studies have demonstrated that patients with white-coat hypertension exhibit few changes in ambulatory BP following antihypertensive therapy *(23,24)*. The typical compromise in recent years has been to include an intermediate cutoff BP entry value for ambulatory BP that is lower than the office BP entry criteria. By using the ambulatory BP criteria, fewer patients will be required in the randomized portion of the study, but the number of individuals screened in the single-blind period is typically increased *(1,10,19)*. Even in 2007, it remains commonplace to recruit about 130–140% of the required final number of patients who can be evaluated to assure that the statistical power required to show the desired changes from baseline will be achieved.

MULTICENTER TRIALS TO EVALUATE ANTIHYPERTENSIVE THERAPY

A multicenter trial is a clinical trial conducted simultaneously by several investigators working in different institutions but using the same protocol and identical methods in order to pool the data collected and analyze them together *(25,26)*. Two key reasons for conducting multicenter hypertension studies rather than single-center studies is to enhance patient recruitment and to make the study group more "representative" of the entire patient population, as there may be unique or homogeneous local population characteristics from a single center.

In North and South America, Europe, and Japan, sponsors of antihypertensive drug trials often select centers based on personal experience with the center, reputation for recruitment, and good study conduct as well as, in some instances, the ability to analyze and report the results of the study. Often at issue is whether it is best to use a large number of centers with a small number of patients per center or a smaller number of centers with a larger number of patients per center. For a common disease such as hypertension, it has generally been easier to standardize, to follow, and to motivate a small number of

centers (i.e., 15–30) with a moderate number of patients (i.e., 10–20) per center. When the criteria for study entry become more complex (e.g., severe hypertension with left ventricular hypertrophy [LVH] or certain ambulatory BP selection criteria), the general trend has been to use more centers and fewer patients per center. This may lead to problems with final analyses, however, as the extreme situation of one to two patients in a center does not enable differentiating between a center-related effect and one related to the treatments. In such cases, the smallest centers are pooled to serve as a larger "center" in the statistical model.

Analyses of Multicenter Hypertension Trials: Relevant Problems for Ambulatory Blood Pressure Recordings

There are several problems specific to multicenter hypertension trials, including those utilizing ambulatory BP measurements. First, there is the "center" factor: incorporation of the center factor into the analysis improves the power of comparison of treatments. One can assess the variability among centers from the residual variability in order to improve the sensitivity in detecting differences between treatments. As mentioned earlier, if the sample size in some centers is very small, then these centers may be pooled into a large center. Second, it is important to evaluate whether the differences between treatment modalities vary outside of random fluctuations across all centers. If a major difference does exist, it may be proven statistically by performing a test of treatment-by-center interaction.

It is important to evaluate the causes of treatment by center interactions because they may invalidate the principal findings of a study *(27)*, including those using ambulatory BP monitoring. Some of the causes of treatment-by-center interactions are listed in Table 2. Differences in patient features from one center to another may result in confounding of the results. An abnormal or unusual frequency of protocol violations, losses to follow-up, or noncompliant patients may occur in one or more centers. When this occurs, it may reflect poor adherence to the protocol or insufficient motivation of the investigators or study coordinators at these centers. For example, when a center has inexperienced or apathetic personnel involved in an ambulatory BP monitoring protocol, there may be excessive data loss during the recording period, poor correlation between cuff and device measurements, or inaccuracy with regard to drug dosing and recorder hookup times *(4,8,28)*.

Table 2
Causes of Treatment-by-Center Interactions in Multicenter Clinical Trials

Differences in patient features from one center to another
Abnormal frequency of protocol violations, losses to follow-up, or noncompliance in one or more centers
Outlier center (small number of "doubtful" cases)
Real variations of differences between treatments according to centers

From ref. *28*.

Outlier centers, possibly because of a small number of doubtful cases, may decrease credibility concerning these data and may also cause a center effect. However, tests for outliers may be misleading in a large clinical trial. For example, if three or four centers are identified as outliers, it is possible that these are the clinics that are doing a good job while the others are not. Thus, statistical tests for outliers, which are essentially tests of homogeneity, must be used carefully and intelligently by the statisticians in charge of the final analyses. Finally, real variations of differences between treatments according to centers may occur and restrict the general applicability of the results.

Bias in a Multicenter Trial Using Ambulatory Blood Pressure Monitoring

Bias enters into a multicenter trial through two primary mechanisms: selection bias and misclassification bias. An example of selection bias in an antihypertensive drug trial involving ambulatory BP monitoring might be recruiting a more severely hypertensive population to avoid inclusion of white-coat hypertensives. Many investigators have learned to avoid screen failures (Fig. 1), which has a possible financial impact on the center, so they will enroll either a patient with higher clinic pressures or one who has a "known" ambulatory BP from a previous trial. Misclassification bias in the multicenter trial is exemplified by clinic BP measurement error (e.g., using improper methodology for measurement) and may induce a center effect if untrained or inexperienced personnel are used. Misclassification bias is probably uncommon in studies using experienced investigators and coordinators, but recently multinational multicenter trials led to the use of centers inexperienced in performing clinical research and measurement errors have become more prevalent.

Practical Concerns in the Conduct of Multicenter Trials That Use Ambulatory Blood Pressure Recorders

The use of ambulatory BP monitors in a clinical trial requires the availability of skilled, trained technicians. Multiple devices are necessary in order to complete a clinical trial in a timely fashion, to facilitate the scheduling of large numbers of participants, and to minimize the impact of mechanical problems when they occur. These requirements increase study costs but are critical to the success of the trial. An additional concern is the possibility that the data for some individuals may be excluded from analyses because of the poor quality of an ambulatory BP recording or mechanical difficulty *(29)*. Rarely, the use of ambulatory BP monitoring may hinder recruitment efforts because certain individuals may decline participation in a trial as a result of the perceived burden of wearing and returning a recorder. Appel et al. *(29)* have reported that patient recruitment efforts improve when the technique is presented as a standard part of the study. Then the expectation is that the ambulatory BP data collection is a primary part of the study as opposed to an optional or ancillary procedure.

IMPORTANCE OF THE PLACEBO EFFECT IN CLINIC VS AMBULATORY BLOOD PRESSURE

It remains standard practice to include a placebo group in clinical trials involving antihypertensive therapy, especially studies that are considered dose ranging or "pivotal" during the earlier phases of drug development. Because of the marked variability of office BP, most investigators have found it necessary to distinguish true drug effect from placebo effect in BP trials. Several factors might create a reduction in BP on placebo, including regression to the mean *(30)*, the presence of a pressor response in the doctor's office that resolves the white-coat effect *(31,32)*, and expectations of the patient and the clinical observer *(5)*. Unfortunately, surreptitious readings may also play a role in BP reductions on placebo.

In contrast to studies that employ clinic pressure as the primary means to obtain the primary study end point, the placebo effect is either minimal or absent when ambulatory BP monitoring is used in antihypertensive drug trials *(33–35)*. The lack of observed placebo effect on ambulatory BP is probably secondary to both the lack of observer bias and the increased number of BP values obtained over a 24-h study period. In contrast, ambulatory BP monitoring probably would not remove regression to the mean or other potential patient factors that

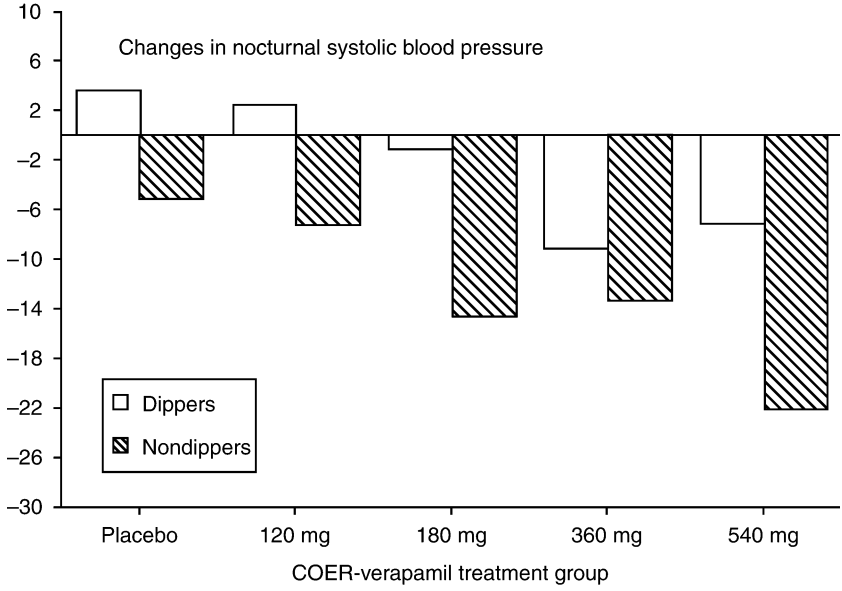

Fig. 2. Changes in nocturnal (10 PM to 5 AM) blood pressure (BP) from baseline measured by ambulatory BP monitoring in dippers (decline in mean BP from the daytime period to the nocturnal period was >10%) contrasted with changes in nocturnal BP in nondippers (<10% decline in nocturnal BP) on placebo and four doses of controlled-onset extended-release (COER) verapamil. (Modified from ref. *36*.)

contribute to the placebo effect. In fact, it is somewhat difficult to separate the regression to the mean effect from the placebo effect and the decrease in a white-coat effect over time.

This phenomenon of regression to the mean in an ambulatory BP monitoring study has been shown quite clearly in a study by White et al. *(36)*. In this trial, patients with hypertension were randomized to receive either placebo or controlled-onset extended-release (COER) verapamil for 8 wk after a 3- to 4-wk single-blind placebo baseline period. The patients were then divided into those patients whose BP fell by >10% during sleep compared to their awake values (dippers) and those whose BP fell by <10% during sleep (nondippers). In the nondipper patients randomized to receive placebo, nocturnal systolic BP fell by 4 mmHg compared to the first baseline study (also on placebo but during the single-blind period). In the dipper patients randomized to receive placebo, nocturnal systolic BP increased by about 4 mmHg compared to the baseline BP. Thus, the spread between the two types of patients in the placebo group for nocturnal pressure was nearly 8 mmHg (Fig. 2).

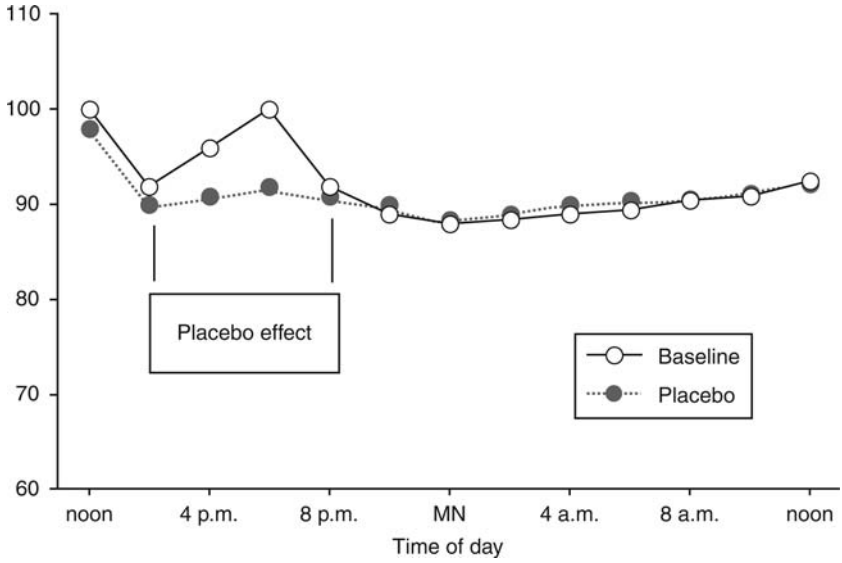

Fig. 3. Ambulatory diastolic blood pressures before and after 4 wk of placebo. The overall means were not significantly different; however, an effect of placebo was observed during the first 8 h after dosing. (Modified from ref. *35*.)

The changes in nocturnal BP on active drug were also consistently greater across all doses and greater in nondippers compared to dippers. Thus, if this substantial regression to the mean on placebo had not been accounted for, the response to active treatment with COER verapamil in the dippers would have been underestimated and the response in the nondippers would have been overestimated.

In a study by Mutti et al. *(35)*, the office BP fell signficantly by 10/3 ± 3/2 mmHg following 4 wk of placebo administration, whereas the overall 24-h BP was unchanged. However, the ambulatory BP did fall slightly during the first 8 h of placebo administration (Fig. 3), which the authors attributed to the white-coat effect. Of note is that this initial fall did not have a statistical effect on the overall mean BP.

In a much longer-term study by Staessen et al. *(37)* in older patients with isolated systolic hypertension, one treatment arm was randomized to placebo for 1 yr. Compared to the baseline period, the clinic systolic BP fell by 7 ± 16 mmHg on placebo and the 24-h systolic BP fell by just 2 ± 11 mmHg. Because the ambulatory BP has a superior repeatability index compared to the clinic pressure, the changes in 24-h systolic BP met statistical significance, whereas the larger mean reduction in clinic

BP showed only a trend ($p = 0.06$). Because this was a patient population with normal diastolic BP, there were no statistically significant changes in clinic or ambulatory diastolic BP on placebo therapy during this study. The authors also noted that the 24-h systolic BP was more likely to decrease on placebo if it was higher at baseline and if the follow-up was longer. The authors discounted regression to the mean or the white-coat effect as having an impact on these placebo effects and recommended that long-term studies in older patients using noninvasive ambulatory BP monitoring require a placebo-controlled design.

ANALYSIS OF AMBULATORY BLOOD PRESSURE DATA IN ANTIHYPERTENSIVE DRUG TRIALS

Data from ambulatory BP studies in hypertension trials can be analyzed in a number of ways (Table 3). The most popular method remains the change from baseline in the 24-h systolic and diastolic BP and the visual assessment of the hourly curves over 24 h. However, the use daytime and nighttime means (or preferably awake and sleep values), blood pressure loads (the proportion of values above a cutoff value during wakefulness [>140/90 mmHg] or sleep [>120/80 mmHg] divided by the total number of BP readings), area under the 24-h BP curve (AUC), and smoothing techniques designed to remove some of the variability from the raw BP data analysis are also among the most popularly utilized methods of analysis *(1–4,10,11)*.

Features of any method of analysis for ambulatory BP data should include the statistical ease of calculation, clinical relevance of the measure, and relationship of the parameter to the hypertensive disease process. Many of these analytical methods meet all of these criteria. For example, the 24-h mean BP remains an important parameter for evaluation in antihypertensive drug trials because it appears to be a strong predictor of hypertensive target organ disease *(2)*, is easy to calculate, utilizes all of the ambulatory BP data, and, as previously mentioned, is remarkably reproducible in both short-term *(6)* and long-term *(7)* studies. The blood pressure load has been used as a simple method of analysis in evaluating the effects of antihypertensive drugs. Blood pressure load has been defined in our laboratory as the percentage of BPs exceeding 140/90 mmHg while the patient is awake plus the percentage of BPs exceeding 120/80 mmHg during sleep *(38)*. A number of years ago, we evaluated the relationship between this BP load and cardiac target organ indexes in previously untreated hypertensives. At a 40% diastolic

Table 3
Methods for Evaluating Ambulatory Blood Pressure Data in Clinical Trials

24-h means (and standard deviation as a measure of variability)
Awake and sleep means based on patient diaries or activity recorders
Hourly means
Blood pressure load (proportion method)
Area under the blood pressure curve
Placebo-subtracted curves showing hourly means
Various data smoothing techniques (including cosinor analyses or fast Fourier transformation)
Modeling of 24-h curves

BP load, the incidence of LVH was nearly 80%, but below a 40% diastolic BP load, the prevalence of LVH fell to about 8%. In contrast, the office BP and even the 24-h average BP were not as discriminating in predicting LVH in this group of previously untreated patients. Thus, in mild to moderately hypertensive patients, one would desire a low (conservatively <30%) BP load while being treated with antihypertensive drug therapy.

In studies in which the patient population has a greater range in BP, the proportional (or percentage) BP load becomes less useful. Because the upper limit of the BP load is 100%, this value may represent a substantial number of individuals with broad ranges of moderate to severe hypertension. To overcome this problem, we devised a method to integrate the area under the ambulatory BP curve and relate its values to predicting hemodynamic indices in untreated essential hypertensives *(11)*. Areas under the BP curve were computed separately for periods of wakefulness and sleep and combined to form the 24-h AUC. Threshold values were used to calculate AUC such as 135 or 140 mmHg systolic while awake and 85 or 90 mmHg diastolic while awake. Values during sleep were reduced to 115 and 120 mmHg systolic and 75 and 80 mmHg diastolic.

Smoothing of ambulatory BP data may be used to aid in the identification of the peak and trough effects of an antihypertensive drug. The extent of variability in an individual's BP curve may be large as a result of both mental and physical activity; thus, evaluating the peak antihypertensive effect of a short- or intermediate-acting drug may be difficult.

Other than the benefits associated with examining pharmacodynamic effects of new antihypertensive drugs, data and curve smoothing for 24-h BP monitoring appear to have little clinical relevance. Furthermore, editing protocols are not uniform in the literature, and missing data may alter the balance of mean values for shorter periods of time. To avoid excessive data reduction in a clinical trial, one statistical expert suggested that data smoothing should be performed on individual BP profiles rather than on group means *(39)*.

SITUATIONS IN WHICH AMBULATORY BLOOD PRESSURE MONITORING HAS BEEN USEFUL IN ANTIHYPERTENSIVE DRUG TRIALS

Treating the White-Coat Hypertensive Patient

The inclusion of white-coat hypertensive patients in an antihypertensive drug trial that uses only office BP criteria for study entry will have a potentially confounding effect on efficacy, because these patients are not hypertensive outside of the medical care environment *(8,9,13,14)*. Furthermore, patients may develop excessive drug-induced side effects without much change in BP, especially if titration of the dose is based on office pressures.

In a study by Weber et al. *(24)*, a sustained fall in BP was found across a study group taking a long-acting form of diltiazem. In a subset of six patients who had hypertensive office BP readings but whose ambulatory BPs were normotensive (i.e., a white-coat hypertensive group), no significant ambulatory BP changes from placebo baseline (0/1 mmHg) were observed. In contrast, the diltiazem therapy decreased 24-h BPs by 18/13 mmHg in the subgroup of nine patients who were hypertensive by both office and ambulatory BP. Thus, treating white-coat hypertensive patients may be of little to no benefit if the only place where BP reduction is observed is in the medical care environment.

Utility of Ambulatory Blood Pressure Monitoring in Dose-Finding Studies

Since the early 1990s, numerous studies have been performed with ambulatory BP monitoring to fully assess the efficacy of a wide range of doses of new antihypertensive agents. The advantage of ambulatory BP monitoring in dose-finding studies is related in part to the improved statistical power to show differences among

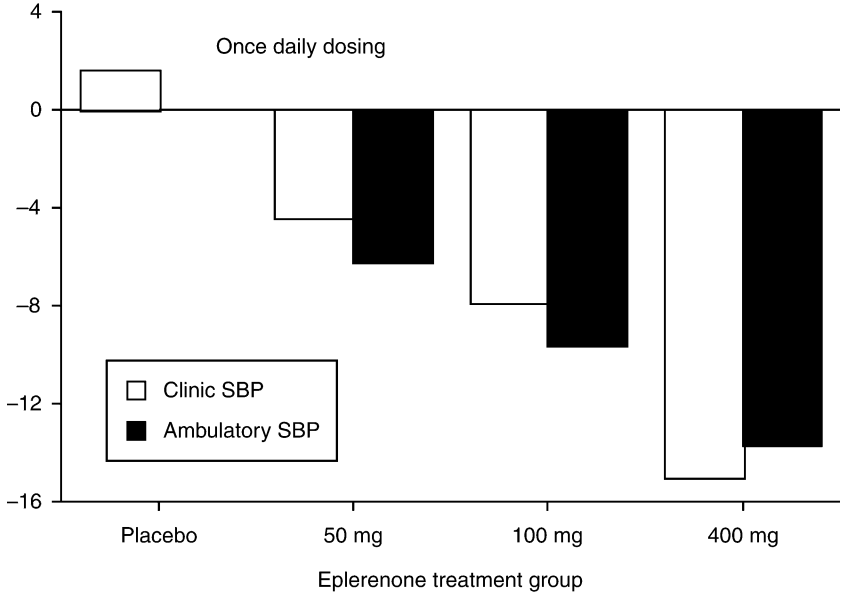

Fig. 4. Changes from baseline in ambulatory vs clinic systolic blood pressure in a dose-ranging trial with a selective aldosterone antagonist, eplerenone. (Data from ref. *40.*)

the treatment groups compared to clinic pressures. Examples are shown next.

Eplerenone

The efficacy of a novel selective aldosterone receptor antagonist, eplerenone, was studied in patients with essential hypertension using a multicenter, randomized, placebo-controlled design *(40)*. In this trial, the drug was assessed using a once-daily dosing regimen of either 25 or 200 mg. Clinic and ambulatory BPs were compared to both baseline values and the effects of placebo. As shown in Fig. 4, there was a dose-related reduction in BP at the trough for both clinic and ambulatory BP. The ambulatory BP values were better at delineating the dose–response than the clinic BP readings.

Utility of Ambulatory Blood Pressure Monitoring in Comparator Trials

Ambulatory BP monitoring has been very helpful in comparing antihypertensive drugs, especially when assessing duration of action. Numerous

examples in the literature illustrate this benefit, including the superiority of ambulatory BP over clinic BP in assessing the trough-to-peak ratio of various agents *(41)*.

Comparisons Within the Same Class

In a multicenter study, Neutel et al. *(42)* compared the β-blockers bisoprolol and atenolol in 606 patients using both clinic and ambulatory BP. Following therapy, trough BP in the clinic was reduced 12/12 mmHg by bisoprolol and 11/12 mmHg by atenolol. Although these changes were significantly different from baseline therapy, there were no differences when comparing the effects of each drug. In contrast, daytime systolic and diastolic BPs (6 AM to 10 PM) and the last 4 h of the dosing interval (6 to 10 AM) were lowered significantly more by bisoprolol than by atenolol. This finding was present whether the assessment was made by examination of the overall means, area under the curve, or BP loads. These data demonstrated that despite there being no difference in office BP, bisoprolol had significant differences in efficacy and duration of action compared with atenolol when assessed by 24-h BP monitoring.

The antihypertensive efficacy of the selective angiotensin II receptor antagonists telmisartan and losartan was compared with placebo in a randomized, parallel group, double-blind trial of 223 patients with stage II and III hypertension *(43)*. After 4 wk of single-blind placebo baseline treatment, patients were randomized to receive 40 mg telmisartan, 80 mg telmisartan, 50 mg losartan, or placebo once daily. Based on clinic BP measurements, the reductions in trough BP were 14/9 mmHg on the lower dose of telmisartan and 16/10 mmHg on the higher dose of telmisartan, whereas on losartan, BP fell by 10/6 mmHg. Changes in BP induced by the 80-mg dose of telmisartan were significantly greater than the reductions in BP observed with losartan. Ambulatory BP monitoring after 6 wk showed that both telmisartan and losartan produced significant reductions from baseline in 24-h mean BP compared to placebo. As shown in Fig. 5, during the 18- to 24-h period after dosing, the reductions in systolic BP with telmisartan (<10.7 mmHg) and 80 mg (<12.2 mmHg) were significantly greater than the changes observed for losartan (<6 mmHg). Thus, ambulatory BP monitoring was able to discern differences in the low dose of telmisartan and losartan, whereas the clinic BP was not able to consistently show these changes. The ability of ambulatory BP monitoring to statistically reveal these smaller changes between treatment groups compared

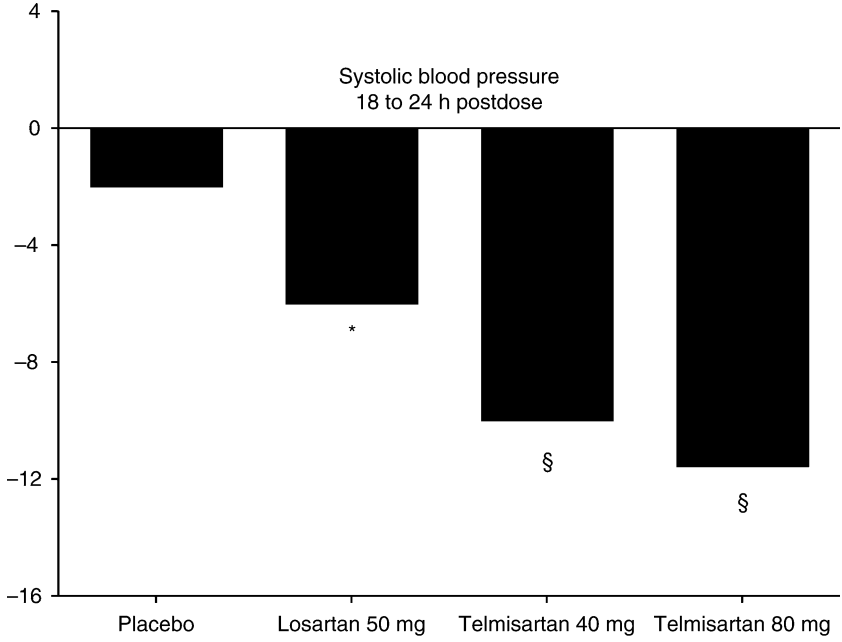

Fig. 5. Adjusted changes from baseline in mean blood pressure for the 18- to 24-h postdose period as measured by ambulatory BP monitoring on two doses (40 and 80 mg) of the angiotensin II receptor blocker telmisartan and 50 mg of losartan. *$p < 0.05$ vs placebo; §$p < 0.05$ compared with losartan and placebo. (Modified from ref. *43*.)

to clinic BP is most likely related to the lower variance that occurs with repeated ambulatory BP studies compared to repeated clinic BP *(1,6,19)*.

Comparisons of Drugs in Different Classes

In a study performed by Stanton et al. *(44)*, the direct renin inhibitor aliskerin (doses of 37.5–300 mg once daily) was compared to the angiotensin II receptor blocker losartan (100 mg once daily) in a clinical trial of 226 patients that used 24-h ambulatory BP monitoring at baseline and following 4 wk of double-blind therapy. There were dose-dependent reductions in daytime ambulatory BP and in plasma renin activity on aliskerin. As is shown in Fig. 6 for the approved doses of aliskerin for the treatment of hypertension (150 and 300 mg once daily), ambulatory BP was reduced throughout the dosing interval. There were no significant differences in changes from baseline in daytime ambulatory systolic BP

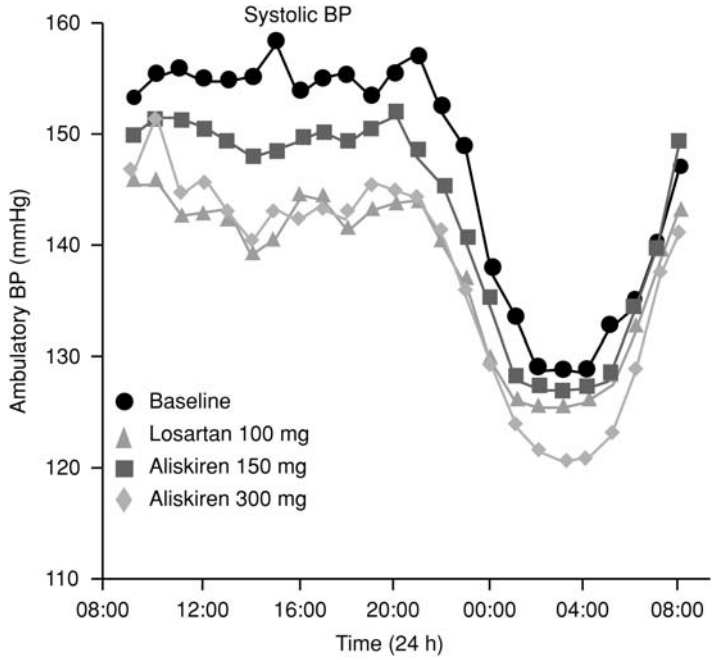

Fig. 6. Twenty-four hour systolic blood pressure profiles for the direct renin inhibitor aliskerin at doses of 150 and 300 mg daily compared to the placebo baseline period and losartan 100 mg once daily. (Modified from ref. *44*.)

among the three active treatment groups (losartan 100 mg, aliskerin 150 mg, and 300 mg once daily). It is noted that nighttime reductions in the BP were greater with aliskerin 300 mg, possibly due to the enhanced secretion and hence, the substrate of renin between 2 and 8 am. Of note, plasma renin activity (PRA) on aliskerin fell by 77–83% while on losartan, PRA rose by 110% *(44).* Although both of these agents have similar plasma half-lives close to 24 h, they have entirely different mechanisms of action. This bears relevance because it is known that as BP and heart rate fall during sleep, plasma renin activity and aldosterone gradually increase. In the morning upon awakening, the sympathethic nervous system is activated, which enhances renin secretion from the juxtaglomerular apparatus in the kidney. Thus, the renin–angiotensin–aldosterone system is further activated in the early morning upon awakening, increasing the contribution of angiotensin to the postawakening surge in BP.

Reductions in ambulatory systolic BP with eplerenone were similar to that of amlodipine during the 24-h dosing interval (Fig. 6). In addition,

both agents were shown to have significant effects on vascular compliance and, not surprisingly, eplerenone was associated with less edema than amlodipine in this patient population.

USE OF AMBULATORY MONITORING TO ASSESS THE EFFECTS OF DOSING TIME

In general, when antihypertensive therapies are administered, there is an attempt to match the effects of a drug to the timing of the BP variability *(45–47)*. In the case of hypertension and coronary artery disease, this imparts a great deal of clinical relevance because BP and heart rate have distinct, reproducible circadian rhythms. In most patients, the BP and heart rate are lowest during sleep and highest during the day. As noted previously by several authors in this volume, most cardiovascular diseases, including myocardial infarction *(48)*, angina and myocardial ischemia *(49)*, and stroke *(50)*, have circadian patterns that are all characterized by the highest incidences in the early morning hours.

Timing of Drug Administration

Several authors have made attempts to alter the effects of conventional drugs by dosing them prior to sleep vs upon arising *(51–53)*. In one of these studies *(51)*, the angiotensin-converting enzyme inhibitor (ACE) quinapril was dosed in the early morning vs at bedtime in 18 moderately hypertensive patients. The study was conducted in a double-blind crossover design with quinapril dosed at either 8 AM or 10 PM for 4 wk in each period. Ambulatory BP monitoring was carried out before and at the end of each 4-wk double-blind period. Daytime BP was reduced similarly by both dosing regimens. In contrast, nighttime systolic and diastolic BP was decreased to a significantly greater extent with the evening administration of quinapril. Measurement of ACE activity showed that evening administration of quinapril induced a more sustained decline in plasma ACE but not a more pronounced change. The findings in this study are of substantial interest because nocturnal BP has largely been ignored in the past *(52)*, and in many types of hypertensive patients the BP during sleep may remain elevated despite "normal" BP measurement in the doctor's office.

Other studies *(54–56)* show that little change in BP or heart rate occurs by altering the dosing time of these long-acting agents to nighttime. However, most of the studies have small sample sizes and

had low statistical power to show changes less than 5–10 mmHg in ambulatory BP. Thus, whether or not altering the dosing time of a long-acting antihypertensive agent truly changes the level of ambulatory BP has not been shown with any great degree of confidence.

AMBULATORY BLOOD PRESSURE MONITORING IN COMMUNITY-BASED TRIALS

Traditional clinical trials in hypertension measure the efficacy of antihypertensive drugs but may not fully assess their effectiveness in clinical practice. Thus, it was relevant to evaluate a community-based trial that could provide this information using an open-label design without being subject to observer bias. To meet this requirement, White et al. *(57)* (Fig. 7) used ambulatory BP monitoring to overcome these shortcomings in a large community-based trial involving more than 600 medical practices in the United States. Patients with hypertension, either untreated or currently on treatment, were started on, or switched to, the angiotensin receptor blocker telmisartan 40 mg daily; after 2 wk, if office BP remained >140/85 mmHg, the dose was increased to 80 mg and, if necessary, hydrochlorothiazide 12.5 mg added after a further 4 wk and continued for the final 4-wk period. Twenty-four-hour ABPM was performed at baseline and at the end of the treatment period. Baseline and treatment ambulatory BP measurements were completed in 940 previously untreated patients and 675 previously treated patients. The average reduction of the entire cohort was –10.7/–6.5 mmHg ($p > 0.0001$; 24-h BP averages were reduced by 12/8 and 8/5 mmHg in untreated and previously treated patients, respectively). In contrast, the office BPs fell by an average of 23/12 and 17/10 mmHg in previously untreated and treated patients. In 401 patients whose baseline 24-h BP was >130/85 mmHg, the mean decrease in 24-h BP was 16.8/11.4 mmHg. Based on the ambulatory BP criteria, the BP was fully controlled (<130/85 mmHg) in 70% of patients and, based on office measurement criteria (<140/90 mmHg), in 79%. Thus, observer and measurement bias was substantial based on the changes from baseline by clinical measurements in contrast to ambulatory BP recordings. The successful use of this procedure in primary care research will create further opportunities to define the effectiveness of treatment in the environment in which it is customarily prescribed.

CONCLUSIONS

The data from the past 15–20 yr of clinical trials now overwhelmingly support the usefulness of ambulatory BP monitoring in the assessment and development of new antihypertensive drugs. Numerous

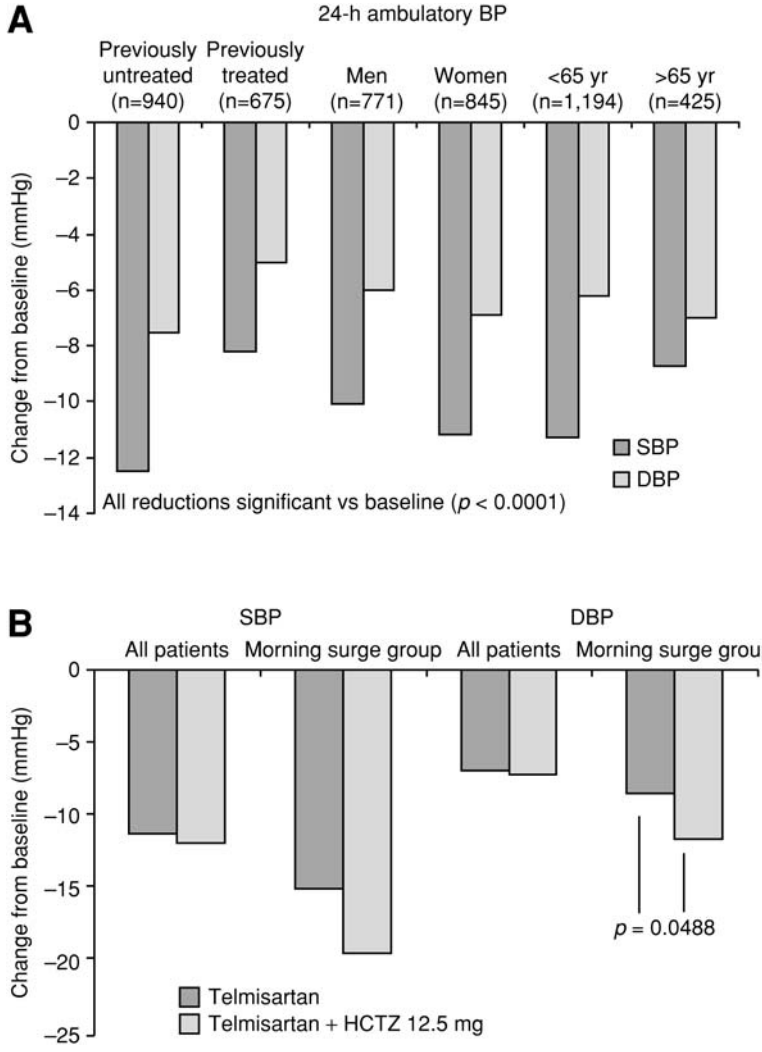

Fig. 7. Effects of telmisartan or telemisartan and hydrochlorothiazide on 24-h ambulatory BP (upper panel) and the last 4 h of the dosing interval (lower panel) from the MICCAT-2 trial. Patients were characterized as having a morning surge if their early morning BP exceeded the preawakening sleep BP by 30 mmHg systolic. (Modified from ref. *57*.)

reports show that ambulatory BP is a powerful, independent predictor of cardiovascular morbidity. Additionally, several studies also show that ambulatory BP monitoring has excellent potential as a tool to aid in the management of hypertension, including determining whether the

initiation, adjustment, and withdrawal of antihypertensive treatment should be considered. Finally, based on most analyses, ambulatory monitoring of the BP is, at worst, cost-neutral and should become cost-effective in most countries when used for the appropriate clinical diagnoses and charged for at reasonable costs.

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19 Ambulatory Blood Pressure Monitoring in Clinical Practice

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CONTENTS

INTRODUCTION

Although ambulatory blood pressure (ABP) monitoring has played a vital role in hypertension research for more than 30 yr, its widespread use in routine clinical practice is unfortunately limited *(1–3)*. Factors contributing to its under-utilization include the cost of the equipment; the tendency for support staff to avoid its use for reasons of unfamiliarity; the unlikelihood of recouping reimbursement from third-party payers; and the perceived lack of evidence supporting a clinical prognostic value for the procedure. However, in recent years these obstacles have been increasingly surmounted. Competition among manufacturers is making more equipment types available and is likely to reduce the cost

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of equipment, Medicare and other third-party payers have started reimbursing for some procedures *(4)*, and, most importantly, the medical literature is increasingly supportive of a prognostic value for ABP monitoring that is superior to office blood pressure measurements *(5–16)*.

Thus, physicians with an interest in hypertension may consider employing ABP monitoring more readily within their own practices. This chapter explores the considerations for such an undertaking.

Overcoming the "Intimidation" Factor

If, as often occurs, office blood pressures are challenging to interpret, the prospect of interpreting the clinical relevance of between 50 and 100 readings provided by the ABP monitoring procedure is understandably daunting—not to mention the use of the ABP device and associated software. However, these concerns are easily overcome with a systematic approach that is easily learned.

Acquiring and reviewing a patient's electrocardiogram (ECG) tracing provides a useful analogy. To acquire the ECG tracing, one needs special equipment—the ECG machine. Similarly, obtaining an ABP recording requires an ABP device. Trained medical support staff interact with the patient and the ECG machine in acquiring the ECG tracing, as is the case with the ABP device when performing the ABP monitoring procedure. Finally, the physician interprets the ECG tracing in accordance with a systematic overview first learned as a medical student and then fine-tuned over years of practice. Similarly, the interpretation of the ABP monitoring report is also best approached systematically. The amount of office time required to obtain an ABP recording is about double that needed to acquire an ECG, but still easily manageable, even within the time constraints of a modern medical practice. Thus, using the ABP monitor in clinical practice requires considerations of equipment, staff training, and an approach to interpreting the data.

EQUIPMENT

The ABP Monitor

ABP monitoring equipment is evaluated in detail in Chapter 4. Obviously, the selected monitor must be validated to produce consistently accurate readings over a wide range of pressures. Validation should meet the requirements of the Association for the Advancement of Medical Instrumentation (AAMI) in the United States *(17)* and those of either the British Hypertension Society (BHS) *(18)* or the European

Table 1
ABP Monitoring Devices Meeting the Validation Criteria of the Association for the Advancement of Medical Instrumentation and Either the British Hypertension Society or the European Society of Hypertension

Manufacturer	*Models*	*Website*
Spacelabs Medical	90207 90217	www.spacelabs.com
DelMar Reynolds	P6 Pressurometer	www.delmarreynolds.com
SunTech	Oscar PowerPack	www.suntechmed.com
Takeda	TM 2421	www.pmsinstruments.co.uk
Disetronic Medical Systems	CH-DRUCK Profilomat	www.schiller.ch
Omron	HEM7471C	www.omronhealthcare.com

Society of Hypertension's Working Group on Blood Pressure Monitoring *(19)*. Although many devices exist, most are not validated. Select a device having at least dual validation—by the AAMI and either the BHS or European Society of Hypertension, as indicated in Table 1.

The ABP Monitor Cuff

Apply the usual clinical considerations in selecting the appropriate cuff size for use on the patient's upper arm *(20)*. Most ABP manufacturers provide small and large cuffs for a nominal extra charge. For adult ambulatory clinical practice, regular and large cuffs should be available.

Other Considerations

One must consider the ancillary costs when selecting a device. A single ABP monitoring requires two to four AA batteries, and every monitoring procedure should start with fresh batteries. Consider computer access and printing costs, although these are usually minimal and readily supported by the clinic's existing office equipment. Evaluate maintenance requirements and warranties and the availability of the manufacturer's technical support. Consider the calibration maintenance requirements, which are performed against a mercury sphygmomanometer according to the manufacturer's directions and at least annually.

STAFFING REQUIREMENTS AND TRAINING

A nurse or medical assistant with interest and experience in blood pressure measurement can master the use of an ABP monitor after brief

training. All that is required is an understanding of traditional blood pressure measurements, cuff selection and fitting techniques, monitor function and initialization, report generation, and a review of the technical quality of the data. Most manufacturers provide this instruction through instruction manuals, videotapes, and DVDs accompanying the purchased equipment. The BHS's website *(21)* provides much valuable information, including web-based training in blood pressure measurement and a thorough evaluation of ABP monitors meeting the Society's validation criteria.

ABP MONITOR INITIALIZATION

ABP monitor initialization refers to the instructions programmed into the device in preparation for the monitoring procedure (Table 2). Trained staff can accomplish this in 10–15 min of uninterrupted time in front of a computer running the initializing program or a device-initializing interface unit. After entering the patient's personal details, the monitoring or cuff inflation frequency is selected, depending on the number of blood pressure measurements required per hour. A reasonable choice is to conduct a recording every 20 min throughout the entire 24-h monitoring period. More readings (every 15 min) or fewer readings (every 30 min) can also be considered, but most of the protocols establishing a prognostic use for ABP monitoring-recorded blood pressure recommended at least every 30 min *(5–11)*. To minimize patient inconvenience, some protocols decreased the inflation frequency during the hours of sleep to one per hour *(8)*. In view of some trials finding an enhanced prognostic value for nighttime blood pressure *(5,10)*, this may be inadvisable if each hour of the monitoring period is to have equal weight in the evaluation of the blood pressure profile.

Many devices emit a soft beep 5 s prior to cuff inflation, warning patients that a blood pressure measurement is imminent. This allows a patient to minimize excessive arm movement while continuing current activities. During initialization, this beep is deactivated during the presumed hours of sleep.

Setting the appropriate time intervals for what is considered daytime or nighttime is important, because the separate evaluation of these periods may enhance the prognostic power of the ABP monitoring recording *(5,7–10)* and allows for determining the dipper or nondipper status of the patient.

Daytime should encompass a period of at least 6 h, during which the patient is awake and actively engaged in his or her usual daily activities. Reasonable choices are 8 AM to 4 PM or 6 AM to 6 PM. In contrast,

Table 2
Considerations for Initializing and Applying the Ambulatory Blood Pressure Monitor

Allow for an uninterrupted 15–20 min of computer access
Enter patient details
Select monitoring frequency—every 20–30 min throughout the monitoring period
Identify periods for daytime and nighttime
Mute alarm at night
Set the data edit parameters
Select the appropriately sized cuff
Select the appropriate arm—measure blood pressure (BP) in both arms: if systolic BP difference <10 mmHg, use nondominant arm; if systolic BP difference >10 mmHg, use higher pressure arm

nighttime should include at least a 6-h period when one is reasonably assured that the patient will be asleep, such as 11 PM to 5 AM or 12 AM to 6 AM. Some protocols entail the use of a patient diary to capture awake and asleep times more precisely, which are then entered into the program at the time of data download. However, it is important that daytime captures active time and that nighttime captures sleeping time. It is not necessary for the combined daytime and nighttime periods to span the entire 24-h monitoring period.

All ABP monitoring recordings contain isolated readings much higher or much lower than the majority. This raises the issue of artifactual readings that should not be considered in the ABP monitoring report. Most ABP monitor manufacturers accomplish this during the initialization process by setting the blood pressure limits—physiologically improbable blood pressure levels above and below which results in the exclusion of the reading from analysis. These limit values should be reviewed and set. For systolic blood pressure, reasonable limits are <70 mmHg or >260 mmHg; for diastolic blood pressure the corresponding limits would be <40 mmHg or >150 mmHg. Some manufacturers also use pulse pressure (<20 mmHg or >150 mmHg) and heart rate (<40 bpm and >120 bpm) limits. It must be noted that most of the recent trials establishing the prognostic value of ABP monitoring did not use limit values to exclude any readings, and where manufactures did not allow for this the limit values were set as high and low as possible *(5–11)*.

Finally, many ABP monitoring devices have a small screen that displays the blood pressure reading for a short period of time after each measurement. It is probably a good idea to disable this option after the

first three to five readings. This allows the staff to assess if the monitor is functioning correctly at commencement of the procedure and also prevents the patient from visualizing every blood pressure reading, which can be distracting, influence behavior, and adversely affect the objectivity of the recording.

PATIENT INSTRUCTIONS

A well-informed patient enhances the chances of a good quality recording and a more acceptable ABP monitoring experience. The most important instruction is to insist that the patient partake in normal daily activity—including going to work if employed. Actively discourage the patient from engaging in unusually sedentary activities just because they are wearing the ABP monitor. Similarly, discourage any unusual activities and participation in any vigorous exercise (even if this is part of the patient's routine), as excessive arm movement interferes with the collection of the blood pressure data. If patients cannot be persuaded to conduct the ABP recording under typical lifestyle circumstances, it detracts greatly from the benefits of the ABP monitoring—acquiring multiple blood pressure readings during a patient's usual activities while outside the influence of the doctor's office.

Remind the patient of the warning beep emitted about 5 s before cuff inflation. When hearing this beep, patients should continue with their activities but, when practical, minimize movement in the arm to which the cuff is attached.

The ABP monitor must be worn at night and during sleep. Avoid allowing the patient to remove the monitor during the monitoring procedure. Thus, bathing and showering have to be postponed until the procedure is complete. If this is highly unacceptable to the patient, he or she can be instructed in cuff removal and reapplication before and after bathing, but this requires extra instruction and usually a family member to assist in reapplying the cuff and increases the risk of obtaining an inadequate ABP recording.

Explain the cuff inflation frequency and the monitor's behavior during failed reading attempts. In these instances, a repeat reading is attempted approx 2–3 min after the failed attempt. If this also fails, the next attempt coincides with the next scheduled inflation.

Many devices allow patients to initiate blood pressure measurements, and patients should be instructed as to how and when to do this. This is a useful feature if one is trying to correlate symptoms with blood pressure findings that may occur during periods of lightheadedness, flushing,

headache, or palpitations. In these circumstances, it is also useful to provide the patient with a diary so that the symptoms and their time of occurrence can be recorded.

Finally, instruct the patient as to how to manually deflate the monitor and remove the device if this becomes necessary. Providing the patient with contact numbers to call in the event of problems is also prudent. Experienced staff can often intervene and salvage a failing procedure in these circumstances.

Trained staff can provide patient instruction as well as apply the device in 10–15 min.

ARM SELECTION

Most manufacturers recommend applying the cuff to the patient's nondominant arm because this arm is probably associated with less movement and inconvenience than the dominant arm. However, measure blood pressure in both arms. If the systolic blood pressure difference between arms is <10 mmHg, the cuff should be applied to the nondominant arm; if the BP difference between the arms is >10 mmHg, the cuff should be applied to the arm with the highest reading, irrespective of dominance *(18)*.

INTERPRETING THE ABP MONITORING REPORT

A simple systematic approach to interpreting an ABP monitoring report is the surest way to overcome any perceived difficulties in evaluating the 50–100 blood pressure readings listed on the typical ABP monitoring report. At the outset, one must appreciate the differences between reviewing ABP monitoring results from clinical trials published in the medical literature and interpreting the results of a single monitoring episode in a single patient in the clinic (Fig. 1).

Figure 1A depicts the results of the ABP monitoring assessments of an antihypertensive drug's effect on systolic blood pressure as it is typically presented in the medical literature. It is clearly apparent that when compared with the placebo baseline (upper curve), the drug (lower curve) has reduced systolic blood pressure throughout the dosing interval without any waning antihypertensive efficacy in the terminal hours of the cycle. The typically circadian rhythm of blood pressure is also easily evident. Blood pressure is highest in the morning, remains at a daytime high plateau, decreases in the early evening hours, falls to a nadir in the early morning hours, and then surges to reach the morning high.

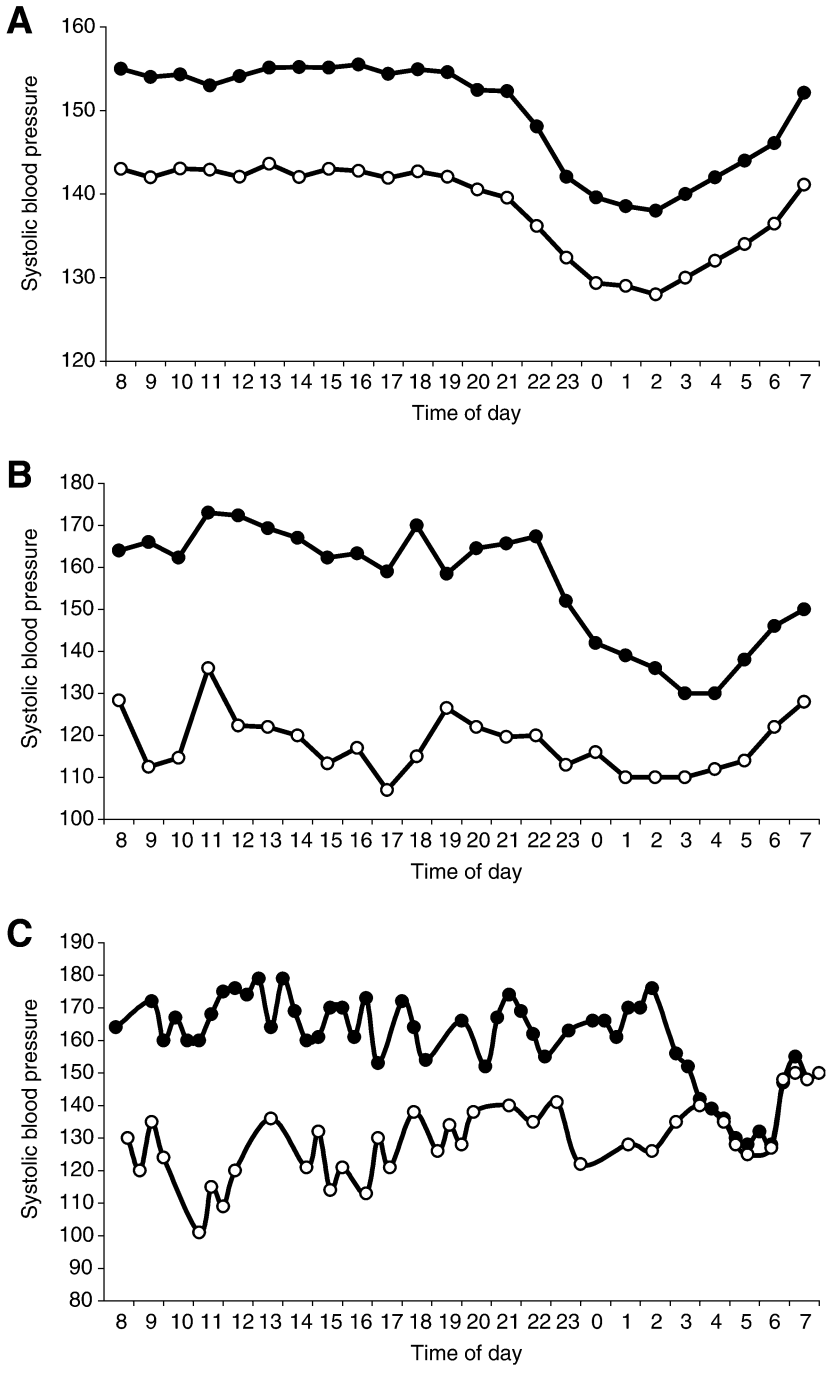

Fig. 1. Ambulatory blood pressure recordings.

However, one must appreciate that the curves in Fig. 1A have undergone inadvertent curve smoothing: first, because the blood pressures recorded in each hour (two to three readings) are averaged to provide an hourly average for a given hour; and, second, because the data of all the patients exposed to the drug are averaged to produce the net effect of the drug. Thus, the ABP monitoring evaluation of the drug effect in a group of patients is depicted in Fig. 1A.

Figure 1B, evaluates the ABP monitoring tracings from different patients, selected at random, from the study sample in Fig. 1A. Figure 1B represents the graphic display of the hourly blood pressure averages, whereas Fig. 1C depicts every reading recorded in another patient. It is immediately apparent that the results in single patients are more variable and that the clear drug effect and the circadian rhythm depicted in Fig. 1A are to some degree lost in the tracings from the single patients.

Furthermore, in most instances cost constraints limit the use of "before" and "after" ABP monitorings in single patients, leaving the clinician to interpret just a single tracing from Fig. 1B, either at the time of diagnosis (upper curves) or after antihypertensive therapy is instituted (lower curves). But this is quite possible and clinically useful provided one appreciates that data for individual patients are quite different from group data typically published in the literature.

Although the format and order of the elements of the printed ABP reports differ among manufacturers, the typical ABP monitoring report should contain most of the elements listed in Table 3.

Once the ABP monitoring procedure is complete and the report printed, begin by evaluating it for technical adequacy. This task may be delegated to a well-trained assistant. Although technical standards differ among manufacturers, at the very least the manufacturers' recommended technical requirements must be met. In general, 75–85% of device inflations should result in a blood pressure recording; the monitoring period should last between 23 and 25 h; most hours (between 18 and 20) of the 24 h of monitoring must contain at least one valid blood pressure reading; ideally there should not be more than two to three consecutive hours without any data; if one is focusing on treatment efficacy in the last hours of the dosing interval, three out of four of the last hours should have at least one valid blood pressure measurement.

After verifying the patient information and the technical adequacy of the ABP monitoring report, one should focus on the summary page (Table 4). This tabulates summary data for the entire monitoring period (24 h) and for the daytime (awake) and nighttime (sleep) periods defined

Table 3
Essential Elements of the Ambulatory Blood Pressure Monitoring Report

Element	*Function*
Patient information	Identifies the correct patient, date, and current antihypertensive therapy.
	Provides useful comparisons for future monitorings.
Summary page	Provides a brief but systematic review of
24-h averages	the ABP monitoring data.
Daytime averages	Predicts cardiovascular risk (*see* Table 5).
Nighttime averages	Allows for day–night comparisons.
BP listings	Allows for easy review of blood pressure
All (raw) data	trends.
Hourly averages	Useful for discussion with the patient.
Removed (edited) data	Fully disclosed by listing "edited" readings for review.
	Assess technical adequacy of recording.
Graphic displays	Provides for additional overview.
Hourly means by time	Assess BP control throughout dosing
All (raw) data by time	interval.
	Provides useful illustrations for the patient.

during monitor initialization. Usually the mean, minimum, and maximum values for each blood pressure and the heart rate are tabulated. Most reports also include the standard deviation of the mean for each parameter.

The 24-h mean value is the most relevant clinical parameter on the report *(5–11)*. Fully utilizing its clinical value requires knowledge of the normal 24-h blood pressure as well as the patient's office blood pressures. Figure 2 depicts an algorithm for the use of ABP monitoring in the management of hypertension *(1)*. This algorithm first utilizes self-monitored blood pressure in ascertaining the presence of a significant disparity between the patient's office and out-of-office readings. This allows for a more efficient use of the ABP monitoring resource—either when establishing a diagnosis of hypertension or when evaluating antihypertensive efficacy—although this step may be dispensed with if the self-monitoring option is not readily available.

Table 4
Typical ABP Monitoring Summary Page

	Min	*Mean*	*Max*	*SD*
24-h				
SBP	128	155.8	173	14.4
DBP	80	96.5	113	10.6
HR	58	77.7	112	8.6
Daytime (8 AM)				
SBP	159	165.9	173	14.4
DBP	83	101.9	113	8.6
HR	76	81.4	86	5.7
Nighttime (12 AM)				
SBP	128	135.1	145	6.3
DBP	80	83.5	88	3.0
HR	60	63.3	70	3.7

SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg); HR, heart rate (bpm); Min, minimum value during defined period; Max, maximum value during defined period; SD, standard deviation of the mean.

The ABP monitoring blood pressure levels mentioned in the algorithm refer to the 24-h mean values, which remain the most relevant clinical parameter from the summary report (Table 4). For those whose ABP is normal (<130/80 mmHg) despite elevated office blood pressure and in whom there is no evidence for cardiovascular risk factors or target organ disease, avoidance of increasing drug therapy is a clear benefit for monitoring procedure *(1)*.

For those whose 24-h ABP is elevated (>130/80 mmHg), there is little doubt that ABP monitoring identifies individuals at higher cardiovascular risk with an ever-increasing number of studies providing supportive evidence (Table 5) *(5–16)*. In each of the studies tabulated in Table 5 *(5–11)*, as well as in other studies *(12–16)*, ABP identified patients with increased cardiovascular risk or target organ damage with greater reliability than did office blood pressures. Moreover, ABP remained a superior predictor of risk even after adjusting the predictive models for office blood pressure and other powerful cardiovascular risk factors such as the presence of heart disease, smoking, lipid levels, and the use of lipid medication *(8)*.

Furthermore, unique elements of the ABP monitoring procedure, such as nighttime blood pressure means, daytime blood pressure means,

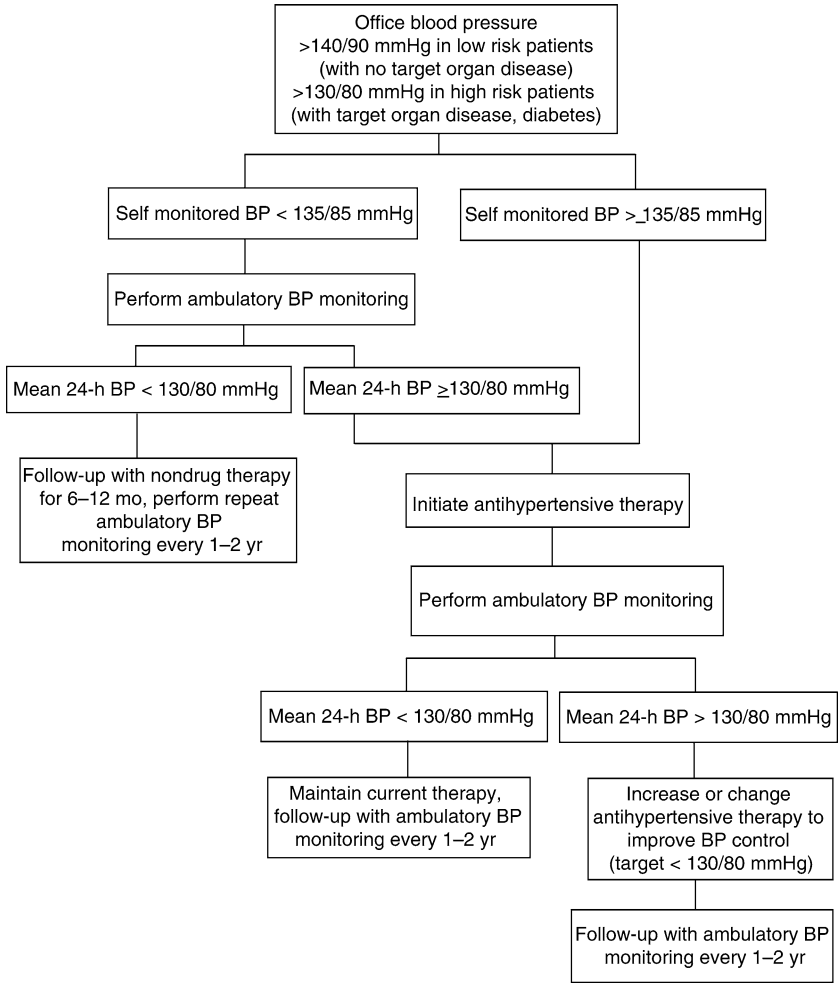

Fig. 2. Use of ambulatory blood pressure in hypertension management.

pulse pressure, and blood pressure variability, enhanced the evaluation of a patient's risk.

The superiority of ABP in predicting cardiovascular risk in patients enrolled in the Syst-Eur10 is illustrated in Fig. 3. Office systolic blood pressures ranging from 160 mmHg (point A on the horizontal axis) to 219 mmHg (point B on the horizontal axis) were associated with a twofold increase in risk (from point A to point B on the vertical axis). In general, ABP monitoring provided for a broader range of blood pressures

Table 5
A Selection of Outcomes Studies Demonstrating That Ambulatory Blood Pressure is Superior to Office Blood Pressure in Predicting Cardiovascular Morbidity and Mortality

Study (ref.) YOP/ST	*Primary outcomes measured*	*ABPM equipment/ ABPM protocol*	*Patient characteristics/ baseline OBP*	*Results*
The Dublin Outcome Study *(5)* 2005/PLPBS	CV mortality from MI, CHF, SCD, CAD, stroke, and other vascular death	SpaceLabs 90207 & 90202 Inflations every 30 min; DT: 9 AM–9 PM; NT: 1 AM–6 AM; no data edits applied	*N* = 4646 Age: 51.5 yr Female: 54.8% OFU: 7.9 yr	10-mmHg ↑ in DT & NT SABP = 12 and 21% ↑ in risk. 5-mmHg ↑ in DT & NT DABP = 2 and 9% ↑ in risk. NT ABP predicts risk even when adjusting for DT ABP. ABP superior to OBP in predicting CV mortality. NT ABP most potent predictor of outcome.
MONICA (16) 2005/ PLPBS(s)	CV and all-cause mortality	Takeda TM-2421 Inflations every 15 min 7 AM–11 PM and every 30 min 11 PM–7 AM; DT: 6–12 AM; NT: 12–6 AM; no data edits applied	*N* = 1700 Age: 41–72 yr Female: 52.1% OFU: 9.5 yr	10-mmHg ↑ in 24 h SABP = 51% ↑ in CV mortality & 18% ↑ in all-cause mortality. The same ↑ OSBP = 25% ↑ CV mortality and 5% ↑ in all-cause mortality. 5-mmHg ↑ in 24h DABP = 43% ↑ in CV mortality and 18% ↑ in all-cause mortality.

(Continued)

Table 5 ***(Continued)***

Study (ref.) YOP/ST	*Primary outcomes measured*	*ABPM equipment/ ABPM protocol*	*Patient characteristics/ baseline OBP*	*Results*
				The same ↑ ODBP = 21% ↑ CV mortality and 6% ↑ in all-cause mortality. When ABP and OBP were considered in multivariate models, only ABP was a significant risk for CV and all-cause mortality.
Uppsala Longitudinal Study of Adult Men *(7)* 2004/PLPBS	Death or hospitalization from CAD or stroke	Accutracker 2 Inflations every 20 min; DT: 10 AM to 8 PM; NT: 12–6 AM; data edits: HR < 30 bpm; DBP > 170 mmHg; 270 mmHg < SBP < 80 mmHg; PP < 10 mmHg	*N* = 872 Age: 70 yr All males OBP: 147/84 mmHg OFU: 9.5 yr	1 SD ↑ in 24-h PP and DT PP ↑ CV morbidity by 32 and 29%, respectively, and independently of OBP and other CV risk factors. DT SBP variability (measured by the SD of DT SBP) provided additional prognostic power independent of 24-h SBP.

Office vs Ambulatory Pressure Study Investigators *(8)* 2003/PLPBS	Total and CV mortality; NF CHF, MI F/NF stroke	ABPM device not specified Inflations at least every 30 min during DT (8 AM–8 PM) and at least every 60 min during NT (8 PM–8 AM); no data edits applied	*N* = 1963 Age: 56.4 yr Females: 48.6% Treated hypertensives OFU: 5 yr	If 24-h SBP > 135 mmHg while receiving treatment, CV outcomes almost twofold greater than those with 24-h SBP < 135 mmHg, independent of OBP. 1 SD ↑ in 24h, DT, and NT SBP ↑ CV outcomes by 34, 30, and 27%, respectively. 1 SD ↑ in 24h, DT, and NT DBP ↑ CV outcomes by 21, 24, and 18%, respectively. Findings independent of OBP and other CV risk factors.
Ohasama Pilot Study *(11)* 1997/PCS	CV and non-CV mortality	Nippon Colin ABPM-630 Inflations every 30 min over 24-h period. NT defined as time in bed established from patient diary. DT defined as the remainder of the 24-h period. Data edits applied	*N* = 1542 Age: 61.7 yr Female: 63.4% OFU: 5.1 yr	Association between ABP and mortality more distinctive than for OBP. CV mortality ↑ significantly for the highest quintiles of 24-h ABP, whereas there was no significant association between OBP and CV mortality.

(Continued)

Table 5 ***(Continued)***

Study (ref.) YOP/ST	*Primary outcomes measured*	*ABPM equipment/ ABPM protocol*	*Patient characteristics/ baseline OBP*	*Results*
				When both 24-h and screening blood pressure values were included in the Cox model, only SABP was related significantly to ↑CV mortality.
SystEur *(10)* 1999/DBPC(s)	Total and CV mortality; NF CHF, MI; F/NF stroke	SpaceLabs 90207 (62.4%); 90202 (19.2%). Inflations at least every 30 min; DT: 10 AM–8 PM; NT: 12–6 AM; no data edits applied	*N* = 808 Age: 69.7 yr Genders not specified OSBP: 160–219 mmHg; ODBP: <95 mmHg OFU: 4.4 yr	At randomization a 10 mmHG ↑ in SOBP = no ↑ in risk but 10 mmHg ↑ in 24-h SABP = 23% ↑ in risk. 10% ↑ in night:day ratio ↑ risk 41%. At randomization, risk of 160 mmHg OSBP = 142 mmHg 24-h SABP, 145 mmHg DT SABP and 132 mmHg NT SABP. In untreated patients SABP a better predictor of risk than SOBP.

Ohasama Study *(9)* 2000/PCS	First symptomatic stroke (transient ischemic attack; cerebral infarction; intracerebral hemorrhage, and subarachnoid hemorrhage)	Nippon Colin ABPM-630 Inflations every 30 min over 24-h period. NT defined as time in bed established from patient diary. DT defined as the remainder of the 24-h period. Data edits applied	*N* = 1464 Age: 61 yr Females: 60% OFU: 6.4 yr	24-h, DT, and NT ABP were linearly related with stroke risk. ABP had the stronger predictive power for stroke risk than did OBP. DT ABP better predicted stroke risk than did NT ABP.

ABPM, ambulatory blood pressure monitoring; bpm, beats per minute; CAD, coronary artery disease; CV, cardiovascular; CHF, congestive heart failure; DBPC, double-blind placebo-controlled; DT, daytime; F, fatal; HR, heart rate; NF, nonfatal; MI, myocardial infarction; mmHg, millimeters mercury; *N*, number; NT, nighttime; OBP, office blood pressure; OFU, observational follow-up; OSBP, office systolic blood pressure; ODBP, office diastolic blood pressure; PLPBS, prospective longitudinal population-based study; PP, pulse pressure; (s), indicates a substudy of a larger trial; SABP, systolic ambulatory blood pressure; SCD, sudden cardiac death; SD, standard deviation; ST, study type; YOP, year of publication; ↑, increase.

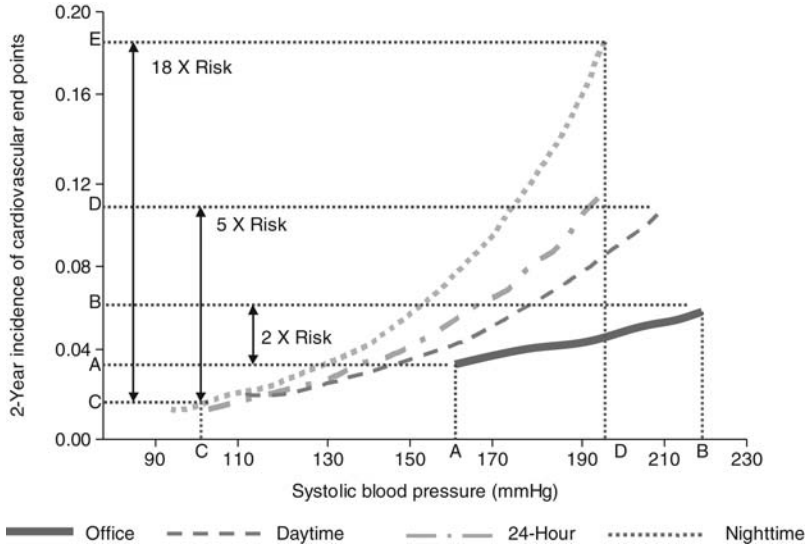

Fig. 3. Office and ambulatory 24-h, daytime, and nighttime systolic blood pressure measurements as predictors of 2-yr incidence of cardiovascular end points in the placebo group from the Syst-Eur Trial.

(from about 100 mmHg at point C to about 200 mmHg at point D on the horizontal axis).

For the 24-h mean and daytime mean ABPs, this was associated with an approx 5-fold increase in risk (from point C to point D on the vertical axis), whereas nighttime blood pressures were associated with an 18-fold increase in risk (from point C to point E on the vertical axis). Thus, when compared with office blood pressure, ABP monitoring provides a broader range of blood pressures that is associated with a more discriminating prediction of cardiovascular risk. Table 5 also lists the ABP monitoring equipment and the ABP monitoring protocols utilized in these pivotal studies.

These findings are important because they come at a time when 24-h ABP monitoring has been approved for reimbursement by Medicare and Medicaid (albeit limited to patients suspected of having white-coat hypertension) *(4)*. However, many national and international guidelines include ABP monitoring not only for the diagnosis of white-coat hypertension, but also for the evaluation of apparent antihypertensive drug resistance, hypotensive episodes associated with antihypertensive medications, episodic hypertension, and autonomic dysfunction *(19,22,23)*.

Comparing daytime and nighttime ABP values from the summary report (Table 4) can also provide further prognostic information. Evaluating the decline of nighttime blood ABP as a percentage of daytime ABP ([daytime mean – nighttime mean]/daytime mean × 100) clarifies patients as either dippers, nondippers, or superdippers. A decline of 10–20% classifies an individual as a dipper, a status associated with a better prognosis even when hypertension exists, whereas those who decline by <10% or >20% are classified as nondippers and superdippers, respectively, both of which are associated with worse outcomes *(10,24,25)*.

The standard deviations of the mean blood pressures reported on the summary page give a simple measure of the variability of the blood pressure. Studies have shown that for identical ABP means, individuals with higher blood pressure variability have a greater degree of target organ damage and worse cardiovascular outcomes *(7,26)*.

Thus, from the ABP monitoring summary page, the higher the 24-h ABP mean, the greater the cardiovascular risk, independent of the office blood pressure and the cardiovascular risk factors; the classification of the patient as a nondipper or superdipper implies poorer cardiovascular outcomes; and the greater the magnitude of blood pressure variability, the greater the degree of target organ damage. Clearly a brief but systematic review of the summary page provides useful clinical information in the management of the hypertensive patient.

Evaluating blood pressure listings (hourly averages or raw data) on the report is also useful. BP values toward the end of the dosing interval should demonstrate adequate blood pressure control (as shown for one patient in Fig. 1B but not another in Fig. 1C), especially when using once-daily antihypertensive medication. Often patients may inquire as to what their blood pressure was at a particular time of interest, perhaps because of symptoms or an event of daily life. When they are shown the blood pressure level of interest and the remaining list of blood pressures, there is often a realization that they live with their blood pressure constantly and not only when in the doctor's office. Viewing and discussing these lists with a patient is quite helpful in confirming their diagnosis (normotension or hypertension) and can be instrumental in convincing some patients that they are indeed hypertensive and in need of therapy.

CONCLUSION

In the management of hypertension today, there remains little doubt that 24-h ABP monitoring is superior to conventional office measurements

in predicting cardiovascular risk, with an ever-increasing list of clinical studies supporting this conclusion. Although resistance to abandoning the mercury sphygmomanometer as the gold standard for diagnosing hypertension is quite entrenched, cardiovascular outcomes in a number of pivotal studies—some of which are shown in Table 5—will help establish ABP monitoring as a more legitimate tool for diagnosing and managing hypertension *(2)*. Incorporating ABP services in one's practice is prudent and quite easily accomplished if the simple procedures outlined in this chapter are followed.

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