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REVIEW

Circadian variations in blood pressure in health and disease: implications for patient management

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Abstract: Traditionally, blood pressure measurements have been performed in office settings and have provided the basis for all diagnostic and therapeutic decisions. However, the development of a clinically relevant 24-hour blood pressure monitoring system has added greatly to the ability of blood pressure values to confer additional clinical information, including prognostic value. Mechanistically, the circadian rhythm of blood pressure is mediated by a complex process as a part of the neurohormonal cascade. Pattern recognition of blood pressure peaks and troughs over a 24-hour period has led to categorization into specific subsets namely, ie, dippers, nondippers, extreme dippers, and reverse dippers. Cardiovascular risk is associated with certain pattern types, as has been demonstrated in large observational and prospective studies. The development of therapies for the purpose of restoring more pathological patterns to normal ones continues to grow. These include both pharmaceutical and device therapy. This article describes the development of 24-hour blood pressure monitoring systems, the identification of circadian blood pressure patterns, and the treatment strategies studied thus far which affect these newer blood pressure parameters.

Keywords: ambulatory blood pressure measurement, nocturnal blood pressure, dippers, nondippers, extreme dippers, device therapy

Introduction

Cardiovascular risks secondary to hypertension have been well defined, and antihypertensive therapy has aided in the reduction of cardiovascular disease. As a result, treatment of hypertension, along with other traditional cardiovascular risk factors, has improved rates of cardiovascular events in the last decade in the US.[1] However, much of the basis for diagnosis and treatment of hypertension is derived from in-office blood pressures.[2] Furthermore, inherent limitations with in-office blood pressure monitoring exist, which include low reproducibility, the white coat effect, and the existence of masked hypertension.[3,4] These shortcomings have led many antihypertensive trialists to examine the diagnostic and prognostic role of 24-hour ambulatory blood pressure monitoring (ABPM). The emergence of this powerful tool has given us insight regarding contribution to risk assessment and goals of therapy. Specifically, normal patterns of rise and fall in blood pressures throughout a 24-hour period are now established, while identification of more pathological peaks and troughs has also been defined. Since the attainment of these reference values, restoration to normal circadian patterns of blood pressure in hypertensives has become a therapeutic aim in some clinical settings. This paper describes the emergence of 24-hour ABPM as a technology, the definition of its clinical and investigational role, and strategies

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of treatment which attempt to convert pathological patterns into normal 24-hour patterns.

Historical background

The performance of blood pressure monitoring throughout the course of a day has its inherent challenges, both physical and technological. Hence, it was not until approximately 40 years ago when the first noninvasive intermittent blood pressure monitoring system was developed.[5] Approximately 134 years passed from the time of the invention of the first blood pressure device by Jean-Leonard Marie Poiseuille to the advent of reproducible, noninvasive blood pressure monitoring.[6] The first intra-arterial blood pressure recording in an unrestricted ambulant man was published in 1969 using the "Oxford system," in which a fine intra-arterial catheter was placed in either the brachial or radial artery. In turn, the catheter was attached to a miniature pressure transducer and a magnetic tape recorder. The system accurately measured beat-to-beat variability in patients performing normal daily activities.[7] However, due to its invasive nature, this system, while very accurate, was considered impractical for routine patient care. In 1962, Hinman et al described the first portable blood pressure monitoring device.[5] The device was developed by the Remler Company in California and comprised a battery-operated recorder worn by the patient. An arm cuff was self-inflated at predetermined intervals and a microphone was placed over the brachial artery. Korotkoff sounds were recorded by the apparatus and later decoded to enable plotting of blood pressure recordings over time.[8] The limitation of the system was that initiation of a pressure reading was patient-controlled, and therefore not useful for overnight blood pressure monitoring. As a corollary, these devices were also large and noisy. With the miniaturization of pump inflation systems and solid-state memory chips, the average 24-hour blood pressure monitor cuff is approximately the size of a pack of cigarettes, not including the cuff portion (Figure 1). Currently, there are over 20 models available for 24-hour ABPM which have been validated by the Association for the Advancement of Medical Instrumentation.[9] Adequate correlation with invasive measurements over 24 hours has been shown with these newer generation monitors. Most clinics in the US set these monitors to take blood pressure at intervals of 15–30 minutes during waking hours and every 30–60 minutes during nighttime hours (Figure 2). The advent of these convenient and accurate devices has enabled more detailed study of the circadian characteristics of blood pressure. Continued development of a noninvasive, continuous blood pressure monitor has yielded promising results. One such device, the Nexfin (BMEYE, Amsterdam, the Netherlands), allows for monitoring of beat-to-beat variability of blood pressure using a finger cuff. Studies are underway in myriad of clinical applications.

Figure 1 A modern 24-hour blood pressure monitor.
Note: Courtesy of SpaceLabs, Inc. (Issaquah, WA).

Home self-monitoring vs 24-hour ABPM

As the development of 24-hour ABPM systems has progressed impressively, the technological advances in home self-measured blood pressure monitoring have been equally remarkable. Currently, consumers have the opportunity to obtain an inexpensive but accurate monitor for home use. This allows the patient to gather more data on blood pressure values throughout the day. As a result of this development, a debate has been sparked regarding whether the use of home monitoring will, in any way, render 24-hour ABPM obsolete.[10,11] Thus far, this does not seem to be the case because home self-measured blood pressure monitoring has many shortcomings, which makes 24-hour ABPM the more powerful tool. Of note, asking patients to wake up at intervals during the night to measure blood pressure is both impractical and will most likely lead to spuriously high values because waking activation feedback will most likely be fueled by sympathetic response. Additionally, while some clinical event outcome data have been garnered from home self-measured blood pressure monitoring values, the breadth of studies does not approach those done with 24-hour ABPM.[12–18] As a result, 24-hour ABPM remains a much more powerful tool for cardiovascular prognostication.

Circadian clock – mechanisms of regulation

One of the earliest known descriptions of circadian rhythm is credited to Jean-Jacques D'Ortous De Mairan, 1729, who described diurnal leaf movements.[19] Nearly three centuries

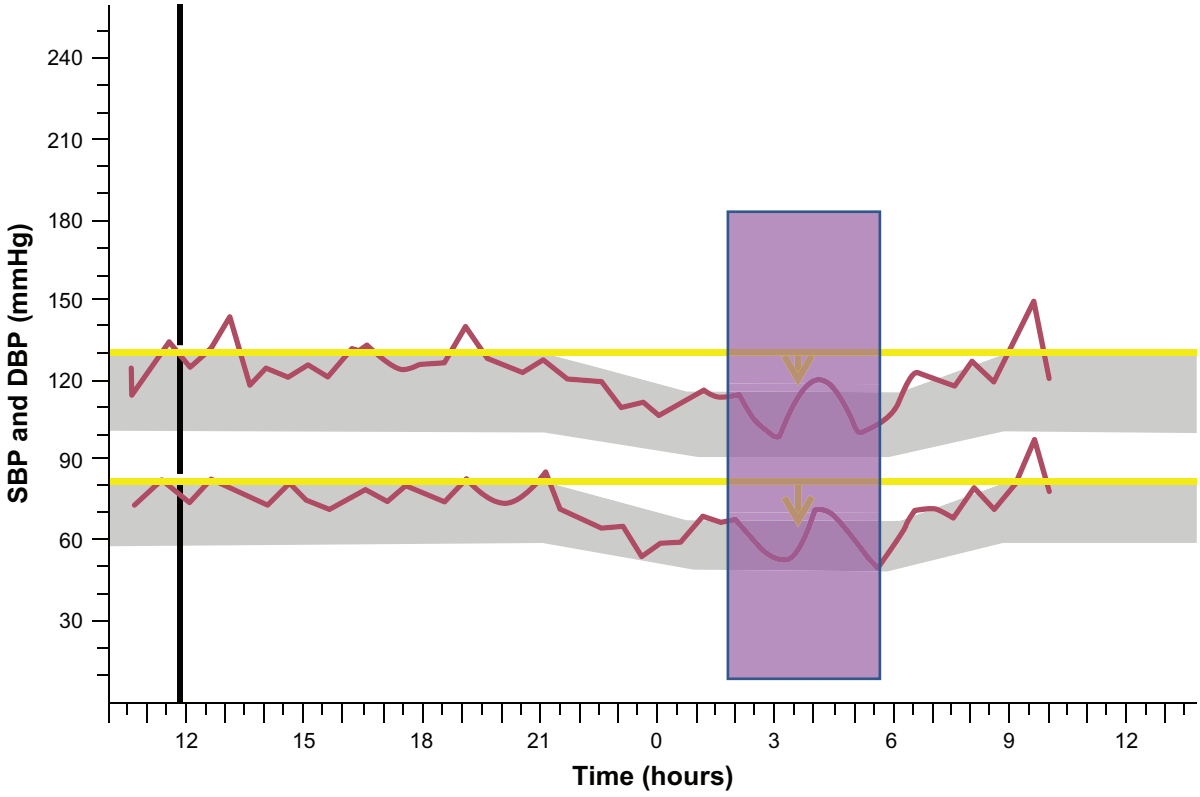


Figure 2 A normal pattern of systolic and diastolic over a 24-hour period. The portion in red highlights the nocturnal dip.

later, having discovered so much regarding circadian biology, we are still searching for answers to the question "What makes the biological clock tick?" From a clinical standpoint, the discovery of circadian influence on heart rate and blood pressure was parallel to the technological advances in blood pressure monitoring. Biological factors governing circadian blood pressure rhythm are discussed here.

In mammals, the mechanism controlling rhythmic physiological processes is located in the suprachiasmatic nuclei of the hypothalamus. This group of approximately 20,000 neurons is referred to as the "central clock."[20] These cells are autonomous, in that they rhythmically express gene products regardless of external influence. Synchronicity of neurons within the suprachiasmatic nuclei is achieved through coupling mechanisms, even in the absence of light.[21] However, these nuclei require "winding" in order to coordinate the timing of rhythms over a 24-hour period. Recognition of light cues by photoreceptors of the eye results in neuronal signaling of the suprachiasmatic nuclei via the retinohypothalmic tract. This stimulus (Zeitgeber) leads to the creation of a temporal relationship between the organism and its environment, as well as maintenance of the phase of oscillating gene expression. This light-sensitive entrainment of the suprachiasmatic nuclei is not universally accepted as the only major impetus for synchronization of diurnal variations in mammalian physiological processes.[22–24] Furthermore, the discovery of autonomous oscillators in other regions of the mammalian brain and peripheral tissues challenges the paradigm that there is only one major clock coordinating biological rhythms.[25] However, for the purpose of this discussion we will focus on the suprachiasmatic nuclei as the central clock, synchronized each day by exposure to light, coordinating rhythmic variations in physiological function. It is for this reason that the suprachiasmatic nuclei is termed the "pacemaker" of circadian rhythms.[26]

Tight control of genetic expression within these pacemaker cells is tantamount to the maintenance of circadian schedules. Two transcription factors, BMAL1 and CLOCK, are known to be key players in the timing mechanism of the suprachiasmatic nuclei.[27] Under the influence of these factors, multiple protein expression changes occur, ultimately affecting neurohormonal discharge.

Various studies exploring the effects of core clock gene mutation have clearly shown a strong association with maintenance of a 24-hour cycle.[28] Activation of clock-controlled genes occurs when clock proteins bind to promoters, enhancer regions, and even intron sequences of DNA. Studies regarding clock-controlled gene expression have shown that vasopressin[29] concentrations within the

suprachiasmatic nuclei and hepatic production of the steroid Cyp2α5[30] are under clock gene influence. Using gene microarray analysis, several groups have demonstrated that up to 10% of gene expression is under circadian control.[31–33] Furthermore, clock-controlled genes expressed as a result of this influence vary across tissue types. It is important to note that the research supporting these findings was conducted with the use of animal models. Correlative studies in human subjects are challenging, but new methodologies have been described.[34]

Clinically, the ultimate concern posed by these molecular details is the end-result effects on circadian blood pressure variations. Multiple neuroanatomical studies have shown that suprachiasmatic nuclei output is mainly restricted to the medial hypothalamus,[35] although there is evidence supporting termination of suprachiasmatic nuclei efferents in the rostral area as well as the thalamus of mammalian brains.[36] The ultimate targets of suprachiasmatic nuclei stimulation are endocrine neurons and preautonomic neurons.[37] Direct connections to hormone-releasing neurons (corticotrophin-releasing hormone, thyrotropin-releasing hormone, gonadotropin hormone-releasing hormone) have been shown, as well as the vasopressinergic effect the suprachiasmatic nuclei exerts on the release of glucocorticoids via the hypothalamic-pituitary-adrenal axis.[38] While these neural connections may indicate a level of control on multiple physiological processes, they do not encompass the magnitude of the effect observed. Signaling of preautonomic neurons influences a vast amount of physiological function. Studies using transneuronal tracers have identified the paraventricular nucleus as the center mediating signals from the suprachiasmatic nuclei to the periphery[39,40] via sympathetic and parasympathetic neurons. Perhaps the best described examples of autonomic control exerted by the suprachiasmatic nuclei are that of melatonin secretion[41] and hepatic control of glucose metabolism.[42] Hence, current conventional thought is that these mechanisms play more than an ancillary role in the changes seen in the cardiovascular system through the course of a day.

Circadian blood pressure patterns identified in normotensives and hypertensives

Many major patterns of night-day variations have been described thus far. Multiple definitions for these patterns have been reported. Here, the definitions from a recent study[43] reporting the prevalence of each pattern in a large hypertensive population are described here (Table 1).

Normal (dipping)

A nonhypertensive individual experiences a nocturnal decrease in both systolic and diastolic blood pressure. A decrease of 10%–20% in the systolic blood pressure is considered normal and is not independently associated with any increased cardiovascular risk in nonhypertensives. The decrease seems to be most pronounced in the first few hours of sleep followed by a surge in the morning hours corresponding with sleep to wakeful state.

Nondipping

This pattern, seen in either normotensives or hypertensives, is characterized by an attenuated decrease in the nocturnal systolic blood pressures, defined as $<10\%$.[4]

Extreme dipping

In this pattern, a decrease of $>20\%$ in nighttime systolic blood pressure is noted.[44]

Rising/reverse dipping

Risers or reverse dippers have systolic blood pressures greater at night than during daytime hours.[45]

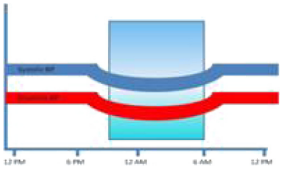
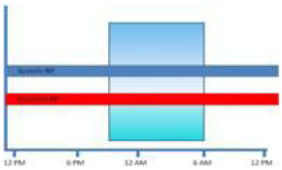
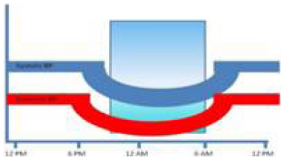
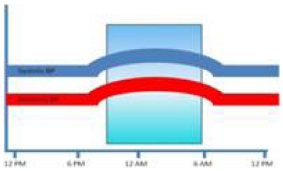
Morning surge

Definitions of the morning surge vary extensively in the literature. Terms are defined as follows: a sleep-trough surge, defined as morning blood pressure (2-hour average of four 30-minute blood pressure readings just after awakening) minus lowest nocturnal blood pressure (1-hour average of three blood pressure readings centered on lowest nighttime reading; a prewaking surge, defined as morning blood pressure minus prewaking blood pressure (2-hour average of four blood pressure readings just before wake-up); and a rising blood pressure surge, defined as morning blood pressure measured on rising minus blood pressure in the supine position <30 minutes before rising.[46] Cutoff levels assigned to each of these have varied from study to study.[47–50] However, no studies have been conducted that show treatment of the morning surge specifically decreases end-organ damage and leads to reduction in cardiovascular events. Hence, this physiological variant is described here for completion.

White coat/masked hypertension

While not classically categorized as deviations from normal circadian architecture, these are diagnoses which are well targeted by 24-hour ABPM. White coat hypertension is considered with the presence of persistently high office

Table 1 Pattern definition and prevalence in untreated and treated patients with hypertension

Pattern type	Definition	Schematic representation	Prevalence in hypertension	
Dipping	Average SBP decrease during the nighttime was 10%–20% from mean SBP during the day		Untreated (n) 50.2% (4302)	Treated (n) 39.9% (13800)
Non-dipping	Average nighttime decreased less than 10% decrease from mean daytime SBP		Untreated (n) 35.0% (2934)	Treated (n) 39.4% (13594)
Extreme dipping	Average SBP during nighttime decreased >20% from mean SBP during the day		Untreated (n) 8.8% (740)	Treated (n) 7.2% (2499)
Reverse dipping	Average SBP during nighttime higher than mean SBP during the day		Untreated (n) 6.0% (502)	Treated (n) 13.5% (4670)

Note: Adapted from de la Sierra et al.[43]

blood pressures with normal self-measured or ambulatory blood pressures. Masked hypertensives, on the other hand, have normal office blood pressure and elevated out-of-office blood pressure values.[51] The use of 24-hour ABPM for the diagnoses of these clinical conditions has been heavily supported by authorities in the field.[52]

Patterns of 24-hour blood pressure values and cardiovascular risk

Initial studies examined 24-hour ABPM data to see if their use enhances diagnostic value over standard in-office pressures. Foci of study then ranged to prognosis and pattern recognition. Here, a brief description of 24-hour ABPM data and their contribution to cardiovascular risk assessment is presented.

The prognostic significance of ABPM was first demonstrated in 1983 by Perloff et al.[53] Of 1076 patients studied, correlation between ABPM values and 10-year risk of fatal and nonfatal events reached statistical significance, whereas clinic measurements could not demonstrate a similar association. In the 1542 patients enrolled in the Osahama study,[54] an increased mortality risk was demonstrated in the subset whose average 24-hour systolic blood pressure was within the highest quintile. No such independent association was shown by office measurements. As reported in the Task Force III publication addressing target-organ damage secondary to hypertension, most ABPM studies analyzed were more closely associated with target-organ damage than were clinic measurements.[55] Thus, ABPM is widely considered superior to office measurements concerning prediction of cardiovascular morbidity and mortality.

In reference to nocturnal pressure changes, O'Brien et al were the first group to demonstrate an increase in the incidence of stroke amongst patients with a blunted or absent fall in nighttime blood pressures.[56] This publication saw the genesis of the terms "dipper" and "nondipper." This categorization of ABPM data dependent upon nocturnal dips was then studied to discover similar associations with other cardiovascular events.

From the PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale) study, Verdecchia et al have produced multiple analyses studying prognosis, blood pressure variability, and pulse pressure amongst patients with essential hypertension. Based on information gathered from 1187 patients, follow-up of approximately 3 years, and use of a cutoff point of <10% to discern dippers from nondippers, the authors found that among sustained hypertensives, nondippers had an increase in cardiovascular morbidity nearly

three times that of dippers (relative risk [RR]: 6.26, 95% confidence interval [CI]: 1.92–20.32 vs RR: 3.70, 95% CI: 1.13–12.5, respectively).[57] In the aforementioned Ohasama study, the authors used cutoff points of >20%, >10% but <20%, >0% but <10%, and no decline in nocturnal blood pressure to classify subjects as extreme dippers, dippers, nondippers, and inverted dippers, respectively. Overall mortality was greatest in inverted dippers and nondippers with no difference seen between dippers and extreme dippers. The same relationship was observed for cardiovascular mortality even after adjustment for daytime, nighttime, and 24-hour blood pressure.[54] In a subgroup of the Syst-Eur (Systolic Hypertension in Europe) trial,[58] 808 patients underwent ABPM at baseline. The incidence of myocardial infarction and stroke was significantly higher in patients with a blunted decline in nighttime systolic pressure, confirming the inverse relationship between cardiovascular risk and nocturnal fall in blood pressure.

Despite the significant amount of evidence put forth from studies such as these, use of the dipper/nondipper classification as a measure of adverse outcome is far from universally accepted.[59] A lack of uniform definitions (day-night parameters, percent decline of nocturnal pressures) is considered a collective limitation in the studies published thus far. In an effort to clarify this, Fagard et al published a study pooling data from three separate trials. In this study, the terms "daytime" and "nighttime," along with "dipping" and "nondipping," were well defined and used consistently in all cases. Given this type of pooling, the total follow-up time amounted to 23,164 patient-years. The incidence of cardiovascular events was worse in reverse dippers ($P \leq 0.05$), whereas mortality was lower in extreme dippers ($P \leq 0.01$) in comparison with dippers after adjustment for confounders and 24-hour blood pressure. Interestingly, outcomes were similar in nondippers and dippers. However, the systolic night-day blood pressure ratio independently predicted all-cause mortality and cardiovascular events ($P \leq 0.001$), even after adjustment for 24-hour blood pressure ($P \leq 0.05$).[60]

Reproducibility of dipping status is considered by some to be a major flaw of utilizing circadian blood pressure variation as a risk marker. A study which illustrates this issue was performed by Hernandez-del Rey et al. In their study, a cohort of 611 hypertensive patients underwent ABPM over a 48-hour period rather than the traditional 24-hour period.[61] When comparing the first 24-hour period with the second, they found that 24% of patients switched dipping status. Similarly, Palatini et al analyzed 508 patients from HARVEST (Hypertension and Ambulatory Recording Venetia Study). ABPM recordings were taken 3 months apart, and overall reproducibility of circadian blood pressure profiles was poor.[62] Omboni et al reported that almost 40% of subjects (n = 180) enrolled in SAMPLE (Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation) were found to have a change in their circadian blood pressure profile.[63] However, these studies do not negate the risks associated with more adverse circadian patterns. Moreover, they highlight the fact that the prevalence of dipping may be underreported, even with the use of 24-hour ABPM.

In order to avoid the pitfalls of dichotomizing a continuous variable, some have suggested the use of thresholds for blood pressure values, which could predict risk with equal or greater accuracy when compared with clinic measurements.[64] In April 2007, investigators from the IDACO (International Database on Ambulatory blood pressure monitoring in relation to CardiOvascular) study group[65] were the first to publish the results of such an undertaking. In this longitudinal study of the general population, 5682 patients from four different countries were followed for a median time frame of 9.7 years. Eight hundred and fourteen cardiovascular events were observed. From the data collected, the authors were able to calculate ambulatory blood pressure thresholds of 24-hour, daytime, and nighttime values for optimal, normal, and ambulatory hypertension, which predicted 10-year cardiovascular risk with similar accuracy as compared with clinic blood pressure measurements.

Measures of target-organ damage, such as increased left ventricular mass,[66,67] silent ischemia,[68] and microalbuminuria,[69] have a higher prevalence in nondippers as compared with dippers. Yet even the most well studied of these markers (left ventricular hypertrophy) has been challenged.[70] Future randomized clinical trials are needed to validate the potential of this powerful clinical tool for developing therapeutic strategies in the management of hypertension.

Pharmacotherapy clinical trials using 24-hour blood pressure monitoring

With the discovery of normal 24-hour patterns of blood pressure using observational studies,[71] clinicians have used 24-hour ABPM as a means of deciphering the superiority of particular drug regimens in establishing and maintaining normal circadian architecture. With its onset, there was great debate amongst the scientific community regarding the use of 24-hour ABPM data to make clinical decisions. However, the Sixth Report of the Joint National Commission (JNC) guidelines were the first guidelines to set normal ranges of

blood pressure during the daytime (<135/85 mmHg) and nighttime (<120/75 mmHg), later to be confirmed by JNC 7[2,72] (normal values are described in Table 2[73]). In addition, 24-hour ABPM has been regarded as a very useful tool because it has several advantages to clinic blood pressure. One such advantage is the lack of a placebo effect with 24-hour ABPM monitoring. In clinical trials testing antihypertensive regimens, the placebo effect is known to elevate clinic blood pressure values. In contrast, 24-hour ABPM does not exhibit this effect, thereby offering an opportunity to establish dose-related antihypertensive effects without the use of a placebo arm.[74,75] In patients on placebo therapy, a mean diastolic blood pressure difference of 2 ± 12 mmHg has been documented in clinic measurements, while it was 1 ± 6 mmHg in ambulatory blood pressure recordings.[75] However, this lack of placebo effect does not persist in longer trial periods. Of note, a 1-year follow-up study of the Syst-Eur trial revealed a 2 ± 11 mmHg fall in 24-hour systolic blood pressure, thereby necessitating a placebo-based control group in longer studies.[76] However, caution must also be exercised when interpreting data from 24-hour ABPM in clinical trials. Notably, 24-hour mean pressures are consistently lower than those obtained in the clinic. Hence, guideline values defining normotension for in-office readings should not be used in their interpretation.[77] Additionally, blood pressure reductions from treatment are smaller in increment with 24-hour mean values in comparison with in-office readings. This can be explained by lower mean nighttime reductions in pressure because reductions are smaller in numerical magnitude. However, it is possible to interpret this overall reduction incorrectly as being less significant when 24-hour ABPM readings are compared with clinic results.[78] With these considerations, the following section describes recent antihypertensive agent trials in which 24-hour pressure reductions were used as endpoints.

Ambulatory blood pressure measurements first saw their application in clinical trials approximately 30 years ago to study ambulatory pressures in patients on beta-blockers, an issue that continues to be relevant in considering efficacy of traditional beta-blockers.[79,80] Since then, hallmark studies have shown important corollary results with the use of 24-hour ABPM.[79,80] One such study, the HOPE (Heart Outcomes Prevention Evaluation) trial,[81] demonstrated the potential importance of 24-hour blood pressure control in regards to cardiovascular events. This study demonstrated that the angiotensin-converting enzyme inhibitor, ramipril, significantly reduced cardiovascular morbidity and mortality in patients at high risk for cardiovascular events. However, only a modest mean reduction of office blood pressure (3/2 mmHg) was noted in subjects. In one substudy of HOPE,[82] 38 patients with peripheral arterial disease underwent 24-hour ambulatory blood pressure measurement before randomization and after 1 year. Again, ramipril did not significantly reduce office pressures (8/2 mmHg) or daytime ambulatory blood pressure (6/2 mmHg) after 1 year. However, importantly, 24-hour ambulatory blood pressure was significantly reduced (10/4 mmHg, $P = 0.03$), mainly because of a more pronounced blood pressure-lowering effect during the nighttime (17/8 mmHg, $P < 0.001$). The night/day ratio was also significantly lowered in the ramipril group. The authors concluded that the significant reduction in cardiovascular events may have been driven by the more marked effect on the 24-hour ABPM values. An important consideration for these results has to do with the time of dosing of ramipril. All patients in the study received the 10 mg dose at bedtime, thereby causing the peak effect of ramipril to take place during nighttime hours. The overall benefit, with the reduction of cardiovascular events in the ramipril group, despite no significant reduction in in-office blood pressure, begs the question of whether restoration of nocturnal dipping played a significant role in this effect.

The HOT (Hypertension Optimal Treatment) study similarly had a 24-hour ABPM substudy[83] illustrating the converse difference between in-office and ABPM values on antihypertensive study. In this study, patients underwent both office and 24-hour monitoring and were treated for a median period of 2 years. All received the dihydropyridine calcium antagonist, felodipine, and were uptitrated in a stepwise fashion to receive an angiotensin-converting enzyme inhibitor, a beta-blocker, or a diuretic. Average 24-hour, and day and night ambulatory blood pressure values were recorded at baseline (n = 277) and during treatment (n = 347). Randomization to a target office diastolic blood pressure of

Table 2 Normal recommended values set forth by the American Heart Association Council on High Blood Pressure Research

	Optimal BP (mmHg)	Normal BP (mmHg)	Abnormal BP (mmHg)
Daytime	<130/80	<135/85	>140/90
Nighttime	<115/65	<120/70	>125/75
24-hour	<125/75	<130/80	>135/85

Note: Adapted with permission from Pickering et al, Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension*. 2005;45(1):142–161. Copyright 2005 Wolters Kluwer Health.[73]

≤90 mmHg, ≤85 mmHg, or ≤80 mmHg was performed. Additional analyses included computation of trough-to-peak ratio and smoothness index (ratio between the average of the 24-hourly blood pressure reductions after treatment and its standard deviation). Office, 24-hour, and day and night blood pressures were all significantly reduced by treatment, but a smaller reduction in ambulatory blood pressures was noted. Trough-to-peak ratios and smoothness indices were lowest in the highest blood pressure target group and highest in the lowest blood pressure target group. It must be noted here that antihypertensive dosing took place in the morning for all patients. This difference in treatment effect between the HOPE and HOT trials may be a function of when the medication was administered. The authors conclude that this disparate reduction between in-office and ambulatory pressures resulted from higher baseline in-office pressures in the cohort. With treatment, the gap between these two values became closer because both the in-office and ambulatory blood pressure values became more or less superimposed once the diastolic pressure was ≤80 mmHg. However, again, time of administration of the antihypertensive regimen may be of some significance.

Given that these differences between in-office and ABPM were highlighted by several treatment-based studies, the question of which values are of greater clinical relevance remains. One study, conducted by the Ambulatory Blood Pressure Monitoring and Treatment of Hypertension group, sought to compare the two methods of blood pressure measurement. A total of 419 patients (with an untreated, in-office diastolic blood pressure ≥95 mmHg) were randomized to conventional or ambulatory monitoring arms. Antihypertensive drug treatment was adjusted in a stepwise fashion based upon diastolic blood pressure. The study revealed lower pressures by ABPM, thereby allowing more patients to either stop (26.3% vs 7.3%; $P < 0.001$) or halt progression to sustained multiple-drug treatment (27.2% vs 42.7%; $P < 0.001$) in comparison with conventionally monitored patients. Interestingly, both left ventricular mass and reported symptoms were similar in the two groups.[84]

While this previous study showed the ability of 24-hour ABPM to identify normotensives mislabeled as hypertensives, one study used telemedicine in conjunction with 24-hour ABPM to diagnose hypertension better. Specifically, the study employed a telemedicine service which transmitted values from an automatic home blood pressure monitor connected to an ordinary telephone line for the transmission of data to a central computer. In this study, the gold standard for assessment of true hypertension status was 24-hour ABPM. From the total of 74 patients who were randomized to either the telemedicine service or usual care, the telemedicine group showed significant improvement for the detection of essential hypertension when compared with the usual care cohort. Sixty-four percent of patients with essential hypertension were diagnosed with essential hypertension vs just 26% in the usual care group. Furthermore, diagnosis was established earlier in the ambulatory group.[85] The use of telemedicine in conjunction with 24-hour ABPM may prove to be a useful tool in the initial adjustment of a patient's initial therapeutic antihypertensive regimen.

Similarly, 24-hour blood pressure monitoring data have been examined to identify whether a pharmacist-physician team approach to therapy can be utilized to improve treatment goal attainment. One such study in 179 patients with uncontrolled hypertension was performed in a prospective fashion. Patients were either randomized to receive pharmacist-physician collaborative management of hypertension (intervention) or usual care (control) for a 9-month period. In the collaborative management group, pharmacists adjusted antihypertensive therapy in collaboration with the patients' primary care providers while helping with lifestyle modifications and identification of barriers to blood pressure control. Ambulatory blood pressure was measured at baseline and at study end. More pronounced changes were noted in the collaborative management arm: daytime change in systolic blood pressure, 15.2 vs 5.5 mmHg ($P < 0.001$); nighttime change in systolic blood pressure, 12.2 vs 3.4 mmHg, ($P < 0.001$); and 24-hour change in systolic blood pressure, 14.1 vs 5.5 mmHg, ($P < 0.001$). Moreover, significantly more patients in the collaborative management group had their blood pressure at goal at the end of the study (75.0% vs 50.7%, $P < 0.001$).[86]

More recently, clinical trialists have started using 24-hour blood pressure monitoring as a means of demonstrating superior efficacy of one drug over other agents in its class. Studies involving azilsartan medoxomil are examples. One study in particular compared the antihypertensive effects of two doses of azilsartan with valsartan 320 mg and 40 mg of olmesartan in a randomized, double-blind, placebo-controlled fashion using both ABPM and clinic blood pressure measurements. The investigators used change from baseline in 24-hour mean systolic blood pressure as their primary endpoint in 1291 randomized patients. Azilsartan at 80 mg showed more significant decreases in the primary endpoint parameter than both valsartan at 320 mg (−14.3 mmHg vs −10.0 mmHg, $P < 0.001$) and olmesartan at 40 mg (−14.3 vs −11.7 mmHg, $P = 0.009$). The lower dose of 40 mmHg

of azilsartan was noninferior to olmesartan. Interestingly, for clinic systolic blood pressures, both doses of azilsartan were superior to the comparator angiotensin II receptor blockers. The safety and tolerability profiles for all medications were similar.[87]

In line with efficacy, 24-hour blood pressure monitoring in pharmacotherapy trials can illustrate inadvertently divergent data in comparison with one-time clinic measurements. This was seen in the case of trials involving the selective endothelin A receptor antagonist, darusentan. In one study of 849 patients with resistant hypertension receiving at least three antihypertensive drugs, subjects were randomized to darusentan, placebo, or the central α-2 agonist, guanfacine. The coprimary endpoints of the study were changes from baseline to week 14 in trough, sitting systolic blood pressure, and diastolic blood pressure measured in the clinic. Unusually, while there was a significant difference between the darusentan and guanfacine groups, (−15 ± 14 mmHg vs −12 ± 13 mmHg, respectively; $P < 0.05$), no significant differences were seen between the darusentan and placebo groups. However, darusentan reduced mean 24-hour systolic blood pressure more than placebo (−9 ± 12 mmHg vs −2 ± 12 mmHg; $P < 0.001$) or guanfacine (vs −4 ± 12 mmHg; $P < 0.001$) after 14 weeks of treatment. This study highlights an important difference in results when using 24-hour blood pressure monitoring vs more conventional studies. This difference may indeed be more pronounced in patients with resistant hypertension as was demonstrated in this study.[88]

While 24-hour blood pressure monitoring is conventionally used to compare efficacy, this tool may help in illustrating the mechanism of action of antihypertensive medications. This was clearly done in the ACCOMPLISH trial, in which benazepril + hydrochlorothiazide was compared with benazepril + amlodipine. In the initial published study, cardiovascular events were less frequent in patients using the amlodipine-based therapy (absolute risk reduction 2.2%; $P < 0.001$). However, only a small difference was noted in blood pressure reduction in this arm (mean difference in blood pressure between the two groups was 0.9 mmHg systolic and 1.1 mmHg diastolic; $P < 0.001$ for both systolic and diastolic pressures).[89] To elucidate blood pressure differences further, a substudy[90] was performed in a subset of 573 subjects who underwent ABPM. Readings were obtained every 20 minutes during a 24-hour period. The treatment groups did not differ significantly in 24-hour mean daytime or nighttime blood pressures with mean between-group differences of 1.6, 1.8, and 1.2 mmHg, respectively. Blood pressure control rates (24-hour mean systolic blood pressure <130 mmHg on ambulatory blood pressure monitoring) were greater than 80% in both groups. However, nighttime systolic blood pressure provided additional risk prediction after adjusting for the effects of the drugs. Given this very similar reduction in 24-hour blood pressures, the authors concluded that the benefit seen in cardiovascular events was most likely linked to a property of the benazepril-amlodipine combination which goes beyond basic blood pressure reduction, ie, pleiotropic effects.

Another therapeutic strategy being examined in trials is the use of pharmacotherapy as a means of restoring risk-associated nocturnal blood pressure patterns (eg, nondipping, reverse dipping) to normal dipping. In line with this, additional comprehensive effects in patients with either dipping or nondipping patterns in the setting of antihypertensive therapy are now being studied more carefully.

Several studies have been conducted using several classes of antihypertensive agents, namely alpha-blockers,[91] loop diuretics,[92] dihydropyridine calcium channel blockers,[93] angiotensin-converting enzyme inhibitors,[94,95] and angiotensin receptor blockers.[96,97] All of these studies showed significant reductions in sleep-time systolic and diastolic blood pressure values.[98] However, a study of torsemide[92] uniquely showed a significant reduction in bedtime, awake-time, and sleep-time mean systolic blood pressure and diastolic blood pressure values when administered at bedtime.

Combination therapy trials have been conducted in a similar regard. One such study, ie, REZALT,[99] from a group in Japan, focused on the efficacy and tolerability of olmesartan-azelnidipine combination therapy as compared with monotherapy with either agent. Categorically, all arms were studied both for 24-hour blood pressure control as well as for specified hours during the daytime, nighttime, and early morning. Additionally, the presence or absence of nocturnal dipping was also recorded in patients while on therapy. In 839 patients with 24-hour ABPM data, high-dose combination therapy was associated with significantly greater antihypertensive effects on 24-hour ABPM compared with either monotherapy in all of the time periods. Mean systolic and diastolic reductions with combination therapy in the daytime were −22.6/−14.1 mmHg, −21.2/−12.5 mmHg at nighttime, and −20.6/−11.9 mmHg in the early morning (all $P < 0.05$ vs all other treatment groups). The antihypertensive effects of combination therapy were significantly greater than those with monotherapies, regardless of dipping pattern at baseline (all $P < 0.05$) in all of the time periods, with the exception of the nighttime reduction with low-dose combination vs olmesartan monotherapy in dippers. This study highlights newer

time-based parameters by which the therapeutic efficacy of antihypertensive agents is gauged.

While this study tracked blood pressure changes and the influence of combination therapy on circadian pressures, a study by Herimda et al[100] also showed benefit for overall cardiovascular risk with the lowering of sleep-time blood pressures. The MAPEC study was designed to study the use of bedtime antihypertensive medications at bedtime. In this study, 2156 hypertensive individuals were randomized to ingest all their antihypertensive medications in the morning vs taking one or more medications at bedtime. Patients underwent 24-hour ABPM for 48 hours at baseline and every 3 months for a mean follow-up time of 5.6 years. Patients randomized to the nighttime medication administration arm were noted to have a greater decrease in sleep-time relative systolic blood pressure (2.9 ± 7.4 mmHg vs −1.5 ± 6.7 mmHg; $P < 0.001$). Moreover, the nighttime medication group also showed a significantly lower relative risk of total cardiovascular events (all-cause mortality, myocardial infarction, angina pectoris, coronary revascularization, heart failure, acute arterial occlusion of the retinal artery, hemorrhagic and ischemic stroke, and transient ischemic attack) because only 11.95% experienced a clinical event vs 27.8% of the conventional morning-dosed arm.

The restoration of normal nocturnal dipping using antihypertensive agents by changing the time of administration is now being developed conceptually as chronotherapy continues to emerge as a potential means of improving blood pressure architecture. In a study from Japan, 71 hypertensives were classified as dippers (n = 36) or nondippers (n = 35). The investigators shifted the administration of a long-acting antihypertensive agent from daytime to bedtime in the nondippers. By doing so, the investigators yielded results showing that in-office and 24-hour ambulatory blood pressure did not change, but the circadian blood pressure increased slightly and nocturnal blood pressure decreased markedly. The nocturnal dip increased from 2.6% to 15.5% ($P < 0.0001$), whilst the nocturnal dip in diastolic blood pressure increased from 5.6% to 16.9% ($P < 0.0001$). As a result, 71% of the nondippers converted to dipping nocturnal patterns.[101]

Similar results were seen in patients with resistant hypertension on combination therapy. In a study of 250 hypertensive patients receiving three agents for the treatment of hypertension, subjects were randomized to one of two groups. In the first group, one of the drugs in the regimen was changed; however, dosing of all three remained in the morning while in the other group, the new drug was dosed at night. Blood pressure was measured for 48 hours before and after 12 weeks of treatment. In patients on morning dosing, no effect on ambulatory blood pressure was noted, while the baseline prevalence of nondipping slightly increased after treatment. On the other hand, the group with morning and nighttime dosing showed a significant decrease in ambulatory blood pressure (9.4/6.0 mmHg; $P < 0.001$). Prechronotherapy, 16% of the patients in this group were dippers at baseline, which increased to 57% after therapy ($P < 0.001$).[102]

Restoration of nocturnal dip has been associated with an improvement in left ventricular ejection fraction. One study examines this association in the setting of dihydropyridine therapy in type 2 diabetic hypertensives. In all, 54 patients were openly randomized to either amlodipine or long-acting nifedipine. Of these, ambulatory 24-hour ABPM and echocardiographic examinations were performed in 42 patients before and after 1 year of treatment. A reduction of 17% in systolic blood pressure and a 12% reduction in mean arterial pressure was recorded, but no difference was noted between the two arms. Of these 42 subjects, eight became "new dippers" at the end of the study. In these new dippers, an improvement in ejection fraction (69.6% ± 7.2% to 75.8% ± 7.4%; $P < 0.05$) was shown after 1 year of therapy. This difference was significant when compared with other patients who either stayed nondippers or dippers (9.4% ± 10.9% vs −1.2% ± 11.8%; $P < 0.05$) after the therapeutic time period.[103]

Device therapy to modify circadian blood pressure patterns

Given the association of adverse cardiac events with nondipping and extreme dipping patterns of blood pressure over a 24-hour period, devices used in various clinical conditions have been studied to ascertain whether their beneficial effects also influence circadian blood pressure changes. A synopsis of the studies conducted in this regard is presented here.

The use of continuous positive airway pressure (CPAP) systems has been shown to improve early signs of atherosclerosis, thereby impeding progress to clinical coronary artery disease.[104] Additionally, C-reactive protein, a marker shown to predict cardiovascular risk independently,[105] has been associated with a reduction of levels in those on CPAP therapy.[106] Similarly, in the CANPAP (Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure) trial which was designed to address the issue of benefits from CPAP therapy in patients with heart failure and central sleep apnea, improvement was seen in ejection fraction and 6-minute walk distance. Moreover, transplant-free survival was noted to be increased in the CPAP therapy arm in those

subjects with adequate diminution of nocturnal apneic episodes (apnea-hypopnea index < 15).[107] Similarly, the use of CPAP therapy has been associated with improved circadian blood pressure architecture. One such study sought to evaluate the circadian pattern of blood pressure and the effects of nasal CPAP in patients with obstructive sleep apnea. Twenty-four-hour blood pressure monitoring was conducted in 38 male patients with obstructive sleep apnea with and without nasal CPAP. Of these, 58% of subjects were nondippers, defined as having an average <10 mmHg decrease in systolic and/or <5 mmHg decrease in diastolic blood pressure from daytime to nighttime values. Additionally, daytime hypertension (defined by the high cutoff of 160/95 mmHg) was present in 11 of the 38 patients. Nasal CPAP treatment for 3 days changed 15 of the 22 "nondippers" to "dippers" while reducing the number of patients with daytime hypertension to five ($P < 0.05$).[108]

The development of antihypertensive devices is ongoing, and promising results have been yielded from feasibility studies. One device, the Rheos® system (CVRx Inc, Minneapolis, MN), uses baroflex activation therapy by chronically stimulating the carotid sinus using a pulse generator (Figure 3). Preliminary results have shown improved blood pressure reduction in 45 patients with resistant hypertension (systolic blood pressure >160 mmHg) on three or more antihypertensive agents. In ABPM, a mean decrease in systolic blood pressure (−13 ± 3 mmHg; $P < 0.001$) and diastolic blood pressure (−8 ± 2 mmHg; $P < 0.001$) was noted at 1-year follow-up. Likewise, a decrease in 8 mmHg was noted in diastolic blood pressure values.[109] However, data on circadian rhythms from this promising trial have yet to be released. If conversion from a nondipping to a dipping pattern is seen in patients, this device would provide a novel therapy to improve circadian blood pressure rhythm. These data are eagerly awaited.

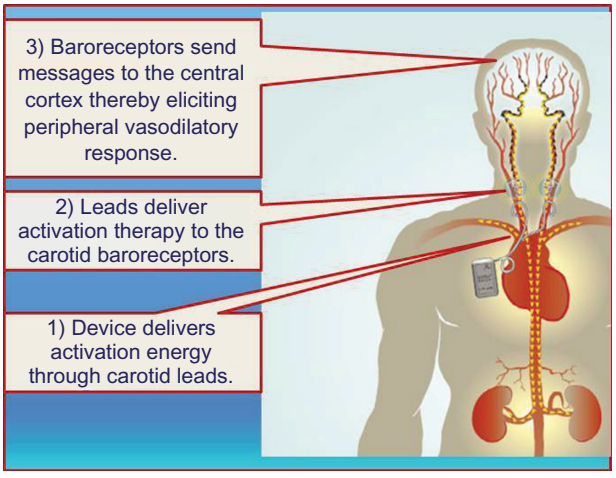


Figure 3 A schematic representation describing the mechanism of action of the Rheos® system.
Note: Courtesy of CVRx Inc, Minneapolis, MN.

The issue of circadian blood pressure rhythm has also been addressed in patients requiring ventricular assist device support for severe heart failure. This population has been noted in studies to have pronounced disturbances in the normal circadian variation in blood pressure.[110,111] Restoration of normal 24-hour blood pressure variation has been reported in patients with severe heart failure months after heart transplantation.[112] Slaughter et al retrospectively studied patients with HeartWare HVAD® therapy as a bridge to cardiac transplantation. In this study, HVAD flow (L/minute), motor speed (rpm), and power (watts) were collected every 15 minutes after device implantation. The general mechanism of ventricular device support is shown in Figure 4. By day 30, the difference in flow between midnight and 4 am was noted to be 37% greater than on day 7 ($P < 0.002$). As a corollary, the morning increase, defined as the increase in flow and power between 4 am and 9 am, was recorded to be 33% greater on day 30 than on day 7 ($P < 0.002$).[113] Further evaluation of restoration of circadian blood pressure patterns secondary to left ventricular assist device therapy as an adjunct goal of therapy, potentially impacting functional capacity and mortality, would be of great clinical interest.

Summary

The use of 24-hour ABPM has beneficially augmented the prognostic value derived from blood pressure measurements. In addition to providing more reproducibility, they have added prognostic value. Moreover, their use has enabled both researchers and clinicians to target another therapeutic aim. Pattern recognition has also identified variations with associated cardiovascular risk. The restoration of these more pathological patterns to normal architecture using either pharmacotherapy or device therapy may confer an outcome benefit. However, judicious use of 24-hour ABPM and its ability to guide antihypertensive therapy continues to be a vexing issue for many clinicians because very little is addressed in the formulated guidelines. Hence, in consideration of the data compiled thus far by various investigators, the recommendations are as follows:

Use of 24-hour ABPM

While the use of 24-hour ABPM to diagnose both white coat and masked hypertension is well established and guideline-driven,[2] its use to control blood pressure better over a 24-hour period may be warranted, especially in higher-risk patients, such as those with renal insufficiency or pre-existing coronary

artery disease. As described above, amelioration of 24-hour blood pressure architecture not only decreases mean blood pressure values but has also been shown to have effects on established risk factors, such as left ventricular hypertrophy and hard clinical outcomes.

Antihypertensive therapy

While reduction in in-office blood pressure continues to be the primary therapeutic goal of antihypertensive regimens, the use of agents should also be tailored to restore nocturnal dipping, which is an essential, physiological phenomenon requiring preservation to decrease overall cardiovascular risk. To this end, the administration of longer-acting agents at bedtime may be beneficial because peak effects will take place during sleep-time hours. Moreover, medications with shorter half-lives (eg, traditional beta-blockers) could adversely affect the nocturnal dip and may in part explain their adverse effects when used in the setting of primary hypertension.[114] Hence, data from 24-hour ABPM may help tailor therapy to preserve normal 24-hour variations.

Device therapy

Current devices used during sleep-time, such as CPAP machines, may exert additional benefit by decreasing pressures during hours of use. Future development of devices such as the Rheos® system should monitor blood pressure and potentially augment nocturnal blood pressure reductions. Lastly, as the prevalence of left ventricular assist device therapy continues to flourish, systems should also be programmed to preserve the nocturnal dip.

Disclosure

The authors report no conflicts of interest in this work.

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