Ambulatory Blood Pressure Monitoring: Coming of Age in Nephrology

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ABSTRACT
The number of patients undergoing ambulatory blood pressure monitoring (ABPM) and the number of publications using this technique to evaluate the risks and effects of high blood pressure on target organs has been increasing, and dramatically so, in the last 5 years. Much of this growth has centered on the role of the blood pressure load (the percentage of systolic or diastolic readings above a preset value during a specific time period) and the changes in blood pressures levels that occur with sleep. Although many studies are focused on the interaction between blood pressure (as assessed by ABPM) and the heart, interest is growing in the application of ABPM to the practice of nephrology. This paper discusses some of the technical aspects of ABPM, followed by a review of five areas of clinical research using ABPM, and which are relevant to renal medicine: microalbuminuria, renal function, renovascular hypertension, dialysis (hemodialysis and continuous ambulatory peritoneal dialysis), and transplantation. Despite a general lack of reimbursement for performance of the ABPM procedure, the growth in its usage and the willingness of clinicians to withhold or alter therapy on the basis of ABPM readings is testimony to its clinical value in the management of hypertension.

Key Words: Blood pressure monitoring, hypertension, circadian rhythm, transplantation, review

Ambulatory blood pressure monitoring (ABPM) began as an endeavor to improve the understanding of the relationship between blood pressure levels and the development of target organ damage from high blood pressure (1). It has long been known that blood pressure fluctuates greatly within an individual, and that casual office blood pressure readings were not always typical of the hemodynamic profile of any particular patient. Thus, it was logical to obtain more frequent blood pressure readings so that the hemodynamic profile of an individual could be characterized more completely. Several prospective studies have confirmed that ambulatory recordings, compared with office values, improve the predictability of blood pressure as a risk factor for target organ damage (2,3). As blood pressure monitors were developed and subsequently automated, it became possible to obtain readings even when a patient was asleep. This additional dimension expanded the pursuit of the relationship between hypertension and its effects on target organs to include an evaluation of the behavior of blood pressure during sleep, in addition to the daytime.

Investigation of the nocturnal blood pressure pattern has yielded further information on the relationship between high blood pressure and target organ damage such as left-ventricular hypertrophy and renal failure (4–6).

Figure 1 shows the number of publications using ABPM. As more reports appeared, and as the monitoring units became smaller and lighter in weight, interest in the clinical and research uses of ABPM has increased. The reasons why physicians in practice request ABPM was assessed by questionnaire in a recent study by Grin et al. (7). The responses by community-based practitioners and subspecialists (including a few nephrologists) were similar. ABPM was requested for the evaluation of borderline hypertension (27%), the adequacy of antihypertensive therapy (25%), the evaluation of the "white-coat" phenomenon (22%; wherein "white coat" is understood to be average in-office diastolic readings > 90 mm Hg with average out-of-office daytime values below 86 mm Hg), investigation of resistance to drug therapy (16%), or for miscellaneous reasons, such as assessment of blood pressure levels during symptoms such as light-headedness (10%).

Many reviews center on the role of using ABPM to evaluate patients for left-ventricular hypertrophy, overall cardiovascular risk, white-coat effect, etc. (8–11). In this review, some of the technical aspects of ABPM, including the diurnal profile and five areas of ABPM usage that are relevant to nephrology, will be covered. The brief coverage of the technical aspects of ABPM seems appropriate, because in the study quoted previously (7), although most community-based practitioners (61%) felt reasonably knowledgeable about ABPM, only 28% of subspecialists considered themselves "well informed" about the technique.

TECHNICAL ASPECTS

ABPM requires the purchase of an ambulatory blood pressure monitor, a computer system or monitor in-
interface, and software that configures the monitor and reads and analyzes the data from the monitor. The monitoring unit is programmed to record blood pressure readings at set intervals during the day (usually 15 to 20 min apart) and night (usually hourly) hours, and should be placed comfortably on the nondominant arm of the individual wearing it, to minimize data loss from arm motion. Once the monitor is in place, it is important to determine if it is reading correctly. Some monitors come with the ability to interpose a “T” piece connector between the cuff tubing and the monitor unit. This allows the attachment of a wall mercury (or aneroid) sphygmomanometer “in-line” with the cuff, so that a routine blood pressure measurement can be taken with a stethoscope over the brachial artery on the same arm to which the ABPM cuff is applied. This requires some practice, as the bleed-down rate occurs in small sudden increments and is not as smooth as when the air is let out gradually during a regular blood pressure measurement. At least three correlating readings should be taken at the time of attachment and again at the time of removal, and usually the auscultated readings are within 4 to 6 mm Hg of the ABPM readings.

A person wearing an automated blood pressure monitoring system needs a certain amount of instruction regarding the device and what to do if there are problems during the time of the ABP monitoring. Although many physicians recommend using a set of printed instructions, we have found it expedient to give patients 5 to 10 min of instruction regarding what to expect while wearing the monitor, in addition to giving them printed instructions and a diary. The more common reasons for losing data are shown in Table 1, and the purpose of the instruction is to point out how data loss happens and what the patient should do to minimize it. The cuff may occasionally need retightening by the patient because it may loosen and slide down the arm after repeated recordings. The monitors typically beep a few seconds before initiating a reading, so that the arm can be placed in a comfortable position for the reading. A recording may be lost if the arm is jostled (such as while riding in a car or bus over a bumpy road) or moved actively, such as in the swinging arm motion of a brisk walk or jog. We recommend that at night, patients place the unit at the head of the bed to minimize the likelihood of their rolling onto and kinking the pressure tubing. If a patient removes the unit when he or she takes a shower, it should be switched off while unattached, and switched back on when reattached. Patients are provided with a diary, and are encouraged to write down times when they are engaged in activities or experience things such as a headache, etc. We find that despite their having a diary, it is still necessary for patients to be interviewed to determine the exact times of their going to sleep, arising from sleep, and medication dosing. Figure 2 is an example of readings taken throughout a 24-h period. This patient indicated the time shown on the figure as his sleeping period, but during his interview, he related rising from bed nearly hourly during “sleep” to void urine because of his prostatic hypertrophy. This condition had become such a longstanding problem that this information was not included as part of his diary entry.

Most units come with the option of “hiding” the results of each recording by having the recorder’s display remain blank, or only show the time of day. Some investigators configure their monitors this way because an occasional blood pressure reading will be elevated out of proportion to other readings, leading to anxiety and needless worry on the part of the patient. In our practice we leave the display on, but recommend that patients not “peek.”

A typical ABP profile for a normotensive subject, a modestly hypertensive patient, and a hypertensive patient without a nocturnal “dip” are shown in the top (A), middle (B), and bottom (C) panels of Figure 3, respectively. The upper and middle panels show a preserved circadian rhythm, with a fall in blood pressure readings during the night, and an increase in readings during the morning hours. The lower panel depicts a hypertensive patient (who was taking antihypertensive medication) who displays the phenomenon of “non-dipping.” The decrease in blood pressure when a person falls asleep is known as the nocturnal
dip, and appears to be related to a diminished activity of the autonomic nervous system, although other features (such as hormonal alterations, reduced physical activity, etc.) occur. As covered below, there is significant interest about the absence of "dipping" in some patients, and in the expression of target organ damage from hypertension.

Interpretation of an ABPM recording depends, in part, on why it was requested. We calculate daytime systolic and diastolic "loads" (i.e., the percentage of systolic and diastolic readings at or above 140 and 90 mm Hg, respectively) and include references to published ranges of blood pressure loads that are gender- and age-specific in our report (12,13). We evaluate the blood pressure profile during patients' sleep to determine if the expected 10% decline in systolic and diastolic pressures (nocturnal "dip") has occurred. Lastly, we comment on the apparent adequacy of blood pressure control and whether there is evidence of a "white-coat" effect, and address any other specific questions if these were written into the referral request. Several definitions of a "normal" ambulatory profile exist, on the basis of percentile readings of normotensive populations (14) or the prevalence of target organ damage such as left-ventricular hypertrophy (15). We use the published ranges of Zechariah et al. (13), which are broken down by decade and gender.

A difficult issue arises when an ambulatory monitor report contains a value or a few values that are clearly much higher or much lower than the range seen within the vast majority of the residual readings. There is no simple method on how to edit this kind of data, however, several useful guidelines have been suggested. Some software programs (such as that provided by Spacelabs, Redmond, WA) have built-in algorithms that reject readings with systolic pressures >260 mm Hg or <70 mm Hg, diastolic readings >150 mm Hg or <40 mm Hg, or unphysiologic pulse pressures (systolic-diastolic) that are >150 mm Hg or <20 mm Hg. Other techniques, including statistically manipulating the other readings in a series of blood pressure recordings around the suspicious value(s) (16) or identifying and eliminating readings with a disproportionate effect on the overall blood pressure profile (17), have also been suggested.

**ABPM AND MICROALBUMINURIA**

An increase in urinary protein excretion occurs in cases of essential hypertension (18). Microalbumin-
ABPM in Nephrology

SYSTOLIC

DIASTOLIC

SLEEP

NOON 4PM 8PM MIDNITE 4AM 8AM NOON
TABLE 2. Comparison between method of blood pressure determination (office versus ABPM) and correlation ($r$) to microalbuminuria in nondiabetic patients with hypertension

<table>
<thead>
<tr>
<th>Investigator (Reference #)</th>
<th>Number of Patients</th>
<th>Office BP Correlates?</th>
<th>ABPM Correlates?</th>
<th>ABPM Better than Office?</th>
<th>Daytime ABPM Correlates?</th>
<th>Nighttime ABPM Correlates?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opsahl et al. (20)</td>
<td>42</td>
<td>Y, S ($r = 0.31$)</td>
<td>Y, S ($r = 0.44$)</td>
<td>Y, NS</td>
<td>Y, S and D ($r = 0.30$ (S) and $0.19$ (D))</td>
<td>Y, S and D ($r = 0.32$ (S) and $0.23$ (D))</td>
</tr>
<tr>
<td>Høegholm et al. (21)</td>
<td>284</td>
<td>Y, S ($r = 0.18$)</td>
<td>Y, S and D</td>
<td>Y, NS</td>
<td>Y</td>
<td>Y, S and D ($r = 0.34$ (S) and $0.29$ (D))</td>
</tr>
<tr>
<td>Bianchi et al. (22)</td>
<td>63</td>
<td>N</td>
<td>Y, S ($r = 0.33$)</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Giaconi et al. (46)</td>
<td>21</td>
<td>N</td>
<td>Y, D</td>
<td>Y, D ($r = 0.48$)</td>
<td>Y, D ($r = 0.48$)</td>
<td>Y, D ($r = 0.48$)</td>
</tr>
<tr>
<td>Redon et al. (47)</td>
<td>141</td>
<td>N</td>
<td>Y, S and D ($r = 0.34$ for both)</td>
<td>Y</td>
<td>Y, S and D ($r = 0.34$ for both)</td>
<td>Y, S and D ($r = 0.34$ for both)</td>
</tr>
</tbody>
</table>

$^a$ BP, blood pressure; ABPM, ambulatory blood pressure monitoring; Y, yes ($P < 0.05$); N, no ($P = $ not significant (NS)); Y, S, yes but only systolic BP; Y, D, yes but only diastolic BP; Y, NS, yes ($r$, higher $r$ value) but not statistically significantly different from office BP; Y, S and D, yes for systolic and diastolic BP. Blank spaces indicate values/answers not stated.

urina (generally defined as a dipstick-negative test for urinary protein) may also be related to blood pressure levels (19). Some studies suggest a significant correlation between the degree of hypertension as measured in an office setting and microalbumin excretion (20,21), but others do not show a significant relationship (22,23). ABPM has been applied to this issue to address whether the 24-h blood pressure load and/or the nocturnal component of the blood pressure profile clarify the relationship between blood pressure and microalbuminuria excretion further.

Table 2 presents findings from several representative studies that have examined office-based blood pressure and ABPM in evaluating patients for a relationship between the blood pressure and urinary microalbumin excretion. Direct comparisons between these studies are difficult because they differ in how microalbumin data are presented, how the urine samples were collected, and how many urine samples were evaluated. Although these studies vary in which aspect of a 24-h recording of blood pressure (systolic pressure, diastolic pressure, or both) proved to be the better indicator of microalbumin excretion, the consensus indicates that ABPM usually has a stronger correlation to the presence and/or magnitude of microalbuminuria when compared with routine office blood pressure measurements.

Because proteinuria is a predictor of cardiovascular disease in nondiabetic patients (24–26), it appears logical to attempt earlier risk definition using microalbuminuria as the clinical marker and ABPM as the discriminating tool. ABPM may serve to clarify better the characteristics of hypertension within an individual, providing a clearer indication of which patients are at risk for experiencing subsequent complications such as renal impairment if microalbuminuria is a reliable predictor of nephropathy in nondiabetic hypertensive patients, as has been reported by some investigators (24).

**ABPM AND RENAL FUNCTION**

Hypertension is the second most frequent diagnosis for new patients reaching ESRD in the United States (27). Although the natural history of untreated hypertension results in damage to the kidney, the likelihood of ESRD occurring in a hypertensive patient is quite variable, and depends in part on a patient's ethnic background as well as comorbid conditions such as diabetes. For example, several studies attest to a greater likelihood of renal function impairment in hypertensive African-American patients, compared with hypertensive Caucasian patients (28,29).

A recent study by Portaluppi et al. (6) using ABPM noted that patients with established renal failure (creatinine clearance rate < 30 mL/min) were less likely to show a nocturnal dip in blood pressure, and frequently showed an actual increase in nocturnal versus day-night blood pressure levels when compared with the blood pressure profiles of matched essential

Figure 3. ABPM profiles. (A) Profile of a normotensive subject, demonstrating an occasional reading above hypertensive boundaries and showing normal suppression of blood pressure during sleep ("dipper"). (B) Profile showing a modestly hypertensive patient (not on antihypertensive therapy) with preservation of sleep suppression of blood pressure. (C) Profile showing a hypertensive patient who lacks sleep-period blood pressure reduction ("non-dipper"). The dashed lines at 140 mm Hg and 90 mm Hg are gridlines and are for visual reference only.
hypertensive patients. The renal patients were matched to the essential hypertensive patients according to 24-h systolic and diastolic pressures. As a result, the daytime blood pressure measurements of the renal-failure patients were actually lower than those of the essential hypertension patients (as necessitated by matching for mean 24-h blood pressures, because the nighttime pressure measurements were higher for the renal-failure patients than for those of the essential hypertensive patients). Although the renal failure patients had identical 24-h blood pressure “loads,” they showed less variability in blood pressure (i.e., less day-minus-night difference) and this lack of variability was believed to be a contributing factor in the damage to the kidney in the renal failure group. An important strength of this study was the fact that the authors controlled the activity level in their subjects by doing all blood pressure monitoring in a supervised hospital setting.

The study of Harshfield et al. (30) in African-American and Caucasian children and adolescents may provide further insight into the difference in susceptibility of one versus another ethnic group. In their experience, the African-American group (but not the Caucasian group) showed a significant inverse correlation between renal function (assessed by creatinine clearance rate) and nighttime systolic and diastolic blood pressure. This data supports the observation of greater susceptibility to renal impairment from hypertension in African Americans, compared with Caucasians.

These data indicate that higher nocturnal blood pressure levels may be a factor in the loss of renal function. The lack of nocturnal blood pressure suppression reduces the 24-h variability in blood pressure and this more constant 24-h pressure load may contribute to renal failure. This relationship between blood pressure and renal function impairment may be the direct result of the hemodynamic effects of an increased 24-h pressure load on the renal circulation. On the other hand, the lack of nocturnal suppression may be a surrogate marker for other factors, such as increased sympathetic neural activity, less daytime activity, greater circulatory volume expansion, or abnormalities in glucocorticoid/mineralocorticoid or other hormone metabolism in these patients (8).

ABPM AND RENOVASCULAR HYPERTENSION

ABPM has been used in renovascular hypertension to characterize the diurnal profile, examine differences in type (fibromuscular versus atherosclerotic) and extent (unilateral versus bilateral) of occlusive renal artery disease, and to monitor changes in blood pressure over time after stenotic lesion correction.

Most studies, such as those of Middeke and Schrader (31) and Imat et al. (32,33) show a lack of nocturnal blood pressure suppression in secondary hypertension, including renovascular hypertension. However, not all investigators agree. In the observations of Gosse et al. (34), renovascular hypertensive patients, when matched for daytime systolic blood pressure with essential hypertensive patients, show a similar lack of nocturnal dip compared with the essential hypertensive patients, and the authors argued that the level of daytime systolic blood pressure predicted the difference in [day – night] systolic blood pressure.

In evaluation of the type of stenotic lesion, the study of Baumgart et al. (35) indicated that patients with correction of occlusive renal disease show a short-term improvement (within a day), and a continued improvement in the 9 to 11 months after angioplasty, as manifested by a reduction in both blood pressure and antihypertensive medication. In their study, patients with fibromuscular disease, or patients with only one kidney, showed a greater daytime blood pressure response (decline of 29/20 mm Hg systolic/diastolic blood pressure) compared with patients who had atherosclerotic disease and two kidneys (decline of 18/11 mm Hg systolic/diastolic blood pressure) after 9 months of follow up.

ABPM AND DIALYSIS MODALITY

Left ventricular hypertrophy is a common finding among hemodialysis patients, and is a significant predisposing factor in the high incidence of cardiovascular morbidity and mortality in dialysis patients (36). ABPM has been utilized in dialysis patients to determine if changes in the diurnal profile are associated with abnormalities in volume control and autonomic function because these changes are frequently found in dialysis patients and are factors that affect left-ventricular wall thickness.

The study of Cheigh et al. (37) examined blood pressure recordings obtained for 48 h after hemodialysis. Their study showed a substantial incidence of uncontrolled blood pressure (defined a systolic blood pressure >150 mm Hg or diastolic blood pressure >90 mm Hg) in 53 hemodialysis patients already on drug therapy for hypertension. Their patients lacked a nocturnal dip during the monitoring period. Interestingly, their study showed a fall in blood pressure in 72% of black compared with only 30% of white patients immediately after hemodialysis, perhaps because of greater susceptibility of blood pressure to volume control in the group of black patients. More importantly, in eight patients with poorly controlled hypertension, a significant improvement in blood pressure profile (a decrease in systolic load from 77% to 18% and a decrease in diastolic load from 37% to 9%) was achieved after changes in antihypertensive therapy were made on the basis of the original ABPM observations.

Differences in blood pressure profiles between patients on peritoneal dialysis, who should theoretically have less volume fluctuation, versus patients on hemodialysis, who would be expected to show more volume gain between treatments, have been sought. A
comprehensive evaluation of this issue was reported by Luik et al. (38), who evaluated hypertensive and normotensive hemodialysis and continuous ambulatory peritoneal dialysis patients in whom antihypertensive therapy was discontinued at least 3 wk before study. Interestingly, there were no differences in the diurnal patterns between hypertensive or normotensive dialysis patients within each dialysis group, or between hemodialysis as compared with continuous ambulatory peritoneal dialysis patients. Moreover, diurnal variation in the hemodialysis patients was not attenuated on the third compared with the first interdialytic day, when weight gain (volume expansion) would be greater. In this study, only 20% to 25% of dialysis patients were non-dippers, and the hypertensive patients were described as “mild,” thus, it is difficult to generalize these findings to more severely hypertensive dialysis patients. Both groups of dialysis patients displayed less day-minus-night [day – night] difference in systolic, and more strongly in diastolic, blood pressure profiles than in nondialyzed normotensive subjects.

ABPM has served to identify patients on dialysis whose blood pressure profiles could be improved by alterations in antihypertensive drug therapy. Because ABPM is superior to conventional blood pressure recordings in identifying patients with increased left-ventricular mass, and because left-ventricular hypertrophy is common in dialysis patients, ABPM could prove to be a useful tool in improving blood pressure control in this population. Some debate still exists regarding the frequency of dipping, the relationship of dipping to one versus another dialysis modality, and the role of nocturnal blood pressure in left-ventricular abnormalities in dialysis patients. A growing body of literature attests to changes in volume status, autonomic function, hormones, catecholamines, and other factors in the makeup of the circadian blood pressure profile. Although changes in all of these factors occur in patients with ESRD, it is still unclear how, and which of, these factors exert a significant impact on the 24-h blood pressure of dialysis patients.

ABPM AND TRANSPLANTATION

Among the influences that regulate the 24-h circadian rhythm, the sympathetic nervous system appears to be one of the most important factors. Transplantation of solid organs adds the dimension of placing an organ not under direct sympathetic control (at least at first) into the circulation. In addition, the immunosuppressive medications used to maintain the transplanted organ’s acceptance have an effect on blood pressure and on the 24-h profile of blood pressure, particularly prednisone (loss of nocturnal dip (39)) and cyclosporine (general increase in blood pressure (40)).

A loss of the usual nocturnal dip in blood pressure was first reported in heart transplant patients, who not only become non-dippers, but who also demonstrate a lack of fall in heart rate at night (41). Hepatic transplant patients also demonstrate a loss of nocturnal blood pressure reduction during sleep (42), which may be related to the dose of glucocorticoids used for immunosuppression.

Renal transplant recipients often show a loss of nocturnal dipping. An interesting study by Gatzka et al. (43) examined 24-h blood pressure profiles during early, intermediate, and late periods after successful renal grafting. The number of dippers within each group increased as time from transplant elapsed. In the early group (up to 7 months from the date of transplantation), 4 of 15 patients showed the normal nocturnal dip, whereas the intermediate group (7 to 12 months from the date of transplantation) had 7 of 15 dippers, and the late group (>12 months after the date of transplantation) had 11 of 15 patients showing nocturnal suppression of blood pressure. There were no significant differences in serum creatinine levels or cyclosporine dosages among the three groups, but there was a small (and significantly higher) dose of methylprednisolone used in the early group (7 ± 2 versus 4 ± 1 versus 4 ± 1 mg/daily in the early, intermediate, and late groups, respectively). Because reinnervation of renal allografts occurs with time, it is tempting to speculate (as Gatzka and colleagues did) about the role of changes in autonomic function and the increase in dipping with time among the three groups.

The mechanisms underlying the loss of the nocturnal dip in transplant patients are not clear, and probably vary depending on the type and dose of immunosuppressives used, the organ transplanted, and the timing of the blood pressure recording after grafting. Although cardiac denervation may explain the loss of dipping in heart transplant patients, it does not account for the same phenomenon in non-cardiac organ transplantation. The nocturnal heart rate decrease is preserved after hepatic transplantation and it is difficult to invoke excessive sympathetic activation as the explanation for non-dipping in hepatic transplant recipients (44). It may be that circulatory volume increases underlie part of these findings in hepatic and perhaps in renal transplant patients (44). Further studies are needed to clarify the mechanisms underlying these changes.

SUMMARY

ABPM has certain advantages over routine office blood pressure measurement. In the words of Martin Myers (45), “... The ambulatory recorder cannot speak to the patient while taking a reading and it will not adjust the value to the nearest zero.”

From a research standpoint, many ABPM studies evaluate patients at only a single point in time and lack the ability to relate blood pressure as a cause or a consequence of the phenomenon in question, because patients frequently do not have baseline or serial recordings before they develop renal failure.
undergo transplantation, etc. More studies such as those of Taler et al. (44) are needed in this regard. Additional information is needed to clarify whether the load of blood pressure (percentage of high readings), the variability in the blood pressure profile (including day – night) differences, or some function of both predisposes to target organ damage.

From a clinical standpoint, because cardiovascular disease is the leading cause of death in the United States, and is an even more frequent cause of death in renal patients compared with the general population, the linkage between renal failure, heart disease, and blood pressure levels, and the best ways to assess the adequacy of antihypertensive treatment will remain an important issue. As more is understood about the components of the circadian blood pressure rhythm, especially with respect to the environmental input on this pattern, the meaning of nocturnal blood pressure profiles should become clearer. Whereas the lack of reimbursement by many insurers for the performance of the ABPM procedure, the buy-in costs to begin and maintain an ABPM program, and the under-reimbursed time it takes to evaluate each patient's profile may temper the enthusiasm of clinicians to perform this procedure, the growth in its usage and the willingness of clinicians to withhold or alter therapy on the basis of ABPM readings is testimony to its clinical value in the management of patients with hypertension.

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