Should 24-h Ambulatory Blood Pressure Monitoring Be Done in Every Patient With Diabetes?

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SUMMARY — Twenty-four–hour ambulatory blood pressure monitoring (ABPM) is a method widely used in hypertension diagnosis and management. Also in diabetic subjects, it may be a powerful tool for a better stratification of cardiovascular risk related to elevated blood pressure (BP), one of the most important causes of morbidity and mortality in this population. This is due to its capacity, as compared with isolated office measurements, to more precisely diagnose and quantify a high BP condition in daily life and to detect alterations of 24-h BP profiles such as absence of nocturnal BP fall, postprandial hypotension, or an increased BP variability, which may reflect a deranged cardiovascular regulation often associated with a reduced heart rate variability. It is also an important tool to obtain an accurate assessment of the efficacy of antihypertensive treatment over day and night. Admittedly, this method has its disadvantages, which include relatively high cost, problems with validation of the devices (particularly relevant in special populations such as diabetic patients), and undefined diagnostic threshold in high-risk populations. A number of studies have shown that ABPM may be a useful tool in improving outcome and quality of life in diabetes, suggesting that it should be an integral part of the clinical management in this setting. However, due to its limited availability in clinical practice, it may not be easily applied in every diabetic subject and thus priority should be given to those of diabetic patients, who may derive the most evident benefits from the use of this diagnostic tool.

INTRODUCTION — The 24-h ABPM is a method widely used in hypertension diagnosis and management (1–3). Numerous studies over the years have confirmed its advantages over the traditional clinic measurement, including a higher reproducibility, lack of placebo and white coat effect, and, most importantly, its superiority in predicting adverse consequences of hypertension. Additionally, ABPM provides an insight into the features of 24-h BP variability, which cannot be assessed with either clinic or home BP measurement (1–3).

An accurate diagnosis of hypertension and a reliable assessment of its control are of uppermost importance in high-risk subjects, in whom each mmHg of BP reduction translates into an important reduction of hypertension-related morbidity and mortality (1,4). Diabetes is widely recognized to be a condition leading to an important elevation of cardiovascular risk in combination with hypertension, this being relevant both in individual patients and in terms of public health. Indeed, missed hypertension diagnosis or inadequate control of BP levels in diabetic subjects are common (5).

A number of diagnostic and therapeutic tools are available to improve this situation, and ABPM is one of them. Interestingly, the usefulness of ABPM in diabetes is related not only to the possibility of assessing the features of BP elevation over 24 h, but also to its ability to identify BP patterns reflecting an important pathophysiological mechanism underlying the cardiovascular effects of diabetes, namely autonomic dysfunction.

This article is aimed at discussing the evidence supporting use of ABPM in patients with diabetes and, based on this evidence, at suggesting the possible clinical indications for ABPM in individual diabetic patients.

EVIDENCE ON ABPM USEFULNESS IN DIABETES

— All the methodological advantages of ABPM, compared with conventional isolated office BP readings, are fully evident in diabetic subjects, in whom this method, which is operator independent, offers important information related to the large number of BP readings provided, to its ability to offer insight into 24-h BP profiles (including nighttime and morning BP values) and to the possibility to quantify BP variability over the whole 24-h period (2,3). Some studies have shown that reproducibility of BP values in diabetic subjects is probably better with ABPM than with clinic BP (6). Moreover, other favorable features of ABPM, previously demonstrated in uncomplicated hypertensive subjects, also characterize its application in the diagnostic and therapeutic management of diabetic subjects with hypertension. These include the absence of a white-coat effect (i.e., the increase in BP triggered by an emotional reaction to its measurement in the physician's office) and of a placebo effect when assessing response to antihypertensive treatment (2,3).

The above methodological advantages were clearly shown to importantly contribute to the higher predictive value of ABPM in the prognostic stratification of hypertensive patients. Similarly, as in a nondiabetic population, out-of-office BP values obtained through ABPM in patients with diabetes were found to correlate better than office BP with organ (in particular renal) damage (7,8) and cardiovascular events (9).

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WHITE-COAT AND MASKED HYPERTENSION — An important issue related to the parallel use of office and out-of-office BP measurement methods (the latter including also home BP monitoring) in the same subjects when diagnosing hypertension or when assessing its coverage by treatment should be mentioned in this context. It has been reported that, in a significant proportion of subjects, major differences occur in the definition of BP levels obtained with these different approaches to BP measurement. In a general population, the diagnosis of hypertension based on elevated office BP values is not confirmed by out-of-office measurements in >20% of subjects, in whom normal values are found at home or over the 24 h (a condition defined as white-coat hypertension) (10,11). Conversely, in another 10–20% of subjects, the opposite situation is found, namely, an elevation in daily life BP identified by either ABPM or home BP monitoring remains undiagnosed during the clinic or office visit (a condition indicated as masked hypertension) (11). The prognostic significance of white-coat hypertension is uncertain, with these subjects probably being at an intermediate risk level between normotensives and sustained hypertensives (10,11). On the other hand, a number of studies have consistently shown that masked hypertension is associated with an elevated cardiovascular risk, similar to that of sustained hypertension (11).

The data on white-coat hypertension and masked hypertension in diabetic subjects are rather limited. The available information is largely in line with the data obtained in nondiabetic subjects, although some differences should be underlined. There is evidence, for instance, that the prevalence of white-coat hypertension in this population may be lower than in a general population, in particular, when subjects with diabetic nephropathy are concerned (12). This should not be surprising given that these subjects tend to have sustained and marked BP elevation, whereas white-coat hypertension is most common in subjects with BP close to the threshold for hypertension diagnosis. On the other hand, it was suggested that masked hypertension may be present in one out of two subjects with type 2 diabetes and apparently normal clinic BP (13). High prevalence of masked hypertension becomes particularly relevant when we consider that this condition may be associated with higher risk of brain and kidney damage (14,15) and possibly also of cardiac damage (13), which further increases the already very high risk of cardiovascular complications typical of diabetic subjects. As far as white-coat hypertension is concerned, it appears to be associated with a lower risk than sustained hypertension also in a diabetic population (16).

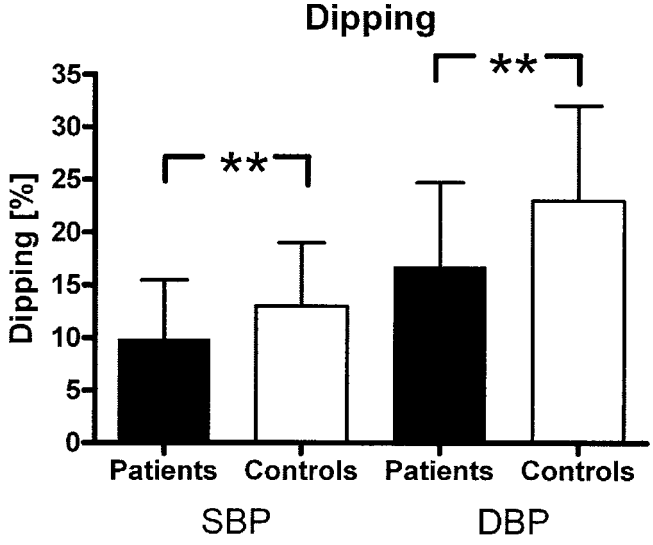

Figure 1—*Size of nocturnal BP fall (dipping) in children with diabetes (■) compared with healthy control subjects (□). DBP, diastolic BP; SBP, systolic BP. Reprinted with permission from Dost et al. (18).*

ASSESSMENT OF 24-H BP PROFILES — One application of ABPM in diabetic subjects that has raised particular interest is the possibility to detect the alterations of day-night BP changes that often characterize such a pathological condition. Specifically, a lack of nocturnal BP fall (nondipping) or even an increase of BP during the night (reverse dipping) is common in this population, with its prevalence reaching ~30% (17,18) (Fig. 1). It was suggested that these conditions may reflect autonomic dysfunction (19), and some authors suggest that they might be used as a clinical marker of diabetic autonomic neuropathy (20). However, it has to be remembered that other pathophysiological mechanisms may also be involved. In particular, obstructive sleep apnea, commonly encountered in obese subjects with type 2 diabetes (21), is a condition frequently associated with the nondipping pattern (22).

Whatever its mechanisms might be, a flattening and, even more importantly, an inversion of day-night BP profile (reverse dipping) was demonstrated to be a marker of complications in the diabetic population (17). In particular, its association with renal damage reflected by urinary protein excretion is evident both in type 1 (23) and type 2 (24) diabetes. The results of some studies suggest that in subjects with type 1 diabetes, elevated systolic BP during sleep precedes the development of microalbuminuria. Such an alteration in nocturnal BP, therefore, should be viewed as a cause (or at least a marker) of renal damage rather than its consequence (25). More recently, similar results were obtained also in type 2 diabetes (26). Nondipping in diabetic subjects may also be associated with an increased overall mortality, but evidence is limited in this regard (27).

In the context of daytime and nighttime BP assessment by ABPM, one has to consider the possibility that the absolute values of nocturnal BP might be more relevant from the prognostic point of view than the relative reduction of day-night BP excursion. This possibility has been recently supported by the results of a number of outcome studies in uncomplicated hypertensive subjects, and some data in this direction have been collected also in subjects with type 2 diabetes (28).

OVERALL BP VARIABILITY AND MORNING BP SURGE — Apart from day-night BP changes, ABPM is able to provide information on other features of BP variability that may be of interest in diabetic subjects and have clinical relevance. One of them is

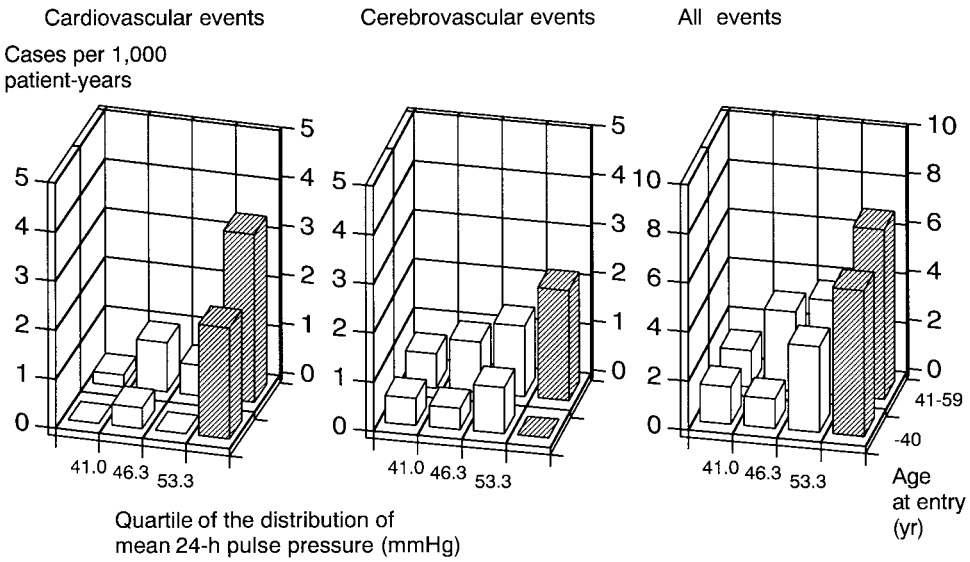

Figure 2—*The rates of occurrences of cardiovascular, cerebrovascular, and all events in diabetic subjects divided by quartile of the distribution of mean 24-h pulse pressure and by age at entry (≥40 and 41–59 years). Reprinted with permission from Nakano et al. (36).*

the overall BP variability, commonly expressed as a standard deviation of average 24-h, daytime, or night-time BP values. This parameter is frequently increased in diabetic subjects, which may be a sign of deranged autonomic control of circulation and/or of an increased arterial stiffness. This appears to be the case in patients with diabetic autonomic neuropathy (29), in particular, when associated with arterial baroreflex impairment (30,31), and may be an independent predictor of cardiovascular complications (32). Autonomic neuropathy is also frequently associated with postprandial hypotension, another specific component of 24-h BP variability, which can also be detected by ABPM (33).

Another important feature of 24-h BP profile is the behavior of BP in the morning. Both excessive morning BP surge (i.e., the extent of BP increase when waking up in the morning) and morning hypertension (high BP level in morning hours) are associated with adverse prognosis in nondiabetic subjects (3). Morning hypertension is common in diabetic patients, and it was shown to predict the progression rate of diabetic nephropathy (34). Although in the studies published so far in diabetic patients, home BP monitoring was applied for the assessment of morning BP behavior, ABPM might be even better in this regard, since it allows a dynamic and more detailed evaluation of BP in the morning hours.

ADDITIONAL PARAMETERS DERIVED FROM 24-H ABPM

— Another advantage of ABPM is that it allows to obtain dynamic information over 24 h not only on systolic and diastolic BP values, but also on some other relevant parameters that can be directly obtained or calculated from ambulatory BP recordings. This technique provides information on heart rate at the time of BP measurements all over the 24 h, and a rough estimate of heart rate variability may also be obtained by computing the standard deviation of average 24-h, daytime, or nighttime heart rate values. Although a reduced heart rate variability in continuous ECG recordings is a well established index of diabetic neuropathy, only one study assessed heart rate variability from ambulatory BP recordings in diabetic subjects. This study confirmed that the degree of heart rate fluctuations also when assessed discontinuously over 24 h by means of intermittent readings is reduced in this population, especially at night (35).

Pulse pressure, i.e., the difference between systolic and diastolic BP, depends on both stroke volume and arterial properties and, when increased, is largely considered a surrogate marker of stiffening of arterial walls. Results of several studies indicate that 24-h pulse pressure may be an independent predictor of vascular complications of diabetes, more powerful than the assessment of pulse pressure in clinic measurements, although it is not clear whether it provides relevant additional information on top of what is already offered by 24-h systolic BP (36) (Fig. 2). In the context of noninvasive methods for evaluating arterial properties, a new index has been recently proposed, based on analysis of ABPM data, known as ambulatory arterial stiffness index. This index consists of the dynamic evaluation of the degree of parallelism in systolic and diastolic BP changes and is calculated as the regression coefficient between the changes in diastolic and systolic BP over 24 h. It has been suggested that ambulatory arterial stiffness index may indirectly reflect the degree of arterial stiffness, and some studies have demonstrated a relationship of ambulatory arterial stiffness index with cardiovascular events and organ damage (37). The precise interpretation of its value as a specific index of arterial stiffness is, however, made difficult by the evidence of a strong correlation between ambulatory arterial stiffness index and the degree of nocturnal BP fall (38), a parameter largely independent from arterial wall properties. Considering that nocturnal BP fall is commonly small or absent in diabetic subjects, it is hardly surprising that ambulatory arterial stiffness index scored worse than 24-h pulse pressure in predicting the progression of renal damage in this population (39).

DIABETES AND PREGNANCY

— Pregnancy is a condition where the interplay between diabetes and hypertension is of particular

importance, since both these conditions adversely influence the pregnancy outcomes. The role of ABPM in this setting is not well established, however. On one side, some studies suggest its possible usefulness in monitoring pregnant women and in the early identification of pregnancy-induced hypertension, especially when nocturnal BP is considered (40). On the other side, according to some authors, ABPM adds little information to that already provided by microalbuminuria assessment as far as prediction of preeclampsia is considered (41).

ABPM IN THE ASSESSMENT OF ANTIHYPERTENSIVE TREATMENT

— An extremely important application of ABPM in hypertension is related to its ability to evaluate the changes in BP induced by antihypertensive therapy with greater accuracy and in a much more detailed fashion than clinic BP measurements, offering information on actual 24-h BP coverage by a given antihypertensive regimen (3). Considering that adequate BP control is of utmost importance in diabetic subjects, the above properties of ABPM make it an essential tool to verify the appropriateness and efficacy of antihypertensive treatment also in this group. The key aspects related to ABPM application in this context include the following: the possibility to identify subjects inappropriately categorized by clinic BP as controlled (masked hypertension) or uncontrolled (white-coat hypertension); the ability of ABPM to assess the impact of treatment on particularly important periods within 24 h (nighttime, morning); and the availability of ABPM-based indexes of adequate duration of antihypertensive effect (trough-to-peak ratio) and of the smoothness of BP reduction by treatment throughout 24 h (smoothness index). In fact, the studies making use of ABPM in diabetic subjects to assess the effects of hypertension treatment have provided some interesting information. In particular, evidence has been obtained that newer oral antidiabetic drugs used in type 2 diabetes (but not the older ones), in particular the thiazolidinediones, may have a beneficial effect on 24-h BP levels and may also improve the day-night BP profile in diabetic (42,43) subjects.

Some information is available also on the influence of currently used antihypertensive regimens on 24-h BP in diabetic patients, including angiotensin receptor antagonists (44) and ACE inhibitors (45,46). These studies have confirmed the efficacy of these compounds in terms of overall 24-h BP lowering, with no significant impact on day-night BP profile. Information has also been obtained by ABPM on the effects of lipophylic calcium-channel blockers on 24-h BP in diabetic patients. These drugs reduced systolic BP variability, monitored on a beat-by-beat basis over 24 h, in diabetic patients with hypertension. This improvement in hemodynamic conditions was associated with an improved autonomic cardiac modulation, as quantified by an increased cardiac baroreflex sensitivity (47).

Importantly, the ability of ABPM to provide more precise information on BP control by treatment might translate into a better clinical practice, through identification of subjects with white-coat hypertension and masked hypertension and by stimulating a more aggressive treatment when this is necessary to achieve therapeutic targets (48).

LIMITATIONS OF ABPM USE IN DIABETES

— Although the usefulness of ABPM in diabetic subjects can hardly be questioned, one also has to consider a few limitations of this technique, which may be important when ABPM is to be applied in a clinical setting in the management of diabetic patients. One of the main concerns when applying oscillometric devices in clinical practice (and current ABPM devices are almost exclusively based on oscillometric measurements) is that the algorithms for BP determination by these techniques are not disclosed by manufacturers. Therefore, the validity of each oscillometric device should by individually checked by independent studies following predefined international protocols. Unfortunately in diabetic patients, the difference between BP values obtained with the reference auscultatory measurement and with the oscillometric method is not necessarily the same found in nondiabetic subjects (49). Therefore, devices with demonstrated validity in standard protocols carried out in nondiabetic subjects may not necessarily turn out to be accurate in subjects with diabetes, possibly because of the altered arterial wall properties typical of such a condition. Thus, ideally, validation studies on oscillometric devices to be used in diabetic patients should be separately performed in this population. Unfortunately, whereas many ABPM devices have been validated in a general hypertensive population, similar studies are lacking in the setting of diabetes. Nevertheless, considering the prognostic superiority of ABPM over clinic BP measurement demonstrated also in diabetic patients, the possibility of a minor inconsistency between auscultatory measurements and oscillometric ABPM values, due to the particular characteristics of these subjects, should not be viewed as a major obstacle in their clinical application.

An obstacle that is clearly more important from the practical point of view is the high cost and limited availability of ABPM systems in general practice. Still, this situation is changing, with the costs of devices becoming lower, the number of centers equipped with the devices increasing, and the reimbursement policies becoming more favorable. For the time being, in most developed countries, an access to ABPM for a high-risk patient, such as one with diabetes, should no longer pose a major difficulty, also in relation to its reimbursement by health insurance bodies.

Finally, an important but still unresolved issue is the definition of ABPM cutoffs for hypertension diagnosis and the identification of therapeutic targets in diabetic subjects. Such thresholds are fairly well defined for nondiabetic subjects at low or intermediate risk. Based on the results of outcome studies, it is believed that a clinic BP of 140/90 mmHg corresponds to ambulatory BP levels of 125–130/80 mmHg for 24 h, 135/85 for daytime, and 120/70 for nighttime (1,2). Conversely, no corresponding definitions are available when considering high-risk patients such as those with diabetes. However, given that in this population clinic BP threshold for hypertension diagnosis and treatment is currently set at values as low as 130/80 mmHg, it should be expected that also ABPM thresholds should be lower by ~5–10 mmHg compared with a nondiabetic population. Given the nonlinearity of the relation between clinic and ambulatory BP, however, ABPM thresholds in diabetic patients need to be defined on the basis of future outcome studies.

CONCLUSIONS: INDICATIONS FOR ABPM IN DIABETIC SUBJECTS

— In summary, ABPM in diabetic subjects may be a powerful tool for a better stratification of the cardiovascular risk related to elevated BP, a condition that is one of the most

important causes of morbidity and mortality in this population. This is of particular importance also on the background of the evidence that, in diabetic patients, office BP frequently fails to identify their exposure to elevated BP in daily life conditions. Moreover, ABPM may also be helpful in detecting alterations in autonomic control of the cardiovascular system, reflected by the absence of nocturnal BP fall, by postprandial hypotension, or by a reduced 24-h heart rate variability and an increased 24-h BP variability. Thus, theoretically, a noninvasive and powerful test such as ABPM could be useful in every diabetic subject.

However, given the limited availability of ABPM in daily practice and the progressive increase in the number of diabetic subjects, it is reasonable to suggest an individualized approach when defining indications to ABPM performance in such a population. As a general principle, ABPM should be applied in those cases where the largest benefits can be expected. In practice, the pros and cons of performing ABPM should be evaluated on a case-by-case basis, taking into consideration a number of key factors, such as the likelihood of misdiagnosing actual BP levels by office BP, the possible benefits associated with a more accurate estimation of 2-h BP levels and variability (as in patients with previous clinical events, such as stroke, myocardial infarction, or impaired renal function), the probability of nocturnal hypertension, and the availability of alternative (and cheaper) solutions for out-of-office BP measurement, such as home BP monitoring.

Based on the above considerations, a few recommendations can be proposed to identify the possible situations in which ABPM might be indicated in hypertensive subjects with diabetes. One such possibility is the finding of clinic BP values close to the threshold levels. This is because these patients are most likely to have white-coat hypertension (if office BP is slightly above the threshold) or masked hypertension (when it is slightly below). In such a case, however, home BP monitoring may be an easier, cheaper, and equally effective (50) way to determine the true status of patients' BP under daily life conditions. When home BP monitoring is not feasible, or its results are not easy to interpret (borderline values, high variability), ABPM should then be performed. Another example of subjects in whom a suspicion of imprecise diagnosis by office BP should be considered are those with signs of organ damage despite apparently normal BP in the physician's office or in the clinic (in diabetic subjects, it is much less likely that the opposite situation is encountered). This may imply that BP is elevated only in their daily life, a condition that needs out-of-office BP monitoring to be identified. Needless to say, such diabetic patients, being exposed at a very high risk, may derive particular benefit from an appropriate diagnosis and an effective treatment of their daily life hypertension.

ABPM may also be of particular importance in subjects already under antihypertensive treatment. Even though home BP monitoring may be sufficient for a long-term follow-up, ABPM is the only way to ascertain that BP is adequately controlled all over the 24-h period and in particular during the night. Nocturnal hypertension should be suspected specifically in subjects likely to have obstructive sleep apneas (obese subjects, snoring history, daytime somnolence), in those with autonomic dysfunction, and in those with organ damage, especially when kidneys are affected (microalbuminuria or overt proteinuria, signs of renal failure). In these cases, some simple measures, such as switching to long-acting compounds or adding an evening dose of antihypertensive drugs, may be effective. However, it should be emphasized in this context that the occurrence of clinical benefits from restoring a normal day-night BP rhythm is only assumed and has not yet been directly demonstrated. ABPM may also help to identify subjects with episodic BP drops (as in the case of postprandial hypotension related to autonomic dysfunction) and should be performed if patient reports typical hypotensive symptoms that have not been otherwise clarified. Also in such cases, the adjustment of antihypertensive treatment or advice on changes in lifestyle may be effective and improve the subject's quality of life. Finally, ABPM may also be useful when identifying patients with episodic BP elevations, in the context of an enhanced BP variability, increased arterial stiffness, and autonomic neuropathy. The identification of these phenomena may trigger appropriate changes in treatment strategies, too, given the prognostic relevance of these findings.

In spite of its advantages, ABPM may not be easily applied in every diabetic subject, both for technical and financial reasons. However, it is important to emphasize that, when appropriately used, this approach may be an extremely useful tool in improving outcome and quality of life of these subjects and therefore should become an integral part of the clinical management, at least in a subgroup of selected diabetic patients.

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