Ambulatory Blood Pressure Monitoring and Type 2 Diabetes Mellitus

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Summary

Hypertension is one of the main risk factors for the onset and progression of chronic complications in type 2 diabetes mellitus (DM).

Ambulatory blood pressure (BP) monitoring (ABPM) provides a better correlation with target organ lesions than BP obtained in the office. Furthermore, it allows the evaluation of distinct BP parameters such as the 24-h, daytime and nighttime systolic and diastolic BP means, BP loads and the absence of nocturnal drop of BP, as well as the identification of white-coat and masked hypertension.

DM patients have higher daytime and nighttime BP means than non-DM patients. In addition, one third of normotensive type 2 DM patients have masked hypertension, which is associated with an increase in albuminuria and in left ventricle wall thickness. On the other hand, the prevalence and effect of white-coat hypertension in type 2 DM patients have not yet been properly evaluated. The absence of nocturnal drop of BP does not add information to the 24 h, daytime or nighttime BP measurements, but the nighttime BP means seem to be relevant in DM retinopathy.

In conclusion, BP determination by ABPM allows better patient risk stratification for the development of DM chronic complications and is an essential instrument for effective BP control in these patients.

Arterial pressure and diabetes mellitus

Type 2 diabetes mellitus (DM) is associated with the development of chronic microvascular and macrovascular complications with high rates of morbidity and mortality[1,2]. The classic and most analyzed risk factors for the development and progression of chronic DM complications are DM duration, hyperglycemia, arterial hypertension (AH), dyslipidemia, and smoking, besides genetic factors[3-8]. The treatment of hyperglycemia and SAH results in primary prevention and reduction of the progression of diabetic retinopathy (DR) and diabetic nephropathy (DN)[9,10]. SAH seems to have particular importance, since the decrease in arterial blood pressure (BP) from 154/87 mm Hg to 144/82 mm Hg in the United Kingdom Prospective Diabetes Study (UKPDS) resulted in a 37% reduction in development of microvascular complications, whereas the drop observed with the intensive treatment of hyperglycemia was merely 25%[9,10].

SAH is prevalent in patients with Type 2 DM, and is currently present in 30% of cases at the time of DM diagnosis and in up to 73% during the clinical course[1,11]. However, pressure homeostasis modifications can occur in DM patients with no evidence of renal disease[12,13].

The objective of this paper is to review the pressure changes present in DM patients and determine the role of ambulatory blood pressure monitoring (ABPM) in the identification of these changes and the indication of ABPM in clinical practice.

Key words

Blood pressure monitoring, ambulatory; diabetes mellitus type 2.

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Ambulatory blood pressure monitoring

ABPM was first performed in the 1960s, when noninvasive equipment was developed which was capable of measuring BP during 24 hours while the patient was carrying on his habitual daily activities. The first ABPM apparatus was bulky, used an auscultatory method for measuring BP, and required manual cuff inflation[14]. It was only in the 1970s that a portable ABPM system was developed, enabling its use in research and clinical practice. Nevertheless, these devices were still heavy and used the auscultatory method, depending on the presence of a palpable and ample brachial pulse, although they did not require manual cuff inflation.

Currently, ABPM performs BP measurements for 24 hours by means of a totally automatic portable device comprised of a monitor weighing approximately 350g, attached at the patient's waist and connected to a conventional rubber cuff (such as those used for BP measurement in the medical office) through a flexible rubber cannula. The cuff is placed on the patient's non-dominant arm and measures the BP at intervals adjusted on the software of the monitor used. Typically, measurements are made every 15-30 minutes during the day and night. BP is measured by the oscillometric method, which captures oscillations caused by the blood flow that begins after the cuff is deflated. Oscillations start before the first Korotkoff sound (systolic BP) utilized by the auscultatory method, and end after the fifth Korotkoff sound (diastolic BP). The greatest oscillation captured by the apparatus is the mean BP. The systolic and diastolic BP values registered on the device are derived from mathematical formulas established for each brand of monitor.

For a monitor to be used in research work or clinical practice, it needs to be validated against measurements obtained by the mercury manometer, which remains the

standard method for BP measurement[15]. Monitors validated according to protocols of the British Hypertension Society (BHS) or the Association for the Advancement of Medical Instrumentation (AAMI), can be identified at this website: e http://www.dableducational.org/sphygmomanometers/devices_3_abpm.htm.

Most studies correlating BP measurement and the development of target-organ lesions in patients with essential SAH, with or without DM, were carried out using as reference the BP value measured in the medical office[9,16,17]. However, recent studies have shown that BP measured by ABPM presents a better correlation with the outcomes of interest than office BP measurement[18,19]. Additionally, the adoption of ABPM measurements as the parameter for follow-up of patients under treatment for SAH was superior in predicting cardiovascular outcomes, compared to the simple office measurement of BP[20].

Use of ABPM allows analysis of parameters previously impossible to be recorded by BP measurements in the medical office, such as 24-hour day and night systolic and diastolic BP, pressure loads, and absence of nocturnal BP fall[21]. In addition, it allows identification of two new categories of patients: with white coat arterial hypertension and with masked arterial hypertension. Each of these parameters will be detailed below.

Mean pressure values

Mean pressure values are determined by calculating the means of the measurements obtained over a 24-hour period. Means of daytime and nighttime BP are defined based on the period of alertness and sleep reported by the patient on the day of the test. The values obtained for each one of these measurements correlate with an increase in the left ventricular mass and greater cardiovascular and general mortality of the population as a whole[22,23]. Based on these mean pressure values, it is possible to calculate the pulse pressure (systolic BP – diastolic BP), which is a marker of greater arterial rigidity.

Pressure loads

Pressure loads are defined by the percentage of BP measurements higher than previously defined values: 24 hours and daytime ≥140/90 mm Hg and nighttime ≥120/80 mm Hg. Pressure loads <20% are considered normal; between 20% and 50% are intermediate; and ≥50% are considered elevated. Pressure load elevation is associated with the development of target-organ damage[24,25].

Absence of nocturnal blood pressure fall

There is a physiological circadian variation of the BP characterized by the lowest BP levels during sleep. Typically, there is a drop in nocturnal BP greater than 10% relative to the mean daytime BP. Thus, the absence of a nocturnal BP fall is defined by a nocturnal BP fall <10% or a night/day index (N/D) (nocturnal BP/daytime BP) >0.9[21]. This calculation is made for the systolic and diastolic readings. The absence of a nocturnal BP fall is associated with the development of target-organ injury and increased mortality in different contexts[26,27].

White Coat Hypertension

White coat arterial hypertension is defined as the presence of SAH in office BP measurements (BP ≥140/90 mm Hg) in patients with normal BP values by ABPM (BP <135/85 mm Hg in daytime measurements). These patients represent 20% to 30% of the population of hypertensive individuals[28]. Patients with this diagnosis are traditionally considered normotensive and in no need of treatment. This position is based on initial studies that show that these individuals experienced no disfavorable events during the clinical course of the disease[29-31]. However, a careful analysis of these reports shows that patients experienced less target-organ injury compared to those with SAH, but both in the presence of antihypertensive treatment, since, in the logistics of the trials, patients were followed-up and treated by their referring physician, who had no knowledge of the ABPM results and defined treatment based on office BP levels.

More recent studies have shown that patients with white coat arterial hypertension have greater left ventricular hypertrophy[22] and greater cardiovascular mortality[32], when compared to normotensive individuals. These findings point to a group of patients with SAH of an intermediate degree of severity in relation to normotensive and hypertensive subjects, i.e., they have greater target-organ injury than normotensive individuals, but when they are treated in the same manner as those with hypertension, they present better clinical outcomes than hypertensive patients do.

Masked hypertension

The most recent category of patients defined by ABPM measurements is that of patients with masked SAH or pseudonormotension. These are individuals with normal office BP levels (<140/90 mm Hg), who are classified as hypertensive by the daytime ABPM measurements of BP (≥135/85 mm Hg) and represent 10% to 20% of individuals with normal office BP values[28]. These patients showed a risk for cardiovascular events similar to that of hypertensive individuals[22,32,33], reinforcing the superiority of the ABPM measurement in defining cardiovascular risk.

Blood pressure monitoring in diabetes mellitus patients

Most studies on pressure patterns in DM patients report BP modifications during the 24 hours, even before the diagnosis of SAH[34,35]. The analysis of each one of the ABPM parameters in patients with DM will be discussed in detail below.

Mean pressure values and diabetes mellitus

Patients with Type 1 DM have higher 24-hour BP means, both systolic and diastolic, in comparison with controls who do not have DM[36,37].

The association between DN and an increase in absolute BP values in ABPM was demonstrated even during early stages of renal injury[12]. One study carried out by our group in Type 1 DM subjects showed that normoalbuminuric and hyperfiltrating individuals (glomerular filtration >134 ml/

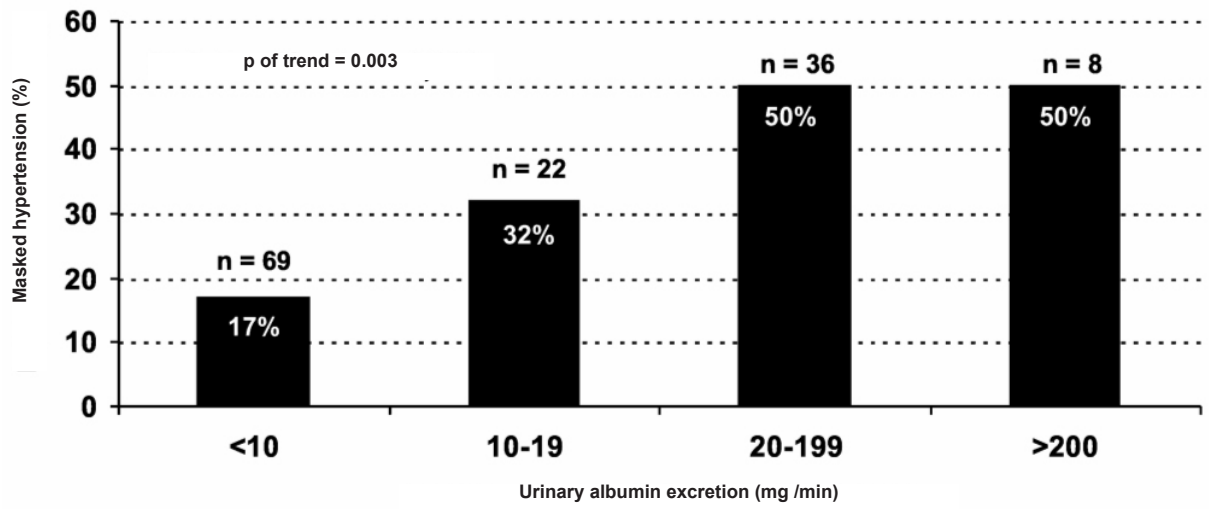

Fig. 1 - *Prevalence of masked hypertension according to urinary albumin excretion.*

min/1.73 m^2) presented higher levels of diastolic nocturnal BP when compared to normofiltrating patients[12]. Similarly, an analysis of 117 normoalbuminuric patients with Type 1 DM in Denmark, grouped according to the median urinary albumin excretion (UAE) (UAE = 4.2 μg/min), showed that patients with higher albuminuria rates presented higher levels of 24-hour systolic BP, both daytime and nighttime, besides higher diastolic BP means over the 24 hours and during the night[38]. These data were confirmed in a prospective study carried out in normoalbuminuric Type 1 DM patients, in which those patients who progressed to microalbuminuria had higher daytime levels of diastolic BP at the initial assessment[39]. Similar results were identified in a cross-section study performed in normoalbuminuric Type 2 DM patients[13]. The 24-hour BP means and the pulse pressures showed positive and significant correlations with the UAE measurement in a sample of 90 Brazilian patients[13]. Likewise, higher 24-hour BP means, both daytime and nighttime, and higher pulse BP and pressure loads were described alongside the progression to more advanced degrees of DN (microalbuminuria and macroalbuminuria) in Type 2 DM patients[40].

In a cross-section study conducted at our institution with 270 Type 2 DM patients, mean BP values in 24 hours, both daytime and nighttime, presented positive and significant correlations with UAE and with left ventricular mass[41]. The systolic BP results were the most consistent and showed the greatest association magnitude, and remained related after adjustments for possible confounding factors.

Similar results were described for the association between BP means in ABPM and DR. Increased nocturnal diastolic BP was associated with the presence of DR in a cross-section study in Danish patients with Type 1 DM[42]. In the same way, in a cohort with Brazilian Type 1 DM patients, the diastolic daytime and 24-hour BP predicted the development and progression of DR[43]. In patients with Type 2 DM, a cross-section survey established a progressive increase in 24-hour systolic and diastolic BP values, both daytime and nighttime, according to the severity of the DR[40].

The evaluation of the association between mean BP values in ABPM and the presence of macrovascular disease was performed cross-sectionally and in Type 2 DM patients. Systolic and diastolic daytime and nighttime BP means, and pulse BP were greater in patients diagnosed with macrovascular disease[40].

Pressure loads and diabetes mellitus

The existence of an association between greater pressure loads and increased UAE was demonstrated in patients with DM Type 1[44,45] and Type 2[13]. Recently, correlations between pressure loads and UAE, left ventricular mass, interventricular thickness, and left posterior ventricular wall in Type 2 DM patients[41] were demonstrated by our group. Similarly, the presence of DR was associated with higher levels of nighttime diastolic pressure loads in this same sample of patients[41].

Absence of nocturnal dipping pattern of blood pressure fall and diabetes mellitus

An elevated prevalence non-dipping pattern of BP fall absence was observed in patients with Type 1 DM[36,37], reaching up to 78% of patients, as compared to 39% of the controls who did not have DM[37]. These changes in ABPM measurements correlate with the presence of cardiovascular autonomic neuropathy (CAN)[46-48]. The studies conducted in Type 2 DM patients showed similar results[34]. Fogari et al[34] analyzed 199 individuals (96 with Type 2 DM and 103 without DM) and demonstrated that the DM patients had a higher prevalence

of nocturnal BP fall abnormalities (no fall or a paradoxical BP rise during the night) in relation to the controls. This difference was similar in the presence or absence of SAH (30% *versus* 31% in normotensive and hypertensive DM individuals, and 6.0% *versus* 6.4% in normotensive and hypertensive controls without DM, respectively)[34].

The greatest prevalence of absence of nocturnal BP fall in the studies carried out in Type 1 DM patients compared to those with Type 2 DM (78% *versus* 30%)[34,37] may be related to greater DM decompensation in the first group. Hyperglycemia modifies circulating plasma volume, and can interfere in renal hemodynamics and blood flow distribution, changing the normal nocturnal BP fall. Additionally, insulin plays an important role in regulating the autonomous nervous system. Improvement in glycemic control for one week in Type 1 DM decreased the ABPM pressure means and increased the BP fall during the night[49], reinforcing the theory exposed.

The absence of a BP fall during sleep was studied in children of Type 2 DM patients, and no differences were found in relation to controls, i.e., individuals with no family history of DM[50]. However, a subgroup of non-diabetic subjects with a family history of Type 2 DM who already presented CAN showed a smaller nocturnal BP fall[50]. This confirms the impression that the absence of nocturnal BP fall is a characteristic related to DM, and is present even in individuals who are susceptible, but without the clinical expression of DM, and is determined by the presence of CAN. Later on it was shown that Type 1 DM patients who are normotensive and normoalbuminuric without a nocturnal BP fall presented a greater prevalence of abnormal CAN tests[51]. In these patients, the absence of a nocturnal BP fall was correlated with UAE in the multiple linear regression analysis[51], suggesting an association between the absence of a nocturnal BP fall and higher UAE levels.

Nevertheless, the contribution of the absence of a nocturnal BP fall in the development and progression of chronic DM complications remains controversial. Most studies that analyzed this ABPM parameter focused on the development and progression of DN. Some authors found positive results[35,40,52-56], while others were not able to establish this relationship[44,57,58]. Most studies were carried out cross-sectionally or with cases and controls, merely suggesting an association between the factor under study (nocturnal BP fall) and the outcome (DN), and some presented statistical analysis and data interpretation susceptible to criticism[54,55]. Only two studies were prospective, both in cohorts of Type 1 DM normoalbuminuric patients, and followed the subjects up until de development of microalbuminuria[39,59]. In the first study, the association between the absence of a nocturnal BP fall and microalbuminuria development disappeared after control for DM duration[59]. In the second study, this association was only evident in the ABPM performed during patient follow-up (and not at the baseline assessment), suggesting that the appearance of microalbuminuria and nocturnal BP increased are concomitant[39,60].

One aspect not taken into account so far in the interpretation of the data from these studies is the mean BP value of patients without a nocturnal BP fall. Most of the results point to greater systolic and diastolic BP values in the groups of patients that progress to microalbuminuria or more advances stages of renal injury[39,40], and in this way, the elevation of BP means, and not the absence of a nocturnal BP fall, would be responsible for the worst outcomes. For this reason, we conducted a study in order to determine the relative importance of several pressure parameters regarding microvascular outcomes (DN and DR) and cardiac structural alterations (left ventricular mass, thickness of the interventricular septum, and of the left ventricular posterior wall) in 270 patients with Type 2 DM[41]. The mean BP values, especially systolic ABPM measurements, showed correlations that were more consistent and of greater magnitude with the outcomes than the blood pressure N/D indices. As to UAE and wall thicknesses of the left ventricle, the N/D indices lost their association after adjustments for potential confounding factors. Nocturnal BP and the diastolic blood pressure N/D index were more relevant and added information to the other BP values only when the outcome analyzed was DR.

White coat hypertension and diabetes mellitus

The prevalence of white coat hypertension was first described as being greater in patients with DM, reaching up to 74% of patients with Type 1 DM[61] and 51% of those with Type 2 DM[62]. Later on, these findings were challenged in Type 2 DM patients. Nielsen et al[63], found 23% white coat prevalence in normoalbuminuric individuals, 8% in microalbuminuric individuals, and 9% in macroalbuminuric patients. Thus, normoalbuminuric patients did not differ from the prevalence expected for essential hypertension patients (20%-30%)[37].

The low prevalence of white coat arterial hypertension in patients with microalbuminuria and macroalbuminuria is a consequence of the high incidence of SAH established in these groups. These data were not replicated, and the repercussions of white coat arterial hypertension diagnosis in chronic complications of DM have not yet been adequately evaluated.

Masked hypertension and diabetes mellitus

The prevalence of masked SAH in Type 2 DM patients is 30%[64], greater than that which is described in medical literature for individuals without DM (10%-20%)[28]. The effect of masked SAH on chronic DM complications was only assessed in a study in Brazilian Type 2 DM patients[64]. Greater UAE, greater prevalence of normal-high albuminuria, microalbuminuria, and macroalbuminuria (fig. 1), and greater left ventricular wall thickness were observed. These associations were independent from the office BP measurements.

Indications for ambulatory blood pressure monitoring in patients with diabetes mellitus

The classic indications for ABPM in patients with Type 1 and Type 2 DM, present in national and international consensuses, are the same as those for patients without DM[21,65]: 1. suspected white coat arterial hypertension; 2. evaluation of resistant SAH (BP not controlled at the office, despite the use of three or more antihypertensive agents with different action

mechanisms); 3. episodic SAH (normal or elevated office BP measurements with a history of greater casual measurements detected at episodic moments); 4. suspected episodes of hypotension; 5. evaluation of antihypertensive treatment efficacy.

In light of the data exposed in this review, we propose an amplification of the classic indications for use of ABPM in patients with DM. Since 30% of Type 2 normotensive patients had masked SAH associated with an increase of UAE and heart cavities thickness, and the fact that nocturnal BP is associated with the presence of DR, we recommend the use of ABPM in all DM patients, in order to enable the diagnosis of masked SAH and the assessment of nocturnal BP.

Final considerations

The study of pressure homeostasis by means of ABPM has made it possible to clarify the role of SAH in the development of target-organ injury in patients with essential SAH. It also allows analysis of new classes of hypertensive individuals (e.g., with white coat arterial hypertension and masked arterial hypertension) and of variables associated with BP that have not yet been studied (e.g., pressure loads and absence of nocturnal BP fall) that alter the prognosis of patients at risk.

The transposition of these results to individuals with DM has confirmed most of the findings, and has therefore added new data to concepts already established. Patients with DM have a high prevalence of masked SAH that is associated with renal and cardiac damage. The prevalence of the white coat arterial hypertension effect in DM patients needs a more careful evaluation. The worst renal outcomes attributed to the absence of a nocturnal BP fall seem to be, in fact, the results of higher values of BP measured by ABPM. Nocturnal BP and the N/D indices of BP seem to be important only for the development of DR.

In summary, BP determination by ABPM is capable of more adequately stratifying patients at risk for developing chronic complications of DM, and has become an indispensable instrument for BP measurement in these patients. Clinical studies with BP treatment based on the control of each of the ABPM parameters are necessary in order to establish the true renal, ocular, and cardiovascular benefits of this treatment strategy in patients with DM.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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