Reproducibility of Ambulatory Blood Pressure Monitoring in Hypertensive Patients with Type 2 Diabetes Mellitus

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Summary

Objective: **To evaluate the reproducibility of ambulatory blood pressure monitoring (ABPM) (SpaceLabs-90207) and placebo effect on ABPM.**

Methods: **Blood pressure was measured in the office and over two ABPM periods with an interval from one to ten months (mean 4.9 months), in 26 patients with type 2 diabetes mellitus and hypertension. Eleven patients (G1) had two ABPMs without taking antihypertensive drugs for 15 days, whereas G2 (N=15) had the second ABPM after administration of a placebo for 15 days.**

Results: **In the evaluation of the coefficient of variation (CV) of diurnal (awake) systolic BP (DSBP), of diurnal (awake) diastolic BP (DDBP), of 24-hour systolic BP (24hSBP) and of 24-hour diastolic BP (24hDBP), the values found were 4.6%, 3.9%, 5.0%, 4.0% for G1 and 4.3%, 5.1%, 3.7%, 5.1% for G2 respectively. We also determined the CV of nocturnal (sleep) systolic and diastolic BP (NSBP and NDBP) for G1 (7.7%; 8.2%) and G2 (5.6%; 6.3%). Heart rate CV during alertness and sleep were: G1=5.9% and 9.0%; G2=6.9% and 5.8% respectively. When the total number of ´patients was analyzed, all variables showed a strong correlation between the first and second ABPM measurements (DSBP, $r = 0.76$; $P < 0.001$; DDBP, $r = 0.65$; $p < 0.001$; 24hSBP, $r = 0.77$; $p < 0.001$; 24hDBP, $r = 0.70$; $p < 0.001$; NSBP, $r = 0.62$; $p < 0.001$; NDBP, $r = 0.52$; $p < 0.01$). Office systolic and diastolic BP and 24hSBP and 24hDBP also showed correlation ($r = 0.65$; $p < 0.001$; $r = 0.57$; $p < 0.01$).**

Conclusion: **Mean of pressure levels measured by ABPM presented good reproducibility and were not affected by placebo.**

Key words: **type 2 diabetes mellitus, arterial hypertension, ambulatory blood pressure monitoring**

Introduction

Arterial hypertension occurs twice as frequently in patients with diabetes mellitus (DM) as compared with normal individuals [1,2]. Macro and microvascular complications of DM are also accelerated by the presence of hypertension [3,4]. Therefore, it has been recommended that patients with hypertension and diabetes be diagnosed and treated early [5]. However, because blood pressure (BP) is a very variable parameter, the standard technique to establish the diagnosis of hypertension remains controversial [6].

In recent years, ambulatory blood pressure monitoring (ABPM) has been introduced in the study of hypertension and has become an important tool to inform clinical decision making [7]. Several pieces of data [8-10] have suggested that mean 24-hour BP presents a better correlation with lesions of target organs than isolated office BP measurements. It has also been demonstrated that ABPM presents higher reproducibility as compared with office BP for hypertensive [11,12] and diabetic hypertensive [13] individuals alike. At present ABPM can be particularly instrumental in detecting autonomic dysfunction and nocturnal blood pressure load increase in hypertensive diabetic individuals [14]. Absence of or reduced BP descent during sleep (nondipping) have been associated with a higher risk of cardiovascular complications [15,16].

Additionally, great differences between measurements taken on two consecutive days have been reported in studies focusing on the reproducibility of the 24hBP mean [17] and on BP descent during sleep [18] measured by ABPM, especially as a result of the variety of devices available in the market, many of which have not yet been tested enough. The ascertainment of the coefficient of variation of ABPM devices will make their results more reliable.

Therefore, this study was designed to assess the reproducibility of ABPM measurements and the placebo effect on ABPM to determine its degree of reliability as to the measurement of pressure levels in patients with type 2 DM and hypertension.

Methods

Patients - Twenty-six patients with type 2 DM and arterial

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hypertension attended at our Hypertension Clinic during a year were assessed and submitted to ABPM at two different times with an interval that varied from one to ten months (mean of 4.9 months). All the patients were submitted to the first ABPM without taking anti-hypertensive medication for fifteen days. The patients were then divided into two groups: group 1 (G1) (N = 11) underwent the same procedure for the second ABPM, whereas group 2 (G2) (N = 15) underwent the second ABPM after using a placebo during fifteen days. Office blood pressure was determined for each patient when the ABPM device was attached. Inclusion criteria were the following: all patients should be between 30 and 75 years of age, with body mass index (BMI) lower than or equal to 40 kg/m^2, type 2 DM treated only with diet or oral glucose-lowering drugs (with no use of insulin), arterial hypertension, normal levels of serum creatinine and 24-hour proteinuria (<150 mg/24h) and no previous history of myocardial infarction, angina and cerebrovascular accident. Individuals that didn't meet the criteria above were excluded from the study. Patients were later classified according to the stage of hypertension (19) based on the mean of three office BP measurements taken with the patient in a sitting position, with a one-minute interval between measurements, on the day of the first ABPM period.

Arterial hypertension was defined, on office assessment, as systolic and diastolic BP ≥140/90 mmHg in repeated measurements [20]. The diagnosis of DM was based on standard criteria [21]. Patients with type 2 DM were those with disease onset after 30 years of age, with no need for insulin since the time of diagnosis. All patients were previously informed of all the procedures they would be submitted to, and agreed to participate in the study. The assessment protocol was approved by the Ethics Committee of the Federal University of São Paulo.

Arterial Pressure Ambulatory Monitoring - ABPM was carried out using the oscillometric method with a portable SpaceLabs - 90207 device (Spacelabs, Inc. Redmond, WA-USA). Patients were submitted to ABPM after the interruption of anti-hypertensive medication for fifteen days or after using placebo for the same period. The monitor was attached in the morning and removed after 24 hours. The individuals were told to maintain their ordinary activities and present a report with the time of each activity. The device was programmed to perform four measurements per hour, and the systolic and diastolic pressure means were ascertained during each hour, during alertness, sleep time and over the 24 hour period. The alertness period included activities from 8 a.m. to 8 p.m., whereas the period between 8 p.m. to 8 a.m. was considered sleep time. Systolic BP measurements above 260 mmHg and below 70 mmHg, and diastolic BP measurements above 150 mmHg and below 40 mmHg were automatically excluded from the analysis. The limit for heart rate detection was between 200 and 20 bpm. The test was accepted if at least 75% of the measurements taken throughout the 24-hour period had been performed successfully. Additionally, the calculation of BP descent during sleep (DS) was carried out using the following formula: systolic DS (%) = (systolic BP during alertness – systolic BP during sleep) x 100 / systolic BP during alertness. The same calculation was carried out to determine diastolic DS. Individuals who presented BP descent during sleep greater than or equal to ten percent (10%) (dippers) as compared with alertness BP were considered normal, whereas individuals who presented descent below these levels were called "nondippers".

Statistical analysis - All the data were presented as mean ± standard deviation or median with interval of variation. For the analysis of correlation, Pearson's or Spearman's correlation coefficients were calculated between variables considering the type of distribution - normal or non-normal - in the population. The coefficients of variation (CV) for all pressure measurements and for the heart rate of the first and second ABPM were also calculated. The CV consisted of standard deviation of the mean of differences divided by the absolute mean of the two samples multiplied by 100. $P < 0.05$ was considered significant. All the analyses were carried out using the Sigmastat program (1992-1994 - Jandel Scientific Corporation- USA).

Results

The age and BMI of the two groups were: G1=59 ± 8 years and 31 ± 5 kg/m^2 and G2=56 ± 8 years and 27 ± 4 kg/m^2, respectively. Table 1 shows pressure measurements assessed by ABPM for each group. There was no statistically significant difference between all the measurements assessed by ABPM between the two groups, and within each group when the first and second ABPM values were compared (Table 1). With respect to the stage of hypertension of G1 patients, three (27%) were stage I patients, six (55%) were stage II patients and two (18%) were stage III patients. As for G2 patients, two (13.5%) were in stage I, six (40%) were in stage II and seven (46.5%) were in stage III. Mean systolic and diastolic BP and heart rate (HR) measured in the office were 173±20, 98±7 and 73±11, respectively for G1 and 166±20, 97±9 and 77±9, respectively for G2.

When we assessed the CV of alertness systolic BP (DSBP), alertness diastolic BP (DDBP), 24-hour systolic BP (24hSBP) and 24-hour diastolic BP (24hDBP), we found the following

	G1 (n=11)		G2 (n=15)	
	1º ABPM	2º ABPM	1º ABPM	2º ABPM
DSBP	146±14	145±14	150±14	148±20
NSBP	135±17	135±19	136±12	137±19
DDBP	91±11	89±8	92±7	90±10
NDBP	79±11	80±12	78±7	79±9
HRD	80±7	83±9	79±12	81±10
HRS	71±10	73±10	68±9	69±10

** There was no statistically significant difference regarding all the measurements assessed by ABPM between the two groups and within each group when the first and second ABPM values.*
DSBP=Systolic BP during alertness; NSBP=Systolic BP during sleep; DDBP=Diastolic BP during alertness; NDBP=Diastolic BP during sleep; HRD=HR during alertness; HRS=HR during sleep.

Table 1 - Pressure measurements assessed by ABPM

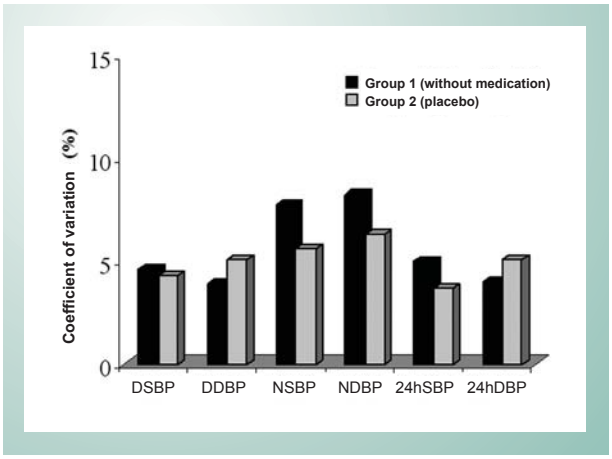

Fig. 1 - *Coefficients of variation of pressure measurements determined by ABPM. DSBP=Systolic BP during alertness; DDBP=Diastolic BP during alertness; NSBP=Systolic BP during sleep; NDBP=Diastolic BP during sleep; 24hSBP=24-hour systolic BP; 24hDBP=24-hour diastolic BP.*

values: 4.6%, 3.9%, 5.0% and 4.0% for G1 and 4.3%, 5.1%, 3.7% and 5.1% for G2, respectively (figure 1). We also determined CV for systolic and diastolic BP during sleep (NSBP and NDBP) for G1 (7.7% and 8.2%) and G2 (5.6% and 6.3%). The coefficients of variation for alertness and sleep heart rate were: G1=5.9% and 9.0%; G2=6.9% and 5.8%, respectively. Analyzing the total number of patients (N=26), all the variables showed strong correlations between the first and second ABPM values (DSBP, $r = 0.76$; $P<0.001$; DDBP, $r = 0.65$; $p<0.001$; 24-hour systolic BP, $r = 0.77$; $p<0.001$; 24-hour diastolic BP, $r = 0.70$; $p<0.001$; NSBP, $r = 0.62$; $p<0.001$; NDBP, $r = 0.52$; $p<0.01$). There were also correlations between office systolic and diastolic BP and 24-hour systolic and diastolic BP ($r = 0.65$; $p<0.001$; $r = 0.57$; $p<0.01$), respectively. When we compared systolic and diastolic DS values for the first and second ABPM values for G1 and G2, we found no significant difference (8.8 %(-2.0 to 14.3) as compared with 5.6 %(-1.7 to 20.7), NS; and 13.7 % (5.5 to 18.7) as compared with 9.0 % (-1 to 30.9), NS for G1 and 8.9 % (-1.2 to 17) as compared with 6.1 % (0 to 19.7), NS; and 14.4 % (2.2 to 31.1) as compared with 13.2% (4.5 to 19.4), NS for G2, respectively). Finally, analyzing both groups jointly, and considering a cut-off value of 10% for nocturnal descent to separate dippers from nondippers, we found that 42% of both diabetic and hypertensive patients changed category for systolic DS and 46% changed category for diastolic DS upon repetition of the monitoring after an interval of one to ten months. As for G1, three (27%) out of eleven patients changed category for systolic DS and six (54%) out of eleven patients changed category for diastolic DS. For G2, eight (53%) out of fifteen patients changed category for systolic DS and six (40%) out of fifteen patients changed category for diastolic DS. When we compared the percentage of patients that changed category within each group, we found no significant difference.

Discussion

The results of our study showed that mean pressure values assessed by ambulatory blood pressure monitoring presented good reproducibility and were not affected by placebo. These findings are similar to few data found in the literature [13,22].

We have previously described (unpublished data) that sleeptime systolic BP in diabetic hypertensive patients related to a high prevalence of left ventricular hypertension. However, when we used BP nocturnal decent, this effect was not observed. This was probably due to the low reproducibility of BP descent during sleep in these patients. This study supports this hypothesis, as it found that 42% of hypertensive individuals with DM changed category (dipping/non-dipping) in a second measurement carried out after an interval of one to ten months. Verdecchia et al [23] documented that 73% of the hypertensive patients remained in the same category (dipping/non-dipping) after a second ABPM with a 3 to 5-day interval, whereas 27% changed from one group to the other. According to data from Stenehjem et al [24], 82% of the patients had their nocturnal pattern (non-dipping) changed to dipping after repeated measurements. This slightly better reproducibility of nocturnal descent in hypertensive subjects as compared with our subjects with DM and hypertension could be partly justified by other factors that influence nocturnal descent in diabetic subjects, including poor glucose level management [25] and diabetic autonomic neuropathy [26,27]. As concerns circadian BP variations in type I diabetic patients, persistent abnormal variability seems to occur early and frequently among those with increased urinary excretion of albumin. Loss of nocturnal descent (nondippers) assessed in two ABPM periods was observed in 80, 58, 18 and 10% of diabetic patients with proteinuria, microalbuminuria, normoalbuminuria and control group respectively [28], which shows that the frequency of this abnormality increases as incipient nephropathy progresses [28-30]. In our study, however, all the patients had normal levels of creatinin and proteinuria in the 24-hour period. Therefore, diabetic nephropathy could not account for the high variability in BP nocturnal descent in our group.

We do not know of any data on the literature regarding the assessment of reproducibility with serial ABPM measurements, followed by ABPM performed after withdrawal of anti-hypertensive medication and with the administration of placebo in hypertensive individuals with type 2 diabetes. Asmar et al [31] observed that, in hypertensive patients, the mean 24-hour BP measured by ABPM was not affected by placebo. In patients with mild to moderate hypertension, Zakopoulos et al [32] demonstrated that systolic and diastolic BP values measured every hour, heart rate and BP descent during sleep were reproducible in four ABPMs carried out over a four-month period. Additionally, Korner et al [33], in a study with children with type I diabetes concluded that BP values assessed by ABPM were reproducible, despite markers of individual characteristics. Davis et al [34], however, demonstrated that the ABPM device itself disturbed sleep, and caused changes to the BP it was supposed to measure. Other causes for BP variability over the 24-hour period included methodological problems with ABPM during the night due to a different hydrostatic variability between the device's cuff and the heart, level of activity during daytime and decreased accuracy of devices when measuring very high BP levels [17,18,35]. Davis et al [34] overestimated systolic BP at 10 mmHg (ABP, Oxford Medical)

and at 6mmHg (TM 2420, A&D), whereas diastolic BP was not affected. This disorder might lead to underestimation of pressure descent during sleep. Other devices (SpaceLabs and Sandoz Pressure System), however, did not present this problem in a study with concurrent assessment of intraarterial pressure [36].

Therefore, our study suggests that ABPM (Spacelabs-90207, Inc. Redmond, WA - USA) is a reliable tool to monitor BP variations and confirms its trustworthiness for use in hypertensive patients with type 2 diabetes mellitus.

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Potential Conflict of Interest

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

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