The Impact of Blood Pressure Variability on Subclinical Ventricular, Renal and Vascular Dysfunction, in Patients with Hypertension and Diabetes

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ABSTRACT

Background: Blood pressure variability (BPV) was proved as a cardiovascular risk factor. One of its mechanisms is related to arterial stiffness and ventriculo-arterial coupling; however its impact on subclinical cardiovascular dysfunction has not been evaluated yet.

Objectives: To assess the relationship between BPV on 24 hours, and subclinical left ventricle (LV), renal, and vascular dysfunction in diabetic and hypertensive patients. Material and methods: We studied 56 patients (57±9 years, 29 men) with mild-to-moderate hypertension and type 2 diabetes, no cardiovascular disease, normal ejection fraction and normal renal function. 24 hours ambulatory blood pressure monitoring (ABPM) was used to assess BPV, daytime (d) and night time (n), by: 1. mean (M); 2. standard deviation of mean (SD); 3. variance (Vr); 4. coefficient of variation (CV); 5. day/night variation: reverse dippers, non-dippers, dippers and extreme dippers; conventional and 2D speckle tracking echo to assess LV function; myocardial deformation was measured as global longitudinal strain (GLS). Endothelial (flow mediated dilation, FMD) and arterial function (intima media-thickness, IMT; pulse wave velocity, PWV), microalbuminuria were tested.

Outcomes: Daytime BPV correlates inversely with subclinical myocardial function evaluated through GLS. Daytime systolic BPV correlates positively with IMT (all rho > 0.30, all p < 0.05). Also, there is a significantly inverse correlation between mean BP and GLS. We found a direct correlation between mean BP, but not BPV, and microalbuminuria (all rho > - 0.30 and all p < 0.05). We found no correlation between BPV and FMD, PWV. There were no differences for GLS, microalbuminuria and FMD between dipper groups.

Conclusions: In diabetic patients with mild-to-moderate hypertension, increased daytime blood pressure variability correlates with subclinical left ventricular dysfunction and arterial function (IMT), while microalbuminuria correlates with elevated blood pressure, but not with blood pressure variability.

Keywords: blood pressure variability, ventricular dysfunction, diabetes, hypertension

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**BACKGROUND**

Hypertension is one of the most important causes of premature death in the world, according to a recent report from the World Health Organization. There are almost one billion hypertensive people worldwide, and the number is still growing. Hypertension is one of the major cardiovascular risk factors, and also the single most important risk factor for stroke (1).

Hypertension and type 2 diabetes mellitus are often found together in the same patient. Diabetic patients have a two-to-three times folded increased risk for developing hypertension as compared to non-diabetic patients, associated with a subsequent higher rate of cardiovascular complications and target organ damage (2). When hypertension and diabetes coexist, there is a more rapid development of atherosclerosis and progression to subclinical, and then symptomatic heart failure (3). Failure to diagnose it from the subclinical stages delays treatment initiation and leads to more frequent complications (4).

In an attempt to lower the burden and the impact of hypertension in the general population, current guidelines emphasize the benefit of blood pressure lowering, and also the importance of a wider approach when assessing the individual cardiovascular risk. 24 hours ambulatory blood pressure monitoring is recommended as useful tool for cardiovascular risk evaluation and reliable management guidance of the hypertensive patient (5).

The concept of blood pressure variability (BPV) has been recently brought back to our attention by Professor Peter Rothwell (Oxford). In 2010 he publishes in Lancet the results of an analysis on blood pressure variability, which demonstrates that blood pressure variability is a strong predictor for stroke and coronary events, independent of brachial mean blood pressure, in hypertensive patients. Moreover, he highlights the additional benefit of reducing blood pressure variability, pointing out to the results of ASCOT trial (“Anglo-Scandinavian Cardiac Outcomes Trial”) as a strong argument. In the “ASCOT Blood Pressure–Lowering Arm”, (ASCOT-BPLA), the amlodipin-perindopril group had lower systolic blood pressure variability when compared to the atenolol-bendroflumethiazide group. Statistical analysis showed that the difference in blood pressure variability accounts for amlodipin-perindopril combination protective effect on cerebral and cardiovascular events, when compared to atenolol-diuretic based therapy (6,7).

Blood pressure variability is poorly explored in diabetic patients. Most of the studies evaluated and confirmed the link between BPV and the development and progression of diabetic nephropathy, assessed by the degree of albuminuria in these patients (8,9). The relation between blood pressure variability and cardiac function has not been evaluated in clinical studies until now, the only available data being conflicting (10) and strictly related to left ventricular hypertrophy as a substitute for ventricular function (11).

 Recently, blood pressure variability has been included for the first time in the guidelines. NICE hypertension guidelines recognize BPV as an independent predictor for future cardiovascular events (12).

BPV is a normal finding in all healthy subjects, as an adaptive mechanism to emotional and physical stimuli (13,14). We supported our hypothesis on the observation that BPV is higher in hypertensive and diabetic patients when compared to normal individuals, the mechanisms being incompletely elucidated yet, and correlated it with cardiac function. ☐

**OBJECTIVES**

To evaluate the impact of blood pressure variability derived from 24 hour ABPM, on subclinical left ventricular dysfunction, renal and vascular function in our study group of hypertensive and diabetic patients. ☐

**MATERIAL AND METHODS**

**Study population**

We studied 56 patients (57 ± 9 years, 29 men) with primary mild to moderate hypertension and type 2 diabetes mellitus, recruited from a clinical trial we have conducted in our clinic (A comparison of Indapamide SR 1.5 mg with Hydrochlorothiazide 25 mg, in combination with an ACE-inhibitor, in patients with mild to moderate hypertension and type 2 diabetes mellitus. The AISHA study. ClinicalTrials.org: NCT00980187), previously reported in this journal, along with the inclusion and exclusion criteria (15): no significant valvular disease; left
ventricular ejection fraction ≥50%; no proven cardiovascular disease; no renal function impairment. The protocol was approved by the National Research Ethics Committee, and each subject gave written informed consent.

All patients had a complete physical examination; ambulatory blood pressure monitoring; conventional and speckle-tracking echocardiography; assessment of arterial and endothelial functions; urinanalysis-albuminuria; amino-terminal propeptide of type I procollagen (P1NP) and carboxy-terminal telopeptide of collagen type-I (CITP) plasma levels.

**Ambulatory blood pressure monitoring**

24 hours-ABPM was performed using a To-noport GE (General Electric) device, in order to assess the following parameters of daytime and night-time variability:

- 24 hours mean SBP and DBP (MSBP, MDBP), daytime (dMSBP, dMDBP), and night-time (nMSBP, nMDBP);
- Standard deviation of the mean, calculated for SBP and DBP (SDSBP, SDDBP), daytime (dSDSBP, dSDDBP), and night-time (nSDSBP, nSDDBP);
- The coefficient of variation for SBP and DBP (CVSBP, CVDBP), representing the degree of BP variation compared to the mean; calculated as standard deviation divided by the mean BP (SD/mean BP); daytime (dCVSBP, dCVDBP), and night-time (nCVSBP, nCVDBP);
- The variance of SBP and DBP (VrSBP, VrDBP), represents a measure of pressure distribution, daytime (dVrSBP, dVrDBP), and night-time (nVrSBP, nVrDBP);
- The dipper profile of the patients, defined as the percent of nocturnal BP drop, as recommended by American Heart Association: \( \text{Dip} = [1 - (nSBP / dSBP)] \times 100\% \): reversed dipper (daytime-night-time BP variation 0%); non-dipper (nocturnal BP is less than 10% higher than the daytime BP); dipper (nocturnal BP is 10-20% higher than the daytime BP); extreme dipper (nocturnal BP is more than 20% higher than the daytime BP). Daytime was defined as 7am to 9 pm, and night-time as 10 pm to 6 am.

The nondominant arm was used for placing the cuff, and the patients were instructed to keep their arm still during cuff inflation.

**Echocardiographic protocol**

Patients were studied in the left lateral decubitus position, with a commercially available ultrasound machine equipped with speckle tracking imaging, using a 2-4 MHz transducer (Vivid 7 Dimensions, GE Medical System). Digital echocardiographic images were acquired during passively held end expiration for off-line analysis using a dedicated software package (EchoPac 9.0.1, GE Medical System). One lead electrocardiogram (ECG) was recorded simultaneously.

Conventional echocardiography consisted of 2D and color Doppler imaging to assess left ventricular structure and global function.

Speckle tracking imaging was used in order to assess longitudinal systolic myocardial deformation, according to the current recommendations (16). A frame rate of 70-80 frames/s was used, with an optimal sector width and depth. The frame in which left ventricular endocardium was best defined was identified, and the border of the endocardium was traced manually, in order to identify the region of interest (ROI) between the endocardial and epicardial borders. All left ventricular walls were divided into 3 segments – basal, medial, and apical. Cardiac time intervals were measured using pulsed wave tracing from the left ventricular outflow tract (aortic valve opening – AVO, and aortic valve closure – AVC). Global longitudinal strain was calculated from 18 ventricular segments from the apical views.

**Ultrasound assessment of vascular function**

Ultrasound studies were performed using an Aloka Prosound α10 (Tokyo, Japan) ultrasound machine. Intima-media thickness (IMT) was measured using B-mode ultrasound at the level of right common carotid artery. The far wall IMT, identified as the region between the lumen-intima interface and the media-adventitia interface, was determined 1 cm below the bulb of the RCCA (17,18) at the end diastole.

Carotid-femoral pulse wave velocity (PWV) was assessed using a validated non-invasive automated device (Complior, Artech Medical, Paris, France). The transducers were placed on the carotid and femoral arterial sites. Carotid-femoral transit time (dt) has been automatically measured. Distance (dD) travelled by the pulse wave was measured with a non-elastic tape, placed over the surface of the body.
Pulse wave velocity was calculated as the distance divided by the transit time (PWV = dD/dt) (17,19).

**Endothelial function** was assessed with the same machine at the level of the right brachial artery. Internal diameter was monitored for 10 minutes: 1 min at rest, 5 min during a forearm ischemia induced by inflation up to 250 mmHg of a pneumatic forearm cuff, and 4 min after deflating the cuff. In order to minimize operator dependent error, a mechanical probe holder was used. Measurements were taken as a mean of five beats of every phase. Flow-mediated dilation (FMD) was calculated as the percent of maximal diameter change at the right brachial artery level, observed during reactive hyperaemia following deflation of the forearm occluding-cuff (17-19).

**Reproducibility.** The reproducibility of deformation parameters measured by speckle tracking was measured in our laboratory in 10 consecutive patients by two observers; intra- and inter-observer variability are reported as 2SD/√2, and reported as percent from the mean value to give the coefficient of variation (CV in %). Meanwhile, detailed studies of comparative reproducibility of the non-invasive ultrasound methods for the assessment of vascular function were reported previously (17); the most reproducible and repeatable parameter was pulse wave velocity (CVs <10%); flow mediated dilation also had good reproducibility (CVs <12%).

**Biological parameters.** All the patients had the following laboratory tests performed: urinalysis— for quantification of albuminuria degree; amino-terminal propeptide of type I procollagen (P1NP) and carboxy-terminal telopeptide of collagen type-I (CITP) plasma levels as markers of myocardial fibrosis, by an electrochemiluminescence assay (ECLIA), using the Roche Elecsys 1010/2010 and Modular Analytics E170 immunoassay analyzers.

**Statistical analysis.** Statistical analysis was performed with SPSS software (version 19.0) (SPSS Inc. Chicago, Illinois), using Spearman and Pearson correlation parameters.

**OUTCOMES**

**Patients.** We have studied fifty six patients with mild to moderate primary hypertension and type 2 diabetes mellitus. On entry into the study, duration from the diagnosis of hypertension was 1-20 months, while duration from the diagnosis of diabetes was 2-12 months. Forty-one (73%) patients were on an ACE-inhibitor, 13 (23%) on an angiotensin receptor blocker, 26 (46%) on a beta-blocker, 21 (37%) on a calcium-antagonist, 25 (45%) on a diuretic, and...
38 (68%) on a statin; 38 (68%) patients were on oral anti-diabetes drugs, while only 3 (5%) were on insulin. Baseline characteristics are given in Table 1.

All patients underwent ambulatory blood pressure monitoring, as described above. The values obtained from assessment of daytime and night time BPV parameters are shown in Table 2.

Daytime BPV parameters inversely correlate with global longitudinal strain: dSDSBP (rho = -0.36), dSDDBP (rho = -0.33), dCVSBP (rho = -0.30), dVrDBP (rho = -0.32) (all p <0.05) (Figures 1-4). Also, daytime systolic BPV parameters correlated positively with IMT: dSDSBP (rho = 0.318), dCVSBP (rho = 0.35), dVrSBP (rho = 0.35) (all p <0.05).

Mean BP is another parameter that correlated with global longitudinal strain: 24 hours MDBP (rho = -0.34), dMDBP (rho = -0.36) (all p <0.05) (Figure 5).

Mean BP also correlated with microalbuminuria: MSBP (rho = 0.39), MDBP (rho = 0.35), dMSBP (rho = 0.31), dMDBP (rho = 0.30), nMSBP (rho = 0.41), nMDBP (rho = 0.43) (all p <0.05).

Regarding the dipper profile, 33.96% of the patients were reversed dippers, 32.8 % nondippers, and 16.98 % were dippers and the same percent were extreme dippers. There were no significant differences between the patients as far as the dipper profile was concerned.

We found no significant correlations between BPV parameters and neither endothelial function, nor myocardial fibrosis markers, although there was a strong correlation between flow mediated dilation and global longitudinal strain for these patients (rho = 0.57, p= 0.000) (Figure 6).

**Study limitations.** A possible limitation might be related to the degree of hypertension, mild to moderate, and the severity of diabetes, both of them being rather well controlled before entering the study (Table 1). However, blood pressure values may significantly vary throughout the day, being missed during clinic visit (20). The duration of diabetes was relatively short, 24 months mean value, however it is known subclinical changes develop long before becoming clinically apparent. Also, most of the patients were already on correct medication for cardiovascular prevention; however the parameters we evaluated begin to change from the subclinical asymptomatic stages of the disease (3,16,21,22).

**FIGURE 2.** Correlation between daytime standard deviation of diastolic blood pressure (dSDDBP) and left ventricular global longitudinal strain; rho = -0.33, p <0.05.

**TABLE 2.** Parameters of daytime and night time, systolic and diastolic, blood pressure variability.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean systolic BP (mmHg)</td>
<td>144 ± 14.8</td>
</tr>
<tr>
<td>Mean diastolic BP (mmHg)</td>
<td>88.8 ± 11.4</td>
</tr>
<tr>
<td>SD systolic BP (mmHg)</td>
<td>17.3 ± 5.5</td>
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<tr>
<td>SD diastolic BP (mmHg)</td>
<td>15.5 ± 5.5</td>
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<tr>
<td>Vr systolic BP (mmHg^2)</td>
<td>325.3 ± 199</td>
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<tr>
<td>Vr diastolic BP (mmHg^2)</td>
<td>266.4 ± 174.6</td>
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<tr>
<td>CV systolic BP (%)</td>
<td>0.1 ± 0.1</td>
</tr>
<tr>
<td>CV diastolic BP (%)</td>
<td>0.1 ± 0.05</td>
</tr>
<tr>
<td>Daytime mean systolic BP (mmHg)</td>
<td>148 ± 15</td>
</tr>
<tr>
<td>Daytime mean diastolic BP (mmHg)</td>
<td>93.6 ± 12.2</td>
</tr>
<tr>
<td>Daytime SD systolic BP (mmHg)</td>
<td>17 ± 5.6</td>
</tr>
<tr>
<td>Daytime SD diastolic BP (mmHg)</td>
<td>15.2 ± 6.6</td>
</tr>
<tr>
<td>Daytime CV systolic BP (mmHg)</td>
<td>0.1 ± 0.03</td>
</tr>
<tr>
<td>Daytime CV diastolic BP (mmHg)</td>
<td>0.2 ± 0.06</td>
</tr>
<tr>
<td>Daytime Vr diastolic BP (mmHg^2)</td>
<td>269.4 ± 233.8</td>
</tr>
<tr>
<td>Daytime Vr systolic BP (mmHg^2)</td>
<td>608.6 ± 268.6</td>
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<tr>
<td>Night time mean diastolic BP (mmHg)</td>
<td>138 ± 17</td>
</tr>
<tr>
<td>Night time mean systolic BP (mmHg)</td>
<td>138.8 ± 17</td>
</tr>
<tr>
<td>Night time SD systolic BP (mmHg)</td>
<td>13.6 ± 6.2</td>
</tr>
<tr>
<td>Night time SD diastolic BP (mmHg)</td>
<td>11 ± 4.5</td>
</tr>
<tr>
<td>Night time CV systolic BP (%)</td>
<td>0.1 ± 0.05</td>
</tr>
<tr>
<td>Night time CV diastolic BP (%)</td>
<td>0.13 ± 0.05</td>
</tr>
<tr>
<td>Night time Vr systolic BP (mmHg^2)</td>
<td>220.8 ± 297</td>
</tr>
<tr>
<td>Night time Vr diastolic BP (mmHg^2)</td>
<td>141.2 ± 126.6</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Blood pressure variability is a concept first introduced in the medical world more than 20 years ago, and reinforced nowadays by the outcomes of several studies including a large number of patients, proving BPV has earned a
place amongst the cardiovascular risk factors.

In our study of hypertensive and diabetic patients, we sought to look for more subtle changes in cardiovascular and renal functions, rather than predict future cardiovascular events, as these have already been proven to be predicted by high blood pressure variability (6, 7). Subclinical cardiac, vascular and renal dysfunctions are earlier markers of future cardiovascular events, and a more aggressive and earlier treatment might reduce the number of future events for these patients. But their relation to BPV has not been poorly evaluated until now, using specific parameters as we did in our analysis.

There is still conflicting evidence as to which types of BP variability measures best predict future cardiovascular events. BP variability during the daytime (23), nighttime (24, 25) and both daytime and nighttime (26) have all been reported to be associated with a higher incidence of CVD or CVD mortality.

In our group of patients, daytime BPV inversely correlated with cardiac function, assessed by global longitudinal strain, using 2D speckle tracking echocardiography technique. The higher the blood pressure variability, the worse longitudinal subendocardial function, assessed by left ventricular global strain. Up to now, there is no other data in the literature regarding this relationship to compare our results with. What we do know is that myocardial deformation assessed by two-dimensional strain is a valuable tool for early detection and quantification of subclinical longitudinal dysfunction, providing prognostic information (27).

We found a positive correlation between daytime BPV and carotid IMT. The higher blood
pressure variability, the more the arterial function, assessed by intima media thickness, worsens. Carotid intima thickness has been used as a surrogate and an independent predictor factor for cardiovascular events. It is a non-invasive validated tool, which can be targeted by blood pressure lowering and lipid lowering medication as a surrogate endpoint in clinical trials, in an attempt to lower the individual risk of future cardiac and vascular events (28,29).

Mean blood pressure was also significantly correlated with left ventricular subendocardial function, the higher mean BP, the lower longitudinal strain. There was a positive correlation between mean BP and microalbuminuria. This is a valuable correlation from the point of view of patients’ follow-up, too, considering microalbuminuria has been proven to be an important prognostic marker for future cardiovascular events (30-32).

The results of our study lead the way for future clinical trials, for a more complex assessment of blood pressure variability, visit-to-visit also, in an attempt to find the medication which might reduce the number of future cardiovascular events by lowering blood pressure variability.

CONCLUSIONS

In conclusion, in patients with mild-to-moderate hypertension and type 2 diabetes, we have demonstrated that higher blood pressure variability is correlated with subclinical left ventricular and arterial dysfunction. Meanwhile, microalbuminuria is correlated with elevated mean blood pressure.

Regarding the clinical impact of this study, our results support the idea that antihypertensive treatment should aim the reduction not only of office measured brachial blood pressure, but more importantly, of blood pressure variability. Antihypertensive agents should “smooth” the blood pressure profile and decrease its variability, in order to reduce the incidence of cardio- and cerebrovascular events.

Conflict of interest: none declared.

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Abbreviations list

ACE = angiotensin converting enzyme
BPV = blood pressure variability
CITP = carboxy-terminal telopeptide of collagen type-I
CV = coefficient of variation
CVD = cardiovascular disease
d = daytime
DBP = diastolic blood pressure
FMD = flow mediated dilation
n = night time
P1NP = amino-terminal propeptide of type I procollagen
PWV = pulse wave velocity
SBP = systolic blood pressure
SD = standard deviation
Vr = variance

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