

Original Article

Increased Blood Pressure Variability in Hypertensive Patients with Left Ventricular Hypertrophy

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ABSTRACT

Objectives: The aim of the study is to evaluate daytime blood pressure variability in hypertensive patients and to quantify its relation to left ventricular hypertrophy.

Design: Observation study conducted between August 2001 and June 2002.

Setting: Non-invasive cardiac laboratory, Medicine Department, Farwania Hospital.

Methods: 100 patients were included in the study. All patients were referred from out-patient clinic in Farwania Hospital with blood pressure more than 140/90 mm Hg. Resting ECG and echocardiography were done to assess left ventricular hypertrophy (LVH). Exercise ECG test was done to exclude patients with ischaemic heart disease. Ambulatory blood pressure was recorded with an auscultatory device to study blood pressure variability (BPV). The patients were classified into two groups: Group I included 60 patients with left ventricular hypertrophy and Group II included 40 patients without left ventricular hypertrophy.

Results: There was a significant increase in age, serum

cholesterol, LVMI and LV diastolic dysfunction ($P < 0.05$), maximum systolic blood pressure and daytime systolic blood pressure load ($P < 0.05$) in patients of Group I than those of Group II. There was a significant increase in, daytime systolic blood pressure ($p < 0.01$), pulse pressure ($P < 0.05$) and the mean blood pressure variability ($P < 0.05$) in hypertensive patients with LVH than those without LVH. Correlation between daytime systolic BP variability and LVH ($p < 0.05$) was also significant. Stepwise logistic multivariate analysis revealed a significant relation with age ($P < 0.05$), hypercholesterolemia ($P < 0.01$), maximum SBP ($P < 0.05$), daytime SBP load ($P < 0.01$) and daytime SBP variability. There were significant increases in age, LVMI, maximum SBP, and daytime SBP load ($P < 0.05$) in the fourth quintile of daytime SBP variability.

Conclusion: There was a significant relation between blood pressure variability and left ventricular hypertrophy. This variability increased with age, hypercholesterolemia and increased BP load.

KEYWORDS: ambulatory blood pressure recording, blood pressure variability, left ventricular hypertrophy

INTRODUCTION

Blood pressure variability (BPV) estimated as a standard deviation of beat-to-beat BP obtained by intra-arterial BP monitoring has been suggested as a risk for hypertension related target organ damage^[1,2]. BPV estimated as a standard deviation of non-invasive ambulatory BP monitoring obtained by every 15 to 20 minutes measurement, is also associated with cardiovascular morbidity and mortality^[3,4]. However, the prognostic significance of blood pressure variability for cardiovascular mortality has not been investigated in the general population. Ambulatory blood pressure monitoring allows the assessment of more than just 24-hour average blood pressure. Attention has long been directed to which components of the 24-hour blood pressure profile may have clinical relevance and add to the information provided by averaging all 24-hour values^[5].

Aims of study :

1. To evaluate daytime systolic and diastolic blood pressure variability in untreated hypertensive

patients.

2. To study the contributing factors.

3. To quantify their relation to the left ventricular hypertrophy.

SUBJECTS AND METHODS**Study subjects:**

One hundred untreated hypertensive patients, 92 men and eight women, were included in the study. All the patients were referred to the Non-Invasive Cardiac Laboratory, Department of Medicine, Farwania Hospital, with systolic blood pressure ≥ 140 mm Hg and diastolic BP ≥ 90 mm Hg respectively, between August 2001 and July 2002. Twenty subjects were referred for high blood pressure and ECG criteria of left ventricular hypertrophy, 25 subjects as dippers or non-dippers and 29 subjects to confirm high blood pressure. Five subjects were found to be hypertensive during routine examination and 21 subjects presented for preoperative assessment for elective non-cardiovascular surgery. Patients with coronary

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artery disease, diabetes mellitus, cerebrovascular disease, significant valvular disease and pregnant women were excluded from the study. Exclusion was based on medical history, physical examination, routine biological chemical tests, exercise ECG and echocardiography.

Ambulatory blood pressure measurements:

Ambulatory blood pressure was recorded with an auscultatory device (Accutacker II). After palpating the brachial artery, the microphone was placed correctly over it. The ambulatory BP was recorded during daytime (6 am to 10 pm) at 30 minutes intervals, and during nighttime (10 pm to 6 am) at 2-hour intervals. Maximum, minimum, average and standard deviation (SD), mean arterial pressure, heart rate, blood pressure load of daytime and night time systolic and diastolic blood pressure and load were calculated. Blood pressure load is the percentage of all systolic and diastolic BP recordings exceeding the threshold of 140/90 mm Hg^[6]. Blood pressure data were edited automatically. Readings with a quality failure code (ECG connection giving erratic heart beats or missing them completely, Korotkoff's sounds that were too weak to be detected, loose cuff or air leak) were rejected. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure. Mean blood pressure was calculated as diastolic blood pressure plus 1/3 of the pulse pressure^[6].

Blood pressure variability:

We focused on short-term BP variability of every 30 minutes rather than circadian BP variation. Short term BP variability was calculated as the SD of daytime ambulatory blood pressure^[7]. Quintile analysis was applied to the day-time systolic BP variability in all patients of the study. For this analysis the patients were divided into four groups:

- First quintile: BP variability less than 16 mm Hg.
- Second quintile: BP variability between 16 and 19.9 mm Hg.
- Third quintile: BP variability between 19.9 and 23.9 mm Hg.
- Fourth quintile: BP variability more than 24 mm Hg.

Echocardiographic study:

Two-dimensional and M-mode echocardiography were performed for all patients enrolled in the study using a Toshiba Power Vision using a 3.5 MHz phased array transducer. All echocardiographic studies were performed by the same cardiologist. Measurements were performed according to the recommendations of the American Society of Cardiology^[8]. The leading edge to leading

edge convention was used. Left ventricular dimensions were measured at or immediately below the tips of the mitral leaflets and were averaged over five heart cycles. Left ventricular mass and left ventricular mass index were also calculated.

Statistical analysis:

Continuous variables are summarized as mean \pm standard deviation (SD). All data were compared using the ANOVA test. Comparison between the two groups was performed with the t-test for continuous variables and the chi-square test for categorical variables. A P-value < 0.05 was considered statistically significant and a P-value < 0.01 was considered highly significant. A stepwise multivariate regression model was used to identify possible independent variables associated with blood pressure variability. The strength of the association with BP variability is presented as 95% confidence intervals. Potential confounding of clinical variables were entered as independent variables. Simple linear regression was used for correlation of the parameters of the study.

RESULTS

There was a significant increase in age, serum cholesterol, left ventricular mass index and diastolic dysfunction of left ventricle in hypertensive patients with LVH ($P < 0.05$), but there was an insignificant difference ($P = \text{NS}$) with regard to gender, smoking status, body mass index and serum triglycerides (Table 1). There was a significant increase in maximum systolic blood pressure recorded and daytime systolic blood pressure load in hypertensives with left ventricular hypertrophy (LVH), than those without LVH (195.56 ± 10.12 versus 179.82 ± 12.32 mm Hg and 82.31 ± 7.22 versus 59.90 ± 8.41 % respectively, $P < 0.05$). However, there was an insignificant difference between both groups ($P = \text{NS}$) with regard to maximum diastolic blood pressure and night-time systolic blood pressure load (120.78 ± 8.65 versus 98.65 ± 8.22 mm Hg and 43.73 ± 6.61 versus 40.82 ± 4.72 %, respectively (Table 2).

There was a significant increase in daytime SBP, pulse pressure and mean BP variability in hypertensive patients with LVH than those without LVH [22 ± 1.98 versus 10 ± 1.12 mm Hg, ($P < 0.01$), 13 ± 1.22 versus 4 ± 0.79 mm Hg, ($P < 0.01$) and 12 ± 1.68 versus 7 ± 1.03 mm Hg, respectively, ($P < 0.05$)], (Fig. 1.) There was a significant correlation between daytime SBP variability and left ventricular hypertrophy ($r = 0.869$, $P < 0.05$), (Fig. 2).

Stepwise logistic multivariate analysis revealed significant relation between age (OD = 2.04, 95% CI = 1.257-3.836, $P < 0.05$), hypercholesterolemia (OD = 3.48,

Table 1

Demographic and echocardiographic data in both groups

Variables	Hypertensives with SBP variability		P-Value
	Group I (n = 60)	Group II (n = 40)	
Age (years): mean \pm SD	55.34 \pm 5.81	43.27 \pm 6.43	< 0.05
Gender (M/F)	55 M/ 5 F	37 M/ 3 F	NS
Smoking status no. (%)	25(41.6%)	20 (50%)	NS
Cholesterol (mmol/dl)	12.43 \pm 2.57	7.3 \pm 1.42	< 0.05
Triglycerides (mmol/dl)	7.12 \pm 1.86	6.83 \pm 1.48	NS
BMI (kg/m ²)	30.32 \pm 4.21	32.11 \pm 3.34	NS
LVMI (gm/m ²)	160.46 \pm 9.49	135.79 \pm 10.88	< 0.05
E/Aratio	0.52 \pm 0.11	0.98 \pm 0.14	< 0.05

BMI=body mass index, F=female, SBP= systolic blood pressure, LVMI=left ventricular mass index.M=male, E/Aratio=early diastolic mitral flow/late diastolic mitral flow ratio

Table 2

Maximum daytime systolic and diastolic BP and daytime and nighttime systolic BPload in both group.

Variables	Hypertensives with SBP variability		P-Value
	Group I (n = 60)	Group II (n = 40)	
Maximum SBP (mm Hg)	195.56 \pm 10.12	179.82 \pm 12.32	< 0.05
Maximum DBP (mm Hg)	120.78 \pm 8.65	98.65 \pm 8.22	NS
Daytime SBPload (%)	82.31 \pm 7.22	59.90 \pm 8.41	< 0.05
Nighttime SBPload (%)	43.73 \pm 6.61	40.82 \pm 4.72	NS

DBP= diastolic blood pressure , SBP= systolic blood pressure

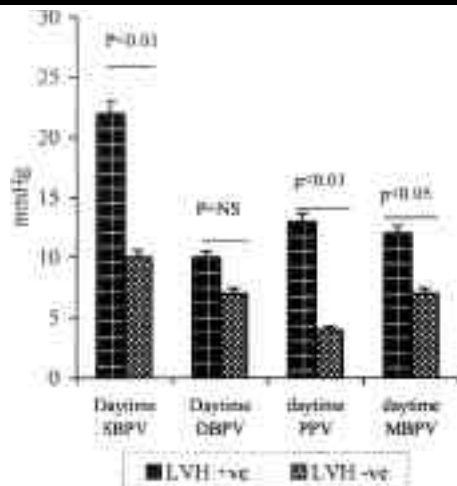


Fig. 1: Blood pressure variability (BPV) between patients with and without left ventricular hypertrophy. MBPV=mean blood pressure variability, PPV=pulse pressure variability.

95% CI = 1.076-5.927, $P < 0.01$), maximum systolic blood pressure recorded (OD = 3.09, 95% CI = 1.068-6.998, $P < 0.01$), daytime systolic blood pressure load (OD = 2.27, 95% CI = 1.178-3.427, $P < 0.05$) and daytime systolic blood pressure variability. No significant relation of daytime diastolic blood pressure load (OD = 0.89, 95%CI = 0.252-1.436, $P = NS$), nighttime systolic blood pressure load (OD = 1.19, 95%CI = 1.154-1.331, $P = NS$) and daytime systolic blood pressure variability (Table 3).

Table 3

Stepwise logistic multivariate analysis of patients' daytime BP variability as regards age, hypercholesterolemia, maximum daytime SBP, daytime and nighttime SBP (No. of observation=100)

Variables	OD	95% CI	P- value
Age	2.04	1.257 - 3.836	< 0.05
Hypercholesterolemia	3.48	1.076 - 5.927	< 0.01
Maximum Systolic BP	3.09	1.068 - 6.998	< 0.01
Daytime Systolic BP load	2.27	1.178 - 3.427	< 0.05
Daytime Diastolic BPload	0.89	0.257 - 1.436	NS
Nighttime Systolic BPload	1.19	1.154 - 1.331	NS

CI = confidence interval, OD = odds ratio, SBP=systolic blood pressure, SE = standard error.

Table 4

Clinical, echocardiographic, and blood pressure measurement variables among quintiles of daytime systolic BP variability in all patients

Variables	Daytime systolic BP Variability (mm Hg)				P-Value
	< 16	16-19.9	20-23.9	≥ 24	
Age (year)	40.2 \pm 5.4	44.3 \pm 2.7	45.1 \pm 5.8	57.7 \pm 4.6	< 0.05
LVMI (gm/m ²)	130.3 \pm 4.2	138.5 \pm 6.4	142.6 \pm 6.5	160.9 \pm 10.6	< 0.05
Max. SBP(mm Hg)	164.4 \pm 6.3	170.9 \pm 7.7	174.3 \pm 8.3	196.7 \pm 9.8	< 0.05
Daytime SBPload (%)	40.2 \pm 3.4	45.5 \pm 4.2	50.4 \pm 7.3	80.8 \pm 5.6	< 0.05
Nighttime SBPload %	30.5 \pm 2.6	32.6 \pm 5.3	35.4 \pm 6.1	38.5 \pm 12.7	NS

LVMI=left ventricular mass index, Max=maximum, SBP=systolic blood pressure.

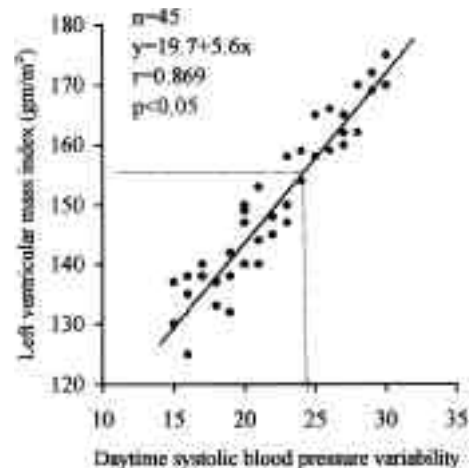


Fig. 2: Correlation between daytime SBPV and left venticle mass index

There was a significant increase in age, left ventricular mass index, maximum systolic blood pressure recorded, and daytime systolic blood pressure load in the hypertensive patients of the fourth quintile ($P < 0.05$), Table 4.

DISCUSSION

The prognostic value of BP variability was first confirmed in long term prospective study of the general population, that is, the greater the SD of ambulatory systolic BP, the greater is the risk of

cardiovascular mortality. BP variability monitored intra-arterially has been suggested to be a risk factor for hypertension-related target organ damage^[1]. BP variability estimated as a standard deviation (SD) of noninvasive, 15 to 20 minutes ambulatory BP monitoring, is also associated with cardiovascular morbidity and mortality^[3,4].

We found that hypertensive patients with left ventricular hypertrophy and systolic BP variability have a significant increase in age, serum cholesterol and left ventricular mass index with significant impaired diastolic dysfunction, maximum systolic BP and daytime systolic BP loads. Also, the patients with systolic BP variability more than 24 mm Hg had a significant increase in age, left ventricular mass index, maximum systolic BP recorded and daytime systolic BP load. By simple regression analysis, the daytime systolic BP variability was significantly positively correlated with left ventricular mass index. As described in various previous reports^[9-12], the BP variability increased as did blood pressure and age. The BP variability was also associated with a prevalence of obesity and hyperlipidemia. To investigate the prognostic significance of BP variability independent from these risk factors, Kikuya *et al*^[7] adjusted the possible confounding for Cox analysis and confirmed a significant linear relation between daytime systolic BP variability and relative risk for cardiovascular diseases. Such a relation was not confirmed by Verdecchia *et al*^[1] who followed up 1372 hypertensive subjects for 2.9 years with non-invasive ambulatory BP monitoring every 15 minutes. The differences in the duration of the follow-up period and in the study population (general population versus hypertensive subjects) may have influenced the variation in results between the two studies. Difference in the age of the participants in the study by Verdecchia *et al*^[4] may also have been a significant factor.

After adjusting HR variability, BP variability was still an independent risk factor for cardiovascular mortality suggesting that BP variability was associated with cardiovascular mortality independent of HR variability. Therefore, it is possible that indirect and intermittent ambulatory BP monitoring might be effective in predicting future cardiovascular morbidity or mortality^[6]. 24-hour BP varies not only because of a reduction in blood pressure during sleep but also because of sudden, fast and short-lasting changes that may occur both during the day and to a lesser extent, during the night^[13]. When quantified as the standard deviations of the BP values recorded intra-arterially over the 48 half hours of a 24-hour monitoring period, this short-term BP variability increases when BP increases. This is also seen when normotensive, mild, moderate, and severe

hypertensive subjects are compared^[10].

It has repeatedly been shown that this phenomenon may have clinical relevance because hypertensive patients with similar 24-hour mean BP values have a significant difference in the BP variability^[14,15,16]. In patients with greater BP variability, overall organ damage and left ventricular mass index increased more at follow-up compared to those hypertensive patients in whom for the same 24-hour BP mean values and BP variability were less^[2]. Finally, carotid artery arteriosclerosis has been found to correlate independently with systolic blood pressure (SBP) or pulse pressure variability in the hypertensive patients of the ELSAstudy^[5].

Whether it is the increased variability that increases organ damage or vice versa remains to be established. We may then understand to what extent this phenomenon can be regarded as a marker of, rather than a factor leading to, cardiovascular disease. A few studies however, have shown an experimentally induced increase in BP variability, with no increase in average BP values followed by cardiovascular damage^[17]. A hypothesis can thus be made that the organ damage accompanying hypertension is in part, due to the extent of the BP variations, thus, not only the average BP excursions around them would have to be reduced by treatment. This has so far been explored only to a limited degree because of the need to use intra-arterial ambulatory blood pressure monitoring to precisely quantify BP variability on a beat-to-beat basis. The need for continuous ABPM to properly quantify BP variability^[13] might explain why other studies have provided us with conflicting evidence on the occurrence of a significant relation between BP variability and end-organ damage, after accounting for the prognostic value of 24-hour average BP values^[4]. Thus, whether BP variability does indeed represent an additional independent factor contributing to cardiovascular risk in hypertension needs to be confirmed by larger prospective studies in which BP variability might be properly assessed. Techniques allowing beat-to-beat BP to be monitored noninvasively in ambulatory patients^[18] hold promise for the future.

To determine independent predictors of blood pressure variability, a logistic multivariate regression analysis model was fitted to the data with BP variability as the dependent variable. We found that age, hypercholesterolemia, daytime systolic BP load and maximum systolic BP recorded were independent predictors of BP variability.

The increase in BP variability in hypertensive and elderly subjects may be partly explained by the diminished baroreflex function associated with

increased stiffness and decreased compliance of the elastic arteries caused by aging and hypertension^{19,20}. A disturbed baroreflex function is related to an exaggerated pressor response to mental and physical stimuli and mediates orthostatic hypotension, postprandial hypotension and other conditions, resulting in increased BP variability²⁰. High BP variability is mediated at least in part, by disturbed cardiac baroreflex function. It is unlikely that impaired baroreflex function is the sole mechanism explaining the relation between high BP variability and poor prognosis. However, it is still uncertain whether a clinical significance of BP variability every 30 minutes is equivalent to that of beat-to-beat BP variability and thus whether BP variability every 30 minutes reflects baroreflex function. Another possible mechanism is that high BP variability injures the blood vessels and consequently causes cardiovascular complications. The effect of phasic BP load on cardiovascular structures is considered to be as important as that of tonic BP load²¹.

Limitations of the study:

1. Nighttime blood pressure variability was not included in the study due to difficulty to record BP every 30 minutes at night during sleep.
2. Heart rate variability was not included in the study due to difficulty to assess HR variability by ambulatory ECG recorded at the same time of BP recording.
3. Relatively small number of patients.
4. Coronary angiography was not done to exclude ischemic heart disease, so we cannot exclude it in spite of negative exercise ECG test; ischemia is considered as a confounding factor.
5. The study of carotid artery wall status was not done, so we recommend further study to assess aortic root and carotid artery function in hypertensive patients with increased BP variability.
6. Assessment of other end organs was not included in the study.

CONCLUSION

BP variability increases in hypertensive patients with increasing age, serum cholesterol, maximum systolic BP and systolic BP load. This may be explained partly, by a disturbance of baroreflex function associated with an increase in arterial stiffness due to aging, by hypercholesterolemia and hypertension. The increased BP variability is associated with increased left ventricular hypertrophy and diastolic dysfunction.

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