ORIGINAL ARTICLE

Blood Pressure Variability and Arterial Elasticity in Hypertensive Subjects

H M Rafidah, MD*, A Azizi, PhD*, M N Noriah, PhD**

*Kulliyyah of Medicine, **Kulliyyah of Pharmacy, International Islamic University of Malaysia, Bandar Indera Mahkota, 25200 Kuantan, Pahang

Summary

Apart from the mean 24 hour ambulatory blood pressure (ABP), the blood pressure variability (BPV) also bears an independent relationship with target-organ damage in hypertension. A reduction in arterial compliance has been demonstrated in hypertension but its relation to BPV is still unknown. The aim of the study is to compare BPV and arterial compliance between hypertensive and normotensive subjects. Eighteen hypertensives and 18 controls were enrolled. Noninvasive 24-hour ABP monitoring was performed with BR-102 monitor (Schiller Inc. Germany). Arterial compliance was determined by the HDI/Pulsewave Research Cardiovascular Profiling Instrument (Hypertension Diagnostic Inc. USA). There were significantly higher systolic, diastolic and mean arterial BPV in hypertensives as compared to normotensive group. Only systolic BPV remained significantly high in hypertensives during night time. There were lower arterial compliances in hypertensive as compared to normotensive group. No significant relationship however was found between BPV and arterial compliance in hypertensive subjects. In conclusion, there were higher BPV and lower arterial compliances in hypertensive subjects as compared to normotensive subjects.

Key Words: Blood pressure variability, Arterial compliance, Hypertension

Introduction

Though hypertension has been known for over a century, its pathophysiology and management remain a problem. It remains to be the major reversible risk factor for cardiovascular disease (CVD) and renal failure. In Malaysia, it was reported that the proportion of death due to CVD in peninsular Malaysia has multiplied more than three-fold since 1965[1]. A high prevalence of hypertension has attributed to this increase. Osman *et al.*,[2] reported that among rural Malay adult, out of 359 people examined, 26% had hypertension which was defined as systolic blood pressure (SBP) more than 140 mmHg and diastolic blood pressure (DBP) more than 90 mmHg. In another study[3], 14% of 963 respondents were found to be hypertensive with 16.8% of them from urban area compared to 12.3% from rural area. This figure doubled in 1996 where report from The Second National Health and Morbidity Survey[4] showed the overall estimated prevalence of hypertension among adults in Malaysia is 29.9%. This figure comprised 14.0% of the self-reported hypertension and 15.9% of undiagnosed hypertension.

Elevated blood pressure (BP) identifies a population at a greater risk for cardiovascular events. This is not because the BP itself causes the adverse effect events but because there is the likelihood that the blood vessels have an abnormal function or structure[5]. Cross sectional[6,7] and longitudinal[8] studies have revealed that apart from the mean 24 hour ambulatory blood pressure, BPV also bears an independent relationship with target-organ damage in hypertension. It is suggested that BPV may be related to the endothelial vascular abnormality. Furthermore, recent advances in

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Corresponding Author: Rafidah Hanim Mokhtar, Kulliyyah of Medicine, International Islamic University of Malaysia, Bandar Indera Mahkota, 25200 Kuantan, Pahang

non-invasive monitoring and vascular imaging have led to a number of indices of arterial function at different levels of the arterial tree, which are now being applied as surrogate markers for CVD[9]. Systemic arterial compliance is one of the indices of arterial function that has been shown to correlate well with cardiovascular risk factors such as age[10] smoking[11] pulse pressure[12] and coronary arteries disease (CAD)[13].

Meta-analysis of recent studies that have examined the impact of hypertension showed that there was a success in decreasing the incidence of stroke[14]. However, comparatively it was not the case for the incidence of CAD[15, 16]. When patients with treated and controlled hypertension were compared with normotensive subjects with similar levels of BP, there was still an approximately 30% higher incidence of CAD among hypertensive patients[17]. It appears that in addition to the inadequate BP control, an important reason for inadequate impact on the incidence of CAD is the fact that there may be multiple mechanisms of hypertension, of which high BP is only one of the features. Is BPV another element in hypertension and is it also a feature in hypertensive Malaysian population? The aim of the study was to compare the BPV (expressed by standard deviation) between hypertensive and normotensive subjects matched for sex, age and weight and to find its relationship to systemic arterial compliance.

Materials and Methods

Study Population

This is a cross sectional study. Subjects were matched with control in terms of age, sex, weight, blood glucose, lipid profile and smoking status. Patients were recruited from Tengku Ampuan Afzan Hospital. The matched controls were from the same resources. The study had been approved by the Ethical Committee of the International Islamic University of Malaysia.

The subjects were either untreated or had stopped taking medication for at least four weeks prior to the study. Hypertension was defined as the average of three clinic readings greater than 140 mmHg systolic and/or greater than 90 mmHg diastolic BP. The measurement was performed by the same investigator using the mercury sphygmomanometer with participants in supine position. BP was measured in the non-dominant arm. SBP was defined by the first appearance of the sound (phase I Korotkoff sound) and DBP was defined by the disappearance of the sound (phase V). Each defined measurement was the average of three values recorded two minutes apart. If any two readings differ by more than 5 mmHg, additional reading was obtained and averaged. Mean arterial pressure (MAP) was calculated as DBP + 1/3(SBP-DBP)[18]. Patients were asked to refrain from smoking or ingesting caffeine 30 minutes prior to the measurement and had at least 30 minutes of rest before measurement begin. The patients were not included if resting BP was at any time noted to be more than 180mmHg systolic and/or 110 mmHg diastolic. Using the same procedure, the control subjects were included if the BP was less than 140/90 mmHg.

Ambulatory Blood Pressure Measurement

Noninvasive ambulatory BP monitoring (ABPM) was performed for a minimum of 24 hours with BR-102 monitor (Schiller Inc. Germany). This recorder fulfills the criteria of the British Hypertension Society and the Association for the Advancement of Medical Instruments[19]. The study was initiated between 0830 to 1000 hour and the ABPM was set to measure blood pressure 15-minute intervals from 0600 hour to 2200 hour and 30 minute interval from 2200 hour to 0600 hour. The non-dominant arm was used for cuff placement. Subjects were instructed to keep their arm immobile during cuff inflation and deflation, but to otherwise go about their daily activities as planned. Taking shower, strenuous exercises, sexual intercourse and caffeine intake were not allowed. Subjects were given a diary to record daily activities and actual sleep time for data analysis. The first two readings were omitted as they might result in inaccurate values from alerting reaction. All blood pressure readings were included if at least 80% of the measurement were accepted. Daytime and asleep averages were calculated based on the patients' diaries.

Arterial Compliance Measurement

Arterial compliance were determined by using the HDI/Pulsewave Research Cardiovascular Profiling Instrument (C-VPI) Model CR-200 (Hypertension Diagnostic Inc. Eagen, MN, USA), a non-invasive arterial pulse pressure sensor. The tonometer sensor array adjusts itself automatically to obtain the optimal waveform at radial artery and repeats its calibration until the waveform is stable. The BP waveform derived from the elasticity indices result from the computer-based averaging of ten consecutive individual arterial BP waveforms collected during a 30-s period. The elasticity indices are of the large arteries (C_1), which measure the capacitative arterial compliance and represent the aorta and major branches, and of the

small arteries (C_2), which measure the reflective arterial compliance and represent the distal part of the circulation. Both C_1 and C_2 will be derived from a third-order four-element modified Windkessel Model[20].

Study Protocol

After the subjects were briefed on the study and informed consent had been obtained, clinic BP measurement and blood samples were taken. The participants were included if they met the inclusion criteria, where the ABPM device was put on at visit two. The next day after the completion of 24 hours BP recording, the diary was collected and the subjects underwent arterial compliance measurement, after lying supine for at least 30 minutes. Measurement of arterial compliance was done by a single operator.

Statistical Analysis

Blood pressure variability was defined as the standard deviation (SD) of the mean of SBP, DBP and MAP. All the BP parameters were analyzed according to the 24 hour period, daytime period and nighttime period. Awake and asleep blood pressures were based on actual times noted in participants' diaries. Data were given as mean ± SD. Comparison between the groups mean was by dependent/paired *t* test. The association between BPV and arterial compliance was measured by bivariate correlation analysis (Pearson correlation coefficient *r*). T test was used to test the significance of the correlation. *P* value of less than 0.05 was taken as the level of significance for all tests.

Results

There were twenty subjects included in the study. Two subjects however did not complete the 24 hours ABPM. Eighteen hypertensive subjects therefore were evaluated and they were matched with eighteen matched control subjects. The clinical characteristic of the subjects were as presented in Table I.

There were significantly higher 24-hour, daytime and night time BPs in hypertensives as compared to the normotensives. As for the BPV, hypertensives had higher 24 hour systolic (P=0.002), diastolic (P=0.025) and mean arterial (P=0.014) BPV and higher daytime systolic (P=0.003), diastolic (P=0.017) and mean arterial (P=0.015) BPV. At night time, there was higher systolic BPV in hypertensives (P=0.017) but not diastolic BPV and mean arterial BPV (Table II).

The hypertensives had significantly lower C_1 (P=0.002) and C_2 (P=0.008) as compared to the normotensives (Figure 1 and 2 respectively). There were however no significant correlations found between C_1 and both 24 hour and daytime BPV in both hypertensives and normotensives as shown in Table III. However, night time BPV analysis showed that in normotensives, there was a significantly positive correlation between C_1 and night time diastolic BPV and mean arterial BPV (Figures three and four respectively). There were no significant correlations found between C_2 and BPV (Table IV).).

Table I: Clinical characteristic of hypertensives and the matched control

N	Normotensive 18	Hypertensive 18
Age (years)	49 ± 10 (28-74)	53 ± 9 (38-64)
Sex (M: F)	12:6	12:6
BMI (kg/m^2)	25.1 ± 3.4	27.0 ± 3.8
Duration of diagnosed hypertension (years)	-	2.6 ± 2.4
Office BP		
SBP	123 ± 10	149 ± 16
DBP (mmHg)	79 ± 7	93 ± 8
MAP	94 ± 7	111 ± 8
Fasting Blood Glucose (mmol/L)	5.4 ± 1.8	5.3 ± 1.0
Total Cholesterol (mmol/L)	5.6 ± 0.9	5.2 ± 1.0
High Density Lipoprotein (mmol/L)	1.6 ± 0.3	1.4 ± 0.3**
Low Density Lipoprotein (mmol/L)	3.4 ± 0.9	3.1 ± 0.8
Triglyceride (mmol/L)	1.3 ± 0.8	1.5 ± 0.9
Total Cholesterol :High Density Lipoprotein ratio	3.6 ± 1.0	3.7 ± 0.8

Data expressed as mean ± standard deviation (SD)
SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, MAP=Mean Arterial Pressure
*P<0.05
**P<0.01

Table II: The comparison of ambulatory BP parameters in hypertension and normotension

24 hours (in mmHg)	Normotensive (n=18)	Hypertensive (n=18)
SBP	117 ± 9	136 ± 12**
DBP	83 ± 6	94 ± 9**
MAP	94 ± 6	108 ± 9**
Systolic BPV	15.6 ± 3.9	19.8 ± 4.3**
Diastolic BPV	13.7 ± 4.8	16.8 ± 4.2*
Mean arterial BPV	13.2 ± 4.5	16.3 ± 4.3*
Daytime (in mmHg)		
SBP	120 ± 10	137 ± 12**
DBP	85 ± 6	95 ± 9**
MAP	97 ± 7	109 ± 9**
Systolic BPV	15.7 ± 4.5	20.1 ± 4.7**
Diastolic BPV	13.8 ± 5.3	17.4 ± 4.7*
Mean arterial BPV	13.0 ± 5.1	16.9 ± 4.8*
Night time (in mmHg)		
SBP	107 ± 9	127 ± 11**
DBP	73 ± 7	86 ± 8**
MAP	85 ± 7	100 ± 7**
Systolic BPV	10.2 ± 3.9	14.2 ± 5.8*
Diastolic BPV	8.6 ± 5.5	10.1 ± 4.6
Mean arterial BPV	8.4 ± 5.0	10.0 ± 5.1

Data expressed as mean ± standard deviation (SD); SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, MAP=Mean Arterial Pressure; BPV=Blood Pressure Variability. *P<0.05, **P<0.01

Table III: Relation of large artery compliance to BPV in hypertensives and normotensives

Variables	Large artery compliance (C1) (ml/mmHg X 10)			
	Normotensive (n=18)		Hypertensives (n=18)	
	r	P	r	P
24 hours				
Systolic BPV	0.342	NS	-0.173	NS
Diastolic BPV	0.452	NS	-0.312	NS
Mean arterial BPV	0.447	NS	-0.235	NS
Daytime				
Systolic BPV	0.321	NS	0.078	NS
Diastolic BPV	0.322	NS	0.026	NS
Mean arterial BPV	0.346	NS	0.054	NS
Nightime				
Systolic BPV	0.326	NS	0.156	NS
Diastolic BPV	0.547	< 0.05	0.077	NS
Mean arterial BPV	0.500	< 0.05	0.170	NS

BPV=Blood Pressure Variability.
NS= not significant

Table IV: Relation of small artery compliance to BPV in hypertensives and normotensives

Variables	Small artery compliance (C_2) (ml/mmHg X 100)			
	Normotensive (n=18)		Hypertensives (n=18)	
	r	P	r	P
24 hours				
Systolic BPV	-0.140	NS	0.090	NS
Diastolic BPV	0.230	NS	-0.026	NS
Mean arterial BPV	0.134	NS	0.026	NS
Daytime				
Systolic BPV	-0.036	NS	0.073	NS
Diastolic BPV	0.244	NS	0.068	NS
Mean arterial BPV	0.181	NS	0.085	NS
Night time				
Systolic BPV	-0.161	NS	0.035	NS
Diastolic BPV	-0.069	NS	-0.024	NS
Mean arterial BPV	-0.093	NS	0.040	NS

BPV=Blood Pressure Variability.
NS= Not significant

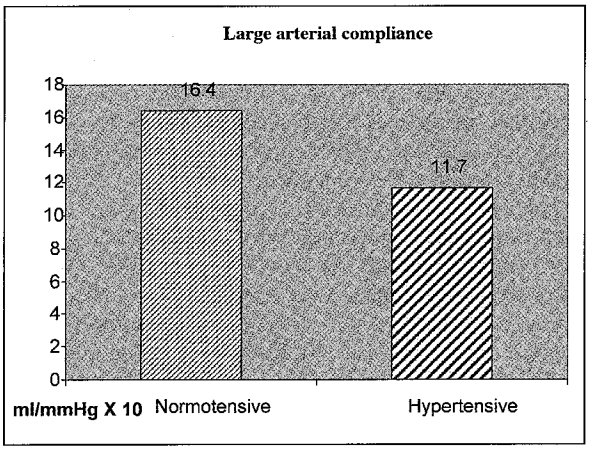

Fig. 1: The comparison of large arterial compliance between hypertensives and normotensives.

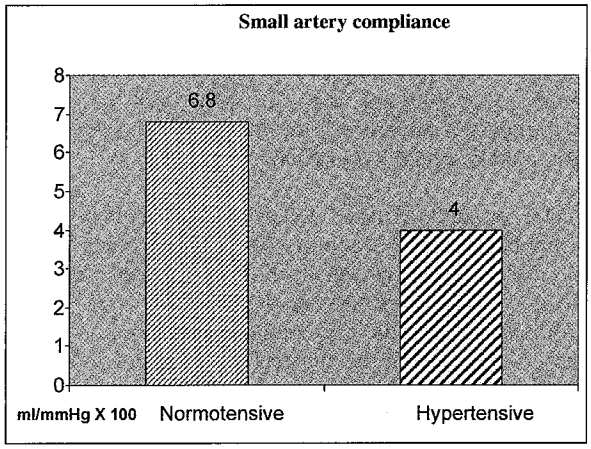

Fig. 2: The comparison of small arterial compliance between hypertensives and normotensives.

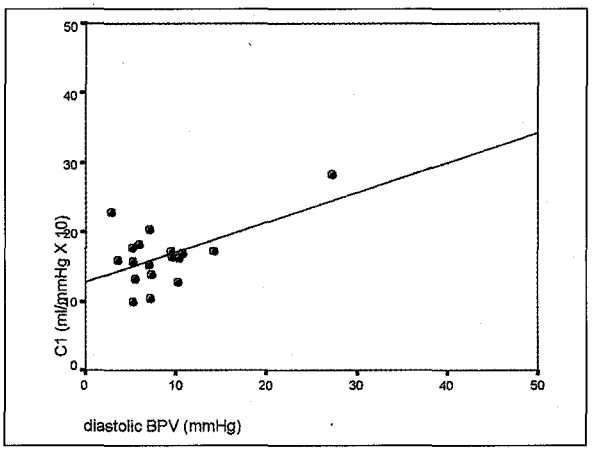

Fig. 3: Scatterplot diagram showing the correlation between C_1 and night time diastolic BPV in normotensives.

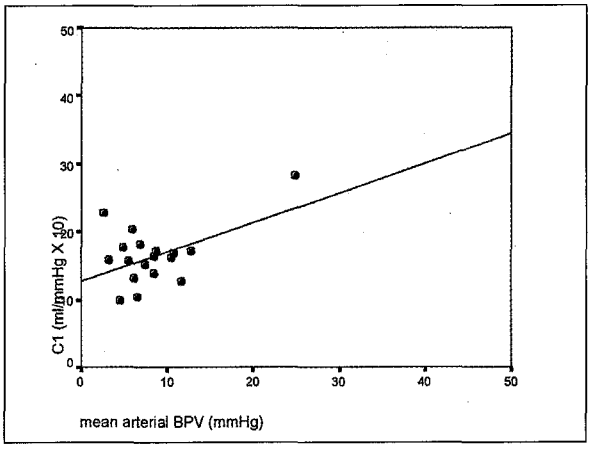

Fig. 4: Scatterplot diagram showing the correlation between C_1 and night time mean arterial BPV in normotensives.

Discussion

The findings of elevated BPV in hypertensives were in agreement with preious observations[6,7,8]. Similar results were also reported for BPV which was measured by continuous non-invasive finger BP recording and analyzed by power spectral analysis method[21]. The study also showed that the BPV was greater in hypertensive subjects whose BP were more severe than the mild essential hypertensive group.

Cohn et al.,[20] reported that the decrease in arterial compliance was only found in the small artery where C_2 was reduced by 21% in the hypertensives subjects. In this study, there was no difference in large arterial compliances in the hypertensive and normotensive groups. However, the subjects in that study[21] were not controlled for sex, and thus did not take into account the influence of gender on arterial compliance[22]. Using similar device, other studies[23,24,25] also found that both large and small arterial compliances were reduced in hypertensives as compared to normotensives. Other methods of measuring arterial compliance or stiffness such as echotracking imaging technique[26] and central augmentation index[27] had also yielded similar results.

Bivariate correlation analysis in this study showed that BPV did not correlate with arterial compliance as measured via pulse wave analysis. The absence of correlation between BPV and arterial compliance may suggest that these vascular properties share a common pathophysiological pathway but both are independent of each other. There have been contradictory reports with regards to the association between the two parameters where some study documented their presence[28,29,30] and others not[31,32]. Studies that supported the relationship however were using indirect measures to reflect arterial compliance such as minimum forearm vascular resistance[28] and diameter changes of the common carotid artery[29] and intima media thickness (IMT)[30] as arterial compliance is known to be closely related to IMT[33]. In 2005, a population study[31] found that both radial and carotid artery distensibilities were not correlated with 24 hour systolic BPV. This is supported by Roman, *et al.*[32] who showed that there were no differences in BPV between subjects with carotid atherosclerosis and those without, stressing that the apparent relation in other studies would be due to dependency towards age and absolute mean pressure.

Secondly, the absence of correlation would probably be contributed by the extent of the severity of atherosclerosis that is needed to influence these vascular abnormalities in hypertensives in this study. Most of the subjects were newly diagnosed hypertensives with the mean duration of disease for 2.6 years. Altered arterial compliance has been shown only in a case of extensive atherosclerosis in patients with clinically manifested CVD in hypertension or hypercholesterolemia[34]. This finding is further supported by the human studies among middle aged

and elderly subjects, in which significant increase in arterial stiffness was only observed in those with carotid IMT values greater than 0.8-0.9 mm [35,36]. This may partly suggest that though there was high BPV and low arterial compliances in hypertensives, they are not related in a causal manner in a mild to moderate severity of atherosclerosis.

Thirdly, the lack of association between BPV and arterial compliance in this study were probably due to the differences in the determinants of the two vascular entities. While arterial compliance may be more influenced by the long term regulating factors such as atherosclerosis and endothelial dysfunction, BPV may be more affected by short term regulating factors. Aorto-carotid baroreceptors are known to be the principal counter-regulators of short-term changes in systolic (and to a much lesser extent diastolic) BP levels[37]. A direct examination of baroreceptors impairment and BPV was provided by a study[38] where subjects who had bilateral carotid body resection displayed lower baroreflex sensitivity (BRS) compared to the controls. These subjects also exhibited higher systolic and diastolic BPV as compared to the controls despite similar mean BP. In hypertension, reduced BRS has been documented by several studies in humans[39,40] as well as in animal[41].

The role of neurohumoral factors are further enhanced by the fact that in night time BPV analysis of the present study, only the systolic BPV remained significantly high. This may suggest that even in the absence of physical activity, the intrinsic factors may play a greater role in regulating the BP independent of physical activity. Human[42] and animal[43] studies suggested the possibility of catecholamines underlying the pathology of hypertension. It may be postulated that increase norepinephrine (NE) or epinephrine (E) may induce bouts of sympathetic nervous system (SNS) burst thus increasing BPV. It has been reported earlier that in the early morning, there is a marked rise in the neural and hormonal sympathetic activity[44], and circadian pattern of catecholamines has been earlier identified, both in normal subjects[45] and in hypertensives[46]. These neurohormonal influences may produce the surge of mean BP, and together with vulnerable impaired baroreceptors, may result in increased night time BPV in hypertensives. Gosse *et al.*,[47] found that the change in SBP on rising was significantly related to the 24 hour systolic variability. The changes in BP on rising was calculated as the difference between the values measured precisely on rising and the last values measured by the device 30 minutes before rising, values which were also part of the night time analysis in the present study.

The limitation of the study is the relatively small sample size in each group. However, this is expected as clustering of risk factors is very common among Malaysians[48], hence it is a difficult task to find subjects with single CVD risk factor. Another limitation is the fact that arterial compliance was measured from radial artery while BPV was derived from the measurement made from brachial artery pressure. Study has showed that auscultatory BP measurement at the radial artery with standard sphygmomanometry overestimates brachial BP[49]. However, this discrepancy is believed to be caused by insufficient occlusion of wrist arteries, due to the positioning of the longitudinal palmar tendon, wrist arteries, and radius and ulna [50]. Furthermore, the study[49] has not only rule out the effect of hydrostatic pressure but also found out that arterial distension was not a predictor of the arm-forearm BP discrepancy. Therefore, it may be assumed that the BP is practically identical in brachial and radial arteries, as had been suggested earlier on[51] and the peak and trough of the radial pulse wave correspond, respectively, to systolic and diastolic blood pressure measured on brachial artery[52].

In conclusion, there were higher BP variability and lower arterial compliances in hypertensive subjects as compared to normotensive subjects. There were however no significant relationship between the two parameters, suggesting the importance of neurohormonal factors in influencing BPV.

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