The Blood Pressure Variability, Arterial Elasticity and Humoral Factors in Subjects with Family History of Hypertension

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

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

SUMMARY

Normotensive subjects with family history of hypertension (FHT) have been reported to have increased left ventricular mass index and reduced ventricular compliance. Of interest is whether blood pressure variability (BPV), which has been associated with target organ damage, is then part of this complex inherited syndrome? The objectives of this study are to determine whether there are any significant differences in BPV, arterial compliance and humoral factors in subjects with FHT as compared to controls. Thirty-five subjects with self reported FHT and 35 matched controls underwent 24 hour BP monitoring (BR-102, Schiller Inc. Germany). Arterial compliance was measured using systolic pulse wave tonometry (HDI/Pulsewave Cardiovascular Profiling Instrument, Hypertension Diagnostic Inc. USA). None of the subjects were hypertensive or diabetic. Out of these numbers, 25 subjects with FHT and 26 controls had measurements of plasma catecholamines, plasma renin and serum aldosterone. Catecholamines were assayed with high performance liquid chromatography, while both renin and aldosterone measurements were by radioimmunoassay. Subjects with FHT have higher night time BPV. There was no significant difference in arterial compliances between both groups. There were increased level of norepinephrine (NE) in subjects with FHT but epinephrine (E), renin and aldosterone levels were similar in both groups. There were no correlations between NE and BPV but E was negatively associated with daytime and mean arterial systolic BPV. In conclusion subjects with FHT demonstrated a higher night time BPV and NE level as compared to controls.

KEY WORDS:
Blood pressure variability, Arterial compliance, Family history of hypertension, Catecholamine, Sympathetic nervous system

INTRODUCTION

It is suggested that hypertension is not simply a disease but rather a complex inherited syndrome of cardiovascular risk factors. Several new findings in normotensive patients with family history of hypertension (FHT) have led to the theory that patients may have coronary artery disease (CAD) before the actual onset of elevated BP. Normotensive subjects with FHT have been reported to have significantly higher cholesterol level[1], increased left ventricular mass index[2], significant reduction in ventricular compliance[3,4], reduced arterial compliance[5,6] and increased neuroendocrine hormones[1] .

The circadian variation of acute myocardial infarction[7,8], sudden cardiac death[9,10] and transient myocardial ischaemia[11] has been reported. It has been observed that the BP also has a definite circadian pattern[12]. The moment to moment changes are termed as blood pressure variability (BPV). Higher BPV has been reported among hypertensives[13]. Higher office BP[3] and 24 hour BP[14,15] has been reported among FHT subjects. As far as BPV is concern, there have been contradictory results by previous studies. Manuck *et al.*[16] found that there was no difference with regards to BP reactivity due to mental stress test in subjects with FHT and the matched control but Lemne[17] revealed that even a mild level of heredity for hypertension leads to increase BPV, in particular 24-hour and daytime systolic BPV. Is BPV then part of the complex inherited syndrome?

The recent advances in 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 CAD[18]. The decline in large and small arteries compliances, reflecting structural or functional changes have been demonstrated[19]. In disease states such as hypertension, diabetes, atherosclerosis and smoking, the reduction in the compliance is prominent at the smaller vessel[20]. As compliance reduction in the disease states has been suggested as a marker for the early stages of vascular diseases, it is interesting to find out whether it is a feature in subjects with FHT, and whether it may explain the underlying pathology of BPV.

The determination of whether humoral factors are associated with the development of hypertension in subjects with FHT so far yielded contradictory results. While Neutel *et al.*[1] found a significantly high norepinephrine (NE) levels in subject with FHT, Manuck *et al.*[16] reported similar plasma level of NE and epinephrine (E) in young normotensive men having either one or two hypertensive parents or normotensive parents. This is supported by another study which found that there was no significant difference in sympathetic activity, measured as muscle sympathetic nerve activity burst[21]. Plasma renin level has been shown to correlate positively with the low frequency component of diastolic BPV in hypertensive subjects[22] but not by other studies[16,23].

This article was accepted: 14 February 2007
Corresponding Author: Rafidah Hanim Mokhtar, Kulliyyah of Medicine, International Islamic University of Malaysia, Bandar Indera Mahkota, 25200 Kuantan, Pahang

Aldosterone, which has been associated with baroreflex dysfunction both in animal[24,25] and human studies[26,27] was not significantly correlated with changes of systolic or diastolic BPV in hypertensives[22]. A study described a negative relationship between aldosterone and systemic arterial compliance[28]. The relationship was not influenced by age or level of BP and was not observed for local arterial compliance in radial artery.

The major proportion of BP variance can be attributed to the genetic factors rather than the environmental factors[29]. The objectives of the study are therefore to determine whether there is any difference in BPV among subjects with FHT as compared to control and whether arterial structural factor, namely arterial compliance or humoral factor such as catecholamines, renin and aldosterone play an important role in modulating the amplitude of fluctuation in BP in subjects without clinical evidence of disease state.

MATERIALS AND METHODS

Study Participant

Thirty-five subjects were matched with 35 controls in terms of age, sex and body mass index (BMI). Subjects were recruited from Tengku Ampuan Afzan Hospital outpatient department and among the medical students of International Islamic University of Malaysia (IIUM). The matched controls were from the same setting. All subjects were normotensives. The study had been approved by the Ethical Committee of the IIUM.

Family history of hypertension was defined as self reported history of hypertension in the first-degree family, which includes biological parents or siblings[30]. Their reports included the knowledge of being aware of the diagnosis of hypertension and knowing that their first degree family members had a regular follow up in clinics. Subject who was unsure of the health status of the first-degree family was not included.

Ambulatory Blood Pressure Measurement and Arterial Compliance

Noninvasive ambulatory BP monitoring (ABPM) and arterial compliance was performed as previously described[13]. Briefly, 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. This recorder fulfills the criteria of the British Hypertension Society and the Association for the Advancement of Medical Instruments[31]. 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.

Humoral Factors Measurement

The studies were carried out in a temperature-controlled room (22-24 ^{0}C) between 8 to 10 am to maintain consistency with the subjects remaining in supine position to minimize diurnal variation[32,33] and posture effects[34] respectively. Brachial vein of the non dominant arm was cannulated with an indwelling intravenous catheter and was kept open with heparin lock. After the instrumentation, the patients were left lying supine in a quite room. After 30 minutes, 3.0 mL of blood was withdrawn from the vein to flush out heparin and 4.0 mL of blood was collected in prechilled lithium heparinate monovettes which were prefilled with 100 µL of an antioxidative solution containing 61g of glutathione and 76g of ethylene glycol tetraacetic acid (EGTA) per litre for analysis of E and NE. These tubes were placed in a container filled with ice cubes to maintain temperature at 4^{0}C. Another 4.0 mL of blood was collected in a non chilled EDTA tubes for plasma renin assay and 2.0 mL of blood was collected in a plain tube for serum aldosterone assay.

For catecholamines, blood samples were centrifuged at 3000rpm for 10 min at 4^{0}C. The plasma were removed and frozen at -70^{0}C. Briefly, for catecholamine absorption, alumina was activated by heating at 200^{0}C for about 2 hours. The method was carried out with a slight modification from the Clinical Neurochemistry Laboratory Procedure Manual[35]. Plasma was thawed at room temperature. In a 2 mL tube, 1.2 ml of plasma was combined with 40 µL of 3,4-dihydroxybenzylamine hydrobromide (DHBA) as the internal standard, 10 mg of activated alumina and 320 µL of 2 mol/L Tris / 20g/L Sodium Ethylene-diamine-tetra-acetic acid (EDTA) at pH 8.7. The sample mixture was then wrist-shaken for 15 minutes, after which it was centrifuged at 9000 rpm for 1 minute. The supernatant was discarded. The alumina retained was washed with 800 µL of distilled water and shook for 1 minute. It is then centrifuged for 1 minute. This process was repeated for three times. For catecholamine desorption, 100 µL of acetic acid was added to the retained alumina. This mixture was vortex-shakened for 15 minutes. It was centrifuged for 1 minute. The supernatant containing acetic acid with the desorbed catecholamine was then filtered through a 0.045 µM syringe filter into a plain eppendorf tube. The first 20 µL withdrawn was discarded. The next 20 µL withdrawn was injected to high pressure liquid chromatography (HPLC) column. Duplicate injections were made to obtain average values. The retention times were 7.1 minutes for NE, 9.0 minutes for E and 11.2 minutes for DHBA. The detection limit for E and NE were 24 pg/20 µL and 23 pg/20 µL respectively. The intra assay coefficients of variations (CV) for NE were 5.8% at 100 pg/ 20 µL and for E 4.0%. The inter assay CV at 100 pg/ 20 µL for NE was 6.4% and for E 9.0%.

For renin and aldosterone, the blood samples were centrifuged at 5000 rpm for five minutes at room temperature and then immediately frozen at -20^{0}C until assayed. Plasma renin was measured using a two site radioimmunometric assay kit (The Nichols Institute Active Renin, Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Aldosterone was measured with radioimmunoassay using a commerciable kit, Coat-A-Count kit (Diagnostic Products Corporation, Los Angeles, CA).

Study Protocol

Clinic BP measurements and blood samples were taken after the subjects were briefed on the study and informed consent had been obtained. The participants were included if they met the inclusion criteria, where the ABPM device was put on at visit 2. The next day after the completion of 24 hour BP

Table I: Clinical characteristic of subjects with family history of hypertension (FHT) and the matched controls

	Controls	FHT
n	35	35
Age (years)	38 ± 13 (20-63)	37 ± 13 (20-60)
Sex (M: F)	18:17	18:17
BMI	24.9 ± 4.6	25.7 ± 4.8
Office BP		
SBP	120 ± 19	119 ± 18
DBP	78 ± 11	79 ± 11
MAP	92 ± 13	92 ± 13
Fasting Blood Glucose (mmol/L)	5.1 ± 1.2	5.3 ± 2.1
Total Cholesterol (mmol/L)	5.5 ± 1.1	5.1 ± 1.1
High Density Lipoprotein (mmol/L)	1.5 ± 0.4	1.4 ± 0.3
Low Density Lipoprotein (mmol/L)	3.5 ± 1.1	3.1 ± 1.0
Triglyceride (mmol/L)	1.1 ± 0.7	1.2 ± 1.2
Total Cholesterol :High Density Lipoprotein ratio	3.8 ± 1.9	3.8 ± 1.4

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 cardiovascular haemodynamic parameters between subjects with FHT and controls

	Controls (35)	FHT (35)
Cardiac ejection time (msec)	333 ± 23	339 ± 25
Stroke Volume Index (ml/beat/m^2)	48.0 ± 6.7	46.6 ± 7.0
Estimated Cardiac Output Index (L/min/m^2)	3.2 ± 0.3	3.2 ± 0.4
Large artery elasticity index (ml/mmHg X 10) or C_1	15.7 ± 4.8	15.3 ± 4.4
Small artery elasticity index (ml/mmHg X 10) or C_2	7.9 ± 3.6	7.9 ± 3.4
SVR (dyne•sec•cm^{-5})	1376 ± 376	1292 ± 347
TVI (dyne•sec•cm^{-5})	131 ± 46	128 ± 44

Data expressed as mean + standard deviation (SD)
SVR=Systemic Vascular Resistance, TVI = Total Vascular Impedance
*P<0.05
**P<0.01

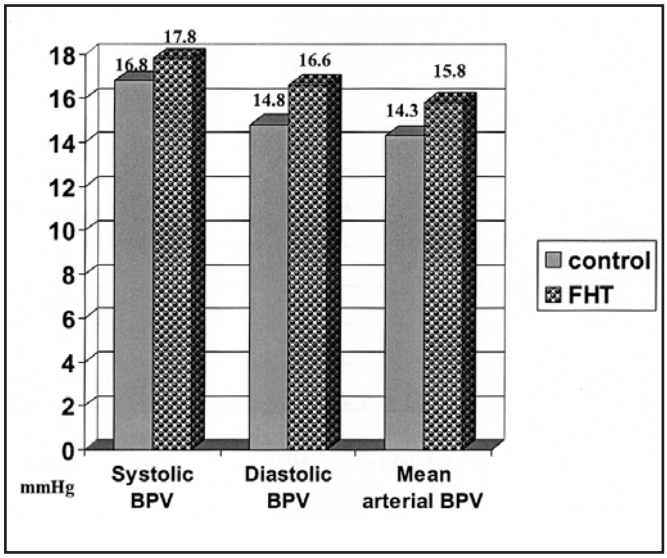

Fig. 1: The comparison of 24 hour blood pressure variability (BPV) in subjects with family history of hypertension (FHT) and the matched controls.

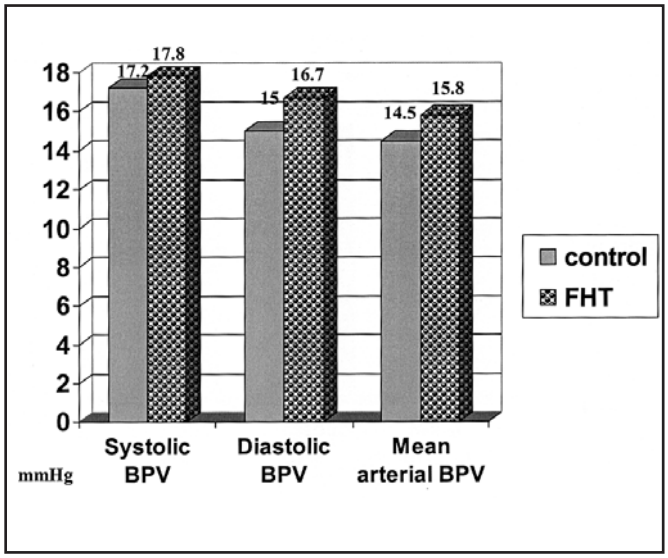

Fig. 2: The comparisons of daytime blood pressure variability (BPV) in subjects with FHT and matched controls.

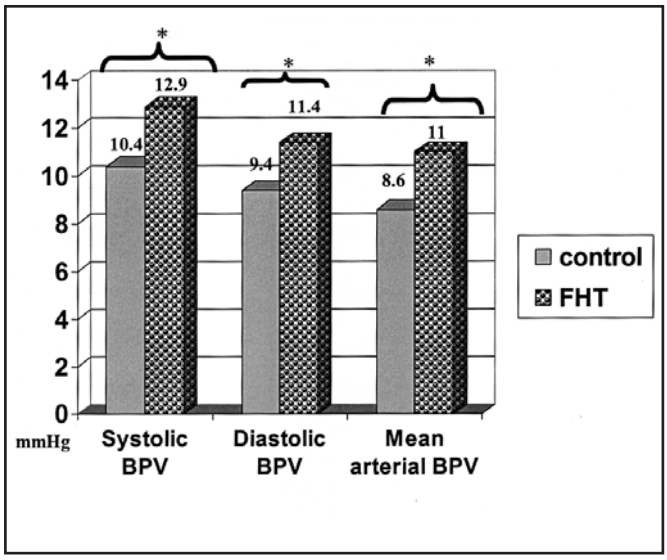

Fig. 3: The comparisons of night time blood pressure variability (BPV) in subjects with FHT and matched controls.

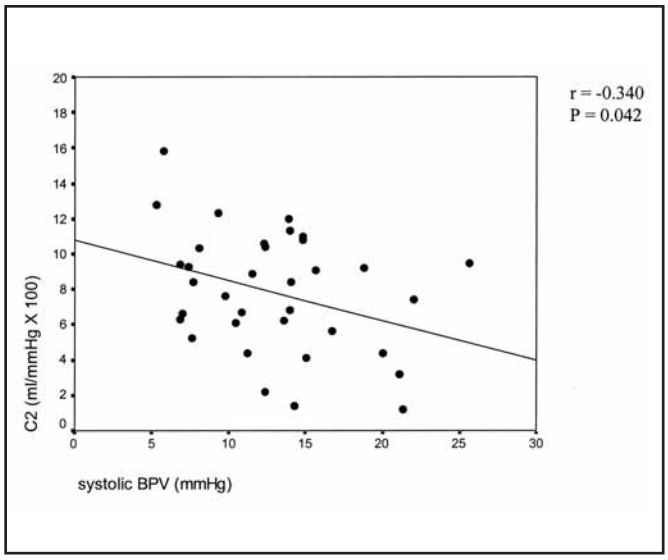

Fig. 4: Scatterplot diagram showing the correlation between small artery compliance (C2) and night time systolic BPV in subjects with FHT.

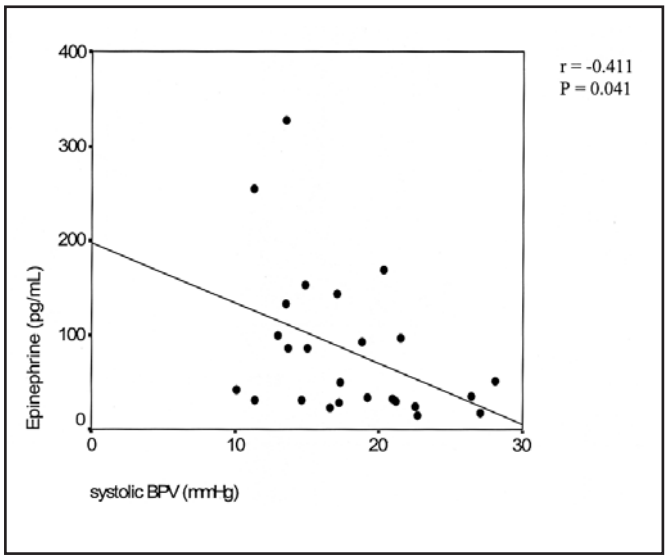

Fig. 5: Scatterplot diagram showing the correlation between epinephrine and daytime systolic BPV in subjects with FHT.

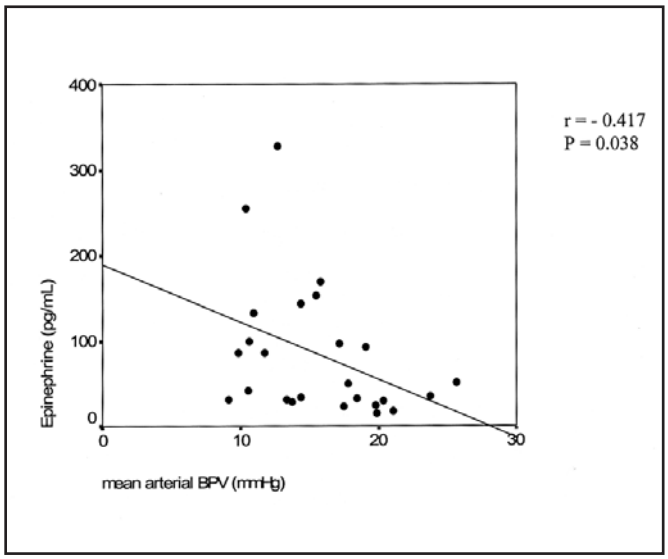

Fig. 6: Scatterplot diagram showing the correlation between epinephrine and daytime mean arterial BPV in subjects with FHT

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.

Subjects who agreed to proceed with humoral factors evaluation were called back three weeks after the initial study. The subjects were told to maintain their normal sleeping habits. Twenty four hours before the study, the subjects were required to abstain from alcohol, nicotine and caffeinated food and beverages, and to avoid activities such as staying up late and excessive exercise that might confound the relation with catecholamine. The subjects were however allowed to eat light breakfast two hours before the study.

Statistical Analysis

BPV was defined as the standard deviation (SD) of the mean of systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP), averaged for each subject individually. They were analyzed according to the 24 hour, daytime and night time period. Awake (daytime) and asleep (night time) BP were yielded based on actual times noted in participants' diaries. Artifacts were defined as any of the following: SBP < 50 mmHg or > 250 mmHg, DBP>SBP or DBP <30 mmHg or > 150 mmHg. No other editing of data was performed. As for arterial compliance, the average of duplicate measurements of C_1 and C_2 were taken.

All data were given as mean $\pm$ SD. Kolmogorov-Smirnov test was performed to determine the normality of the data.

Comparison of the group means were made by paired *t*-test. For data which are not normally distributed, the Wilcoxon Signed Rank Test was used. The statistical differences between group means in humoral study were assessed by unpaired student *t*-test. Mann-Whitney test was used for data that were not normally distributed. The associations between measured parameters were done by bivariate correlation analysis (Pearson correlation coefficient). Student's *t*-test was used to test the significance of the correlation. The level of significance of all tests is determined at $P < 0.05$.

All statistical analyses and diagram plots were performed with SPSS for Windows version 11.5 (SPSS Inc., Chicago, IL, U.S.A.)

RESULTS

There were no significant differences with regards to the biochemical profiles in both groups (see Table I). As for humoral factors analyses, 25 subjects and 26 matched controls had consented to further participate in this study. The remaining subjects refused to participate, cited the reasons of the invasive nature of this study and unavailability during the study period. There were no significant difference in terms of age, sex and BMI between the consented group and the drop outs.

Blood Pressure Variability

There were no significant differences in 24-hour and daytime BPV (see Figure 1 and 2 respectively). However, subjects with FHT have higher night time systolic (P=0.023), diastolic (P=0.036) and mean arterial (P=0.017) BPV as compared to the control subjects (see Figure 3) despite their BP being within the normotensive range.

Arterial Compliance

There were no significant differences in arterial compliances and other vascular parameters in both groups (see Table II).

Correlation analysis of BPV and arterial compliance

There were no significant correlations between the C_1 and BPV in 24 hour, daytime and night time analyses in both FHT subjects and controls. There were also no correlations between C_2 and 24-hour and daytime BPV in both FHT subjects and the controls. However, night time BPV analysis showed that subjects with FHT has significant negative correlation between C_2 and systolic BPV (see Figure 4).

Comparison of Catecholamines, Renin and Aldosterone Assays

There was a significantly high plasma NE level in subjects with FHT (368.31 pg/mL) than controls (282.25 pg/mL). There were however no significant differences in plasma E, renin and serum aldosterone level between the two groups.

Correlation Between Catecholamines, Renin and Aldosterone And BPV

There were no significant correlations between NE, aldosterone and renin with BPV whether in 24 hour, daytime or night time analysis. There was however significant negative correlation between E and daytime systolic BPV and mean arterial BPV (see figures 5 and 6 respectively).

Correlation Between Humoral Factors and Arterial Compliance

There were no significant correlation between NE, E and aldosterone and arterial compliance in both groups. However, there were significant positive correlations between renin and small artery compliance (r=0.470, P=0.015) in subjects without FHT.

DISCUSSION

BPV and Arterial Compliance

Hypertension is associated with increased BPV and reduced arterial compliance. It is however, still debatable as to whether these two abnormalities precede or are merely the consequences of sustained elevated BP. The present study revealed that subjects with FHT showed higher systolic, diastolic and mean arterial BPV in night time analysis compared to the controls. These findings were supported by others[17] who found higher systolic and diastolic BPV during 24 hour and daytime analysis. The difference in the period of analyses would probably be due to the younger mean age of participants in that study (20.2 and 20.6 years) in both groups and uneven distribution of male and female participants where males being more in the FHT group. The present study took into account the fact that gender plays an important role in arterial pressure.

The finding that BPV was increased in subjects with FHT could have several implications. It strengthened the suggestion that genetic factors are expressed to a greater extent in BPV than through mean BP level. Since variability in BP has been shown to be a significant prognostic marker for the subsequent development of hypertension[33] and for increases in target organ damage, the increase detected in the offspring could be of prognostic significance.

There were however, no significant differences in terms of arterial compliance. This finding is supported by Grey *et al.*[37] but not by others[38]. The difference could be in the method used as the former employed the same device whereas the latter used the noninvasive high resolution ultrasonography. Study utilizing pulse wave velocity has also found that FHT does not significantly affect aortic stiffness[30]. This may suggest that the extent of the severity of atherosclerosis has minimally influence this vascular abnormality at this stage. Furthermore, altered arterial compliance has been shown only in a case of extensive atherosclerosis in patients with clinically manifested CAD in hypertension or hypercholesterolemia[39]. This reasoning is further supported in 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 [40-42] and in a middle-age population, the increased IMT did not cause any increase in the common carotid artery stiffness[40].

The Role of Sympathetic Nervous System

Bivariate correlation analysis showed that there was a significant but weak negative correlation between night time systolic BPV and small arterial compliance in subjects with FHT. The correlation that existed during sleep and in the absence of physical activity may enlighten the fact that the primary determinant of BPV in FHT is the autonomic nervous

system and hormonal influence. It has been noted that autonomic abnormalities were demonstrable in subjects with FHT[43] where there were reduced baroreflex sensitivity and increased plasma NE in these subject group. An increase in the ratio of sympathetic to parasympathetic at the cardiac level in normotensives with FHT has also been reported[44]. Another study[45] found that cold pressor test induced sympathetic responses were subnormal in hypertensive patients and those with FHT as compared to the normotensives and subjects without FHT. This is supported by the fact that BRS in normal human is strongly influenced by genetic variance[46]. The study found that the heritability estimate was only attenuated after correction for BMI and BP.

In explaining the small arterial correlation with BPV in subjects with FHT, physiologically, the effects of sympathetic nerve activity is more marked in the peripheral and smaller arteries as these arteries have more sympathetic innervations[47]. It has been postulated that in smaller arteries, the arterial compliances are under the influence of functional changes and are less distensible than larger arteries and respond at a greater degree to increase sympathetic nerve activity[48].

Increase Norepinephrine in Subjects with Family History of Hypertension

The heritability of sympathetic over-activity in human has been the focus of attention to identify the high risk subjects for CVD. In monozygotic twins, skeletal muscle sympathetic nerve firing rates were found to be almost identical in individual pairs, unlike in randomly paired groupings of unrelated subjects in whom a wide range of nerve firing rates was evident[49]. Similarly, twin studies investigating heritability of plasma NE concentrations have attributed approximately 50% of the variance to the genetic factors[50]. Higher level of NE has been reported in subjects with FHT[43, 51-52]. The increase in NE can contribute to hypertension not only by increasing vascular tone but also by altering renal sodium and water homeostasis[53], and by inducing cardiac[54] and vascular remodeling[55].

However, the present study showed that there was no significant correlation between NE and BPV or between NE and arterial compliance in subjects with FHT. The lack of correlation of NE and BPV is probably based on the physiologic components of the sympathetic nervous system itself. The mechanisms that underlie inappropriate sympathetic overactivity, which can be measured either by plasma NE, NE spillover, MSNA or spectral analysis[56] can arise from different sympathoneuronal axis whether from an afferent limb, central neural integration or efferent pathways. In this case, it is likely that due to the multiple possible causes, the increase in NE in subjects with FHT in the present study did not reflect abnormalities at other sympathoneural pathways, including that of baroreflex control. It is also possible that any alteration in baroreflex system causing high BPV and the abnormality in efferent pathway causing high plasma NE level are taking their own route cause without influencing one another. To date, the precise genetic mechanism of baroreflex impairment linked to FHT is not known[56].

Epinephrine is Negatively Correlated with BPV in Subjects with Family History of Hypertension

E has been reported to be increased in hypertensives[57]. There were however contradictory results with regards to E levels in subjects with FHT. Some authors found significant increase[58] but not others[16,59]. In the former[58] however the E level was strongly associated with high individual BP in subjects with FHT as the difference was not seen in the offspring who had low individual BP irrespective of their parental hypertension status.

The negative relationship of E and BPV in subjects with FHT seemed to suggest the importance of biphasic response of E in cardiovascular homeostasis. At low concentration, circulating E stimulates, β_2-adrenoceptors causing vasodilatation while at high concentration, it causes vasoconstriction mediated by a_1 adrenoceptors. Study by Julien *et al.*[60] had suggested it is the vasoconstrictor tone that has been claimed to be necessary for expression of BPV.

Renin Association with BPV and Arterial Compliance

Finally, the finding of similar level of plasma renin and aldosterone in subjects with FHT and control concurred with another study[59]. Even among hypertensives, renin and aldosterone were not significantly different from the matched normotensives [28]. The same study however reported that aldosterone was significantly correlated negatively with systemic arterial compliance in hypertensives. Further analysis showed that the correlation was present only in the normal and high plasma renin activity (PRA) subgroups (where normal PRA was defined as between 0.8-4.0 ng/mL/hour).

The present study also showed that there was no significant correlation between plasma renin and BPV. A study among hypertensives revealed that increased PRA during postural maneuvers correlated with the increase of lower frequency (LF) component of diastolic BPV[22]. LF is assumed to reflect the sympathetic activity and the BPV in this study was derived by the spectral analysis method. However, in this case the increased in PRA had resulted from the changes in posture and might not reflect the true association of plasma renin with increase BPV. The present study however looked at the aspect of plasma renin concentration unaffected by postural factor.

Renin concentration on the other hand was found to be strongly and positively correlated with small arterial compliances in subjects without FHT. The tendency for the arterial compliance to be higher, the higher the plasma renin probably represents an effective regulatory response to a low to normal circulating level of Ang II, a potent vasoconstrictor in subjects without FHT, which is probably lost in subjects with FHT. This is further supported by a study that revealed subjects with FHT have a defective Ang II suppression of plasma renin, which is corrected by AT_1 receptor blockade[61].

Limitation of the Study

The limitation of the study is the fact that the plasma level of NE and E may not reflect fully the sympathoneural and adrenomedullary activities as firstly, the plasma levels are determined not only by the rate at which this catecholamines enter plasma, but also their rate of removal. Second, the

sympathetic outflow to different organ is not uniform and in particular during sympathetic stimulation, sympathoneural responses showed a different pattern across different organs, depending on the kind of stimulus[62].

To further improve the study, serial measurement of humoral factors are recommended with a focus on measurement of regionally released catecholamines which may explain the changes in baroreflex mechanism better.

In conclusion, subjects with FHT demonstrated a higher night time BPV and NE level as compared to controls. There were no association between BPV and NE, but BPV was negatively associated with E in subject with FHT. Small arterial compliance on the other hand was positively correlated with plasma renin in subjects without FHT.

ACKNOWLEDGEMENTS

The authors would like to thank the International Islamic University of Malaysia for the research grant provided (IIUM/504/RES/G/14/3/01/ID978) and Hospital Tengku Ampuan Afzan for the facilities in obtaining study samples. We would also like to thank Miss Maria Singarajah for her technical assistance.

REFERENCES

1. Neutel JM, Smith DHG, Graettinger WF, *et al.* Heredity and hypertension: impact on metabolic characteristics. Am Heart J 1992; 124: 435-40.
2. Celentano A, Galdersis M, Garafalo M. Blood pressure and cardiac morphology in young children of hypertensive subjects. J Hypertens 1988; (Suppl 4): S107-S109.
3. Dekkers JC, Treiber FA, Kapuku G, *et al.* Differential influence of family history of hypertension and premature myocardial infarction on systolic blood pressure and left ventricular mass trajectories in youth. Pediatrics 2003; 111: 1387-93.
4. Graettinger WF, Neutel JM, Smith DHG *et al.* Left ventricular diastolic filing alterations in normotensive young adults with a family history of systemic hypertension. Am J Cardiol 1991; 68: 51-56.
5. Taddei S, Virdis A, Mattei P, *et al.* Endothelium- dependent forearm vasodilatation is reduced in normotensive subjects with family history of hypertension. J Cardiovasc Pharmol 1992; 20: S193-S195.
6. Safar ME, Laurent S, Pannier BM, *et al.* & London, G.M. Structural and functional modification of peripheral large arteries in hypertensive patients. J Clin Hypertens 1987; 3: 360-67.
7. Muller JE, Stone PH, Turi ZG, *et al.* Circadian variation in the frequency of onset of acute myocardial infarction. N. Eng. J. Med.1985; 313: 1315-22.
8. Willich SN, Linderer T, Wegsheider K, *et al.* Increased risk of myocardial infarction in the morning. J Am Coll Cardiol 1988; 11: 28-35.
9. Muller JE, Ludmer PL, Willich SN, *et al.* Circadian variation in the frequency of cardiac death. Circulation 1987; 75: 131-38.
10. Willich SN, Levy D, Rocco MB, *et al.* Circadian variation in the incidence of sudden cardiac death in the Framingham Heart Study Population. J Am Coll Cardiol 1987; 60: 801-06.
11. Parker, JD, Testa MA, Jimenez AH, *et al.* Morning increase in ambulatory ischemic in patient with stable coronary artery disease: importance of physical activity and increased cardiac demand. Circulation 1994; 89: 604-14.
12. Craig MW, Bishop CN & Raftery, AB. Circadian variation of blood pressure. Lancet 1978; i: 795-97.
13. Rafidah, HM, Azizi A, Noriah MN. Blood pressure variability and arterial elasticity in hypertensive subjects. MJM 2006; 61: 189-98.
14. Grewen KM, Girdler SS, Hinderliter A, *et al.* Depressive symptoms are related to higher ambulatory blood pressure in people with a family history of hypertension. Psychosom Med 2004, 66: 9-16.
15. Ravogli A, Silvia T, Villani A, *et al.* Early 24-hour blood pressure elevation in normotensive subjects with parental hypertension. Hypertension 1990; 16: 491-97.
16. Manuck SB, Polefrone JM, Terrel DF, *et al.* Absence of enhanced sympathoadrenal activity and behaviorally evoked cardiovascular reactivity among offspring of hypertensives. Am J Hypertens 1996; 9: 245-55.
17. Lemne CE. Increased blood pressure reactivity in children of borderline hypertensive fathers. J Hypertens 1998; 16: 1243-48.
18. McGrath BP. Cardiovascular risk factors and arterial function. Ins. Book of Abstract: First Asean Medical Conference 2001; 31-32.
19. McVeigh GE, Bratelli CW, Morgan DJ, *et al.* Age related abnormalities in arterial compliance identified by pressure pulse contour analysis. Hypertension 1999; 33: 1392-98.
20. Cohn JN, Finkelstein S, McVeigh G, *et al.* Non-invasive pulse wave analysis for the detection of arterial vascular disease. Hypertension 1995: 26: 503-8.
21. Hausberg M, Sinkey CA, Mark AL, *et al.* Sympathetic nerve activity and insulin activity in normotensive offspring of hypertensive parents. Am J Hypertens 1998; 11: 1312-20.
22. Duprez DA, De Sutter JH, De Buyzere MC, *et al.* Renin-angiotensin-aldosterone system, RR interval, and blood pressure variability during postural changes in borderline arterial hypertension. Am J Hypertens 1995; 8: 683-88.
23. Simsolo RB, Romo MM, Rabinovich L, *et al.* Family history of essential hypertension versus obesity as risk factors for hypertension in adolescents. Am J Hypertens 1999; 12: 260-63.
24. Wang W, McChain J, Zucker I. Aldosterone reduces baroreceptor discharge in the dog. Hypertension 1992; 19: 270-77.
25. Wang W. Chronic administration of aldosterone depresses baroreceptor reflex function in the dog. Hypertension 1994; 24: 571-75.
26. Yee KM, Struthers AD. Aldosterone blunts the baroreflex response in humans. Clin Sci 1998; 95: 687-92.
27. Veglio F, Molino P, Cat Genova G, *et al.* Impaired baroreflex function and arterial compliance in primary aldosteronism. J Hum Hypertens 1999; 13: 29-36.
28. Blacher J, Amah G, Girerd X, *et al.* Association between increased plasma levels of aldosterone and decreased systemic arterial compliance in subjects with essential hypertension. Am J Hypertens 1997; 10: 1326-34.
29. Williams RR, Hunt SC, Haesstedt SJ, *et al.* Are there interactions and relations between genetic and environmental factors predisposing to high blood pressure? Hypertension 1991; 18 (Suppl I): I-29 – I-27.
30. Rajzer M, Klocek M, Kawecka-Jaszcz K, *et al.* Aortic pulse wave velocity in young normotensives with a family history of hypertension. J Hypertens 1999; 17: 1821-824.
31. O'Brien E, Mee F, Atkins N. Evaluation of the Schiller BR-102 ambulatory blood pressure system according to the protocols of the British Hypertension Society and the Association for the Advancement of Medical Instrumentation. Blood Press Monit 1999; 4(1): 35-43.
32. Turton MB & Deegan T. Circadian variations of plasma catecholamine, cortisol and immunoreactive insulin concentrations in supine subjects. Clin. Chem. Acta 1974; 55: 389-97.
33. Katz FH, Romfh P, Smith JA. Diurnal variation of plasma aldosterone, cortisol and renin activity in supine man. J. Clin. Endocrinol. Metab 1975; 40: 125-34.
34. Stewart PM. Mineralocorticoid hypertension. Lancet 1999; 353: 1341-47.
35. Eisenhofer G. Clinical Neurochemistry Laboratory Procedure Manual. Available at: http://www.catecholamine.org/labprocedures.html. Accessed June 18, 2002.
36. de Faire U, Lindvall K, Nilsson B. Noninvasive ambulatory 24 h blood pressure and basal blood pressures predict development of sustained hypertension from a borderline state. Am J Hypertens 1993; 6: 149-155.
37. Grey A, Bratteli C, Glasser SP, *et al.* Reduced small artery but not large artery elasticity is an independent risk marker for cardiovascular events. Am J Hypertens 2003; 16: 265-69.
38. Meaney E, Samaniego V, Alva F, *et al.* Increased arterial stiffness in children with a parental history of hypertension. Pediatr Cardiol 1999; 20: 203-205.
39. Barenbrock M, Spieker C, Kerber S, *et al.* Different effects of hypertension, atherosclerosis and hyperlipidemia on arterial distensibility. J Hypertens 1995; 19: 1712-27.
40. Riley WA, Evans GW, Sharrett AR, Burke, *et al.* Variation of common carotid artery elasticity with intima-medial thickness: the ARIC study. Ultrasound Med Biol 1997; 23: 157-64.
41. Labropoulos N, Ashraf Mansour M, Kang SS, *et al.* Viscoelastic properties of normal and atherosclerotic carotid arteries. Eur. J. Vasc. Endovasc. Surg. 2000; 19(3): 221-25.
42. Zureik M, Temmar M, Adamopoulos C, *et al.* Carotid plaques, but not common carotid intima-media thickness, are independently associated with aortic stiffness. J Hypertens 2002; 20: 85-93.
43. Lopes HF, Silva HB, Consolim-Colombo FM, *et al.* Autonomic abnormalities demonstrable in young normotensive subjects who are children of hypertensive parents. Braz J Med Biol Res 2000; 33: 51-54.
44. Maver J, Strucl M, Accetto R. Autonomic nervous system activity in normotensive subjects with a family history of hypertension. Clin. Auton. Res 2004; 14 (6): 369-75.
45. Lambert EA, Schlaich MP. Reduced sympathoneural responses to the cold pressor test in individuals with essential hypertension and in those

genetically predisposed to hypertension. No support for the "pressor reactor" hypothesis of hypertension development. Am J Hypertens 2004; 17: 863-68.
46. Tank J, Jordan J, Diedrich A, *et al.* Genetic influences on baroreflex function in normal twins. Hypertension 2001; 37: 907-10.
47. Guyton AC & Hall JE.. Nervous regulation of the circulation and rapid control of arterial pressure. In: Guyton AC, Hall JE, eds. Guyton and Hall Textbook of Medical Physiology. WB Saunders Co, 1996: 209-18.
48. Liang YL, Teede H, Kotsopoulos D, *et al.* Non-invasive measurements of arterial structure and function: repeatability, interrelationships and trial sample size. Clin. Sci 1998; 95: 669-79.
49. Wallin BG, Kunimoto MM & Sellgren J. Possible genetic influence on the strength of human muscle nerve sympathetic activity at rest. Hypertension 1993; 22: 282-84.
50. Williams PD, Puddey IB, Beilin LJ, *et al.* Genetic influences on plasma catecholamines in human twins. J Clin Endocrinol Metab 1993; 77: 794-99.
51. Masuo K, Mikami H, Ogihara T, *et al.* Familial hypertension, insulin, sympathetic activity, and blood pressure elevation. Hypertension 1998; 32: 96-100.
52. Ferrier C, Cox H, Esler M. Elevated total body noradrenaline spillover in normotensive members of hypertensive families. Clin Sci 1993; 84(2): 225-30.
53. DiBona GF. Sympathetic nervous system and the kidney in hypertension. Curr. Opin. Nephrol. Hypertens 2002; 11: 197-200.
54. Iaccarino G, Barbato E, Cipoletta E, Fiorillo A, Trimarco B. Role of the sympathetic nervous system in cardiac remodeling in hypertension. Clin. Exp. Hypertens 2001; 23: 35-43.
55. Schiffrin EL. Vascular smooth muscle grow and extracellular matrix deposition: is there a role for the sympathetic nervous system? Journal of Hypertension, 2002; 20: 179-81.
56. Biaggioni I. Sympathetic control of the circulation in hypertension: lessons from autonomic disorders. Curr. Opin. Nephrol. Hypertens 2003; 12: 175-80.
57. Jacobs M-C, Jacques WML, Jacques JW, *et al.* Adrenomedullary secretion of epinephrine is increased in mild essential hypertension. Hypertension 1997; 29: 1303-308.
58. Harrap SB, Fraser R, Inglish GC, *et al.* Abnormal epinephrine release in young adults with high personal and high parental blood pressures. Circulation 1997; 96: 556-61.
59. Lopes HF, Bortolotto LA, Szlejf C, *et al.* Hemodynamic and metabolic profile in offspring of malignant hypertensive parents. Hypertension 2001; 38: 616-20.
60. Julien C, Zhang Z-Q, Barres C. Role of vasoconstrictor tone in arterial pressure lability after chronic sympathectomy and sinoaortic denervation in rats. J Auton Nerv System 1993; 42: 1-10.
61. Herlitz H, Palmgren E, Widgren E, *et al.* Failure of angiotensin II to suppress plasma renin activity in normotensive subjects with a positive family history of hypertension. Clin Sci 2005; 109: 311-17.
62. Folkow B. Physiological aspects of primary hypertension. Physiol. Rev 1982; 62: 347-504.