

Blood pressure variability and arterial elasticity in hyperlipidaemic subjects

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ABSTRACT

Introduction: It is debatable whether the assessment of low density lipoprotein or total cholesterol (TC) alone is sufficient to identify an individual's risk of having myocardial infarction. In the Framingham study, the risk of coronary artery disease was better indicated by an increase in the TC to high density lipoprotein cholesterol (TC:HDL) ratio. The aim of this study is to determine the relationship between blood pressure variability (BPV) and arterial compliances in hyperlipidaemics, which was defined as TC:HDL of more than 5.0 as compared to normolipidaemics.

Methods: 22 subjects with hyperlipidaemia were age-, gender- and weight-matched with normolipidaemic controls. 24-hour ambulatory blood pressure monitoring was recorded and arterial compliances were measured.

Results: There were significantly higher 24-hour systolic (SBP) (19.9 +/- 6.1 mmHg vs. 16.1 +/- 4.4 mmHg, p-value is less than 0.01), diastolic (16.6 +/- 4.7 mmHg vs. 13.9 +/- 4.8 mmHg, p-value is less than 0.05) and mean arterial (16.3 +/- 4.9 mmHg vs. 13.3 +/- 4.7 mmHg, p-value is less than 0.05) BPVs in the hyperlipidaemic group as compared to the normolipidaemic group. There were no significant differences in large and small arterial compliances between groups. There was a significant inverse relationship between SBP and large arterial compliance (r-value equals to -0.46, p-value is less than 0.05). There was no correlation between BPV and arterial compliances.

Conclusion: The BPV was higher in hyperlipidaemic subjects as compared to normolipidaemic subjects. Large arterial compliance was negatively correlated with SBP in hyperlipidaemic subjects.

Keywords: ambulatory blood pressure monitoring, arterial compliance, blood pressure variability, coronary artery disease, hyperlipidaemia

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INTRODUCTION

Hyperlipidaemia increases the risk of coronary artery disease (CAD) and atherosclerotic disease in other vessels. The role of elevated concentrations of serum cholesterol in the pathogenesis of atherosclerosis is well established based on human studies,^(1,2) animal experiments⁽³⁾ and clinical pathological observations.⁽⁴⁾ In the Framingham Study, the total cholesterol (TC) level was found to be an independent risk factor and significantly related to the risk of CAD in young men, and young and older women.⁽⁵⁾ Since lipoproteins are the principal carriers of cholesterol in the blood, an intensive investigation was conducted on the lipoprotein blood level. Low density lipoprotein (LDL) levels were found to highly correlate with CAD. The Lipid Research Clinics Prevalence Study⁽⁶⁾ demonstrated in a ten-year follow-up that LDL cholesterol (LDL-C) was strongly associated with CAD in men with or without CAD at the time of entry into the study. Furthermore, the results of the five randomised clinical trials involving hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) therapy had provided evidence that treatment with simvastatin, pravastatin or lovastatin resulted in a reduction of TC by 20%–25%, LDL by 25%–35% and with decreasing events of CAD.⁽⁷⁻¹¹⁾

It is, however, debatable as to whether the assessment of LDL or TC alone is sufficient and accurate enough to identify an individual at risk for myocardial infarction. High density lipoprotein (HDL) is the lipoprotein that has an anti-atherogenic effect since it lacks apolipoprotein B (APO-B). HDL confers protection against atherosclerotic cardiovascular diseases. An inverse relationship between HDL cholesterol (HDL-C) and CAD has been established in several studies.^(12,13) The growing importance of HDL as a predictor of CAD was supported by the findings in a 26-year follow-up in the Framingham study, where 20% of patients with myocardial infarctions had their cholesterol level below 5.17 mmol/L (< 200 mg/dL), a level considered safe according to most guidelines. Most of the patients who had myocardial infarctions had low TC levels with HDL < 0.91 mmol/L (< 35 mg/dL), emphasising the importance of the TC:HDL-C ratio in determining the atherogenic potential of blood lipids. Risk of CAD events

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increases with the TC:HDL-C ratio.⁽⁵⁾ In the Prospective Cardiovascular Münster (PROCAM) study population, the incidence of myocardial infarction was 17.3% over ten years in patients who had a TC: HDL-C ratio of > 5.0 .⁽¹⁴⁾ This incidence was greater than that seen in patients with high triglyceride (TG) or LDL cholesterol.⁽¹⁵⁾ This ratio was also found to be a better predictor of CAD than TC, LDL, HDL and TG in the Physician's Health Study⁽¹³⁾ and other studies.^(16,17) Because of the important influence of HDL-C at even moderate levels of serum TC or LDL-C, the TC:HDL-C ratio is probably the best guide for therapy with treatment best instituted at ratios > 5.0 , irrespective of the serum TC or LDL-C levels.⁽¹⁸⁾ Asmar et al had found that patients with and without plasma lipid abnormality displayed similar 24-hour mean ambulatory blood pressure (BP).⁽¹⁹⁾ However, there is no study so far that reports differences in blood pressure variability (BPV) in the hyperlipidaemic group (as defined by TC:HDL-C > 5.0) compared to those with normal serum lipid. The aim of the study was to compare the BPV and arterial compliance between hyperlipidaemic and normolipidaemic subjects matched for gender, age and weight.

METHODS

Patients were recruited from the Tengku Ampuan Afzan Hospital and among the medical students of Faculty of Medicine, International Islamic University of Malaysia. The matched controls were from the same resources. The study had been approved by the Ethical Committee of the International Islamic University of Malaysia. 22 subjects with hyperlipidaemia were included in this group. They were either untreated or had stopped taking medication for at least four weeks prior to the study. All the subjects were required to fast for at least 12 hours before antecubital venous blood was taken. The venous blood was taken in a sitting position after the patients had been rested for at least five minutes, with the tourniquet applied for less than one minute, to minimise variation of the lipid levels by the technique. The blood samples were centrifuged within one hour of being drawn. Hyperlipidaemia was defined as TC:HDL-C ratio > 5.0 .

There were 22 controls that were matched for age, gender, body weight, and additional risk factors other than the risk factor being studied. Using the same procedure above, they were included if their TC:HDL-C ratio is < 5.0 . Subjects with any evidence of target organ damage, such as acute myocardial infarction, cerebrovascular accident, renal failure, congestive cardiac failure, valvular defect or with any physical disability that restricted mobility, were excluded from the study. In the sample preparation, a volume of 0.5 ml serum was mixed with 0.05 ml solution containing 0.2 mmol/L phosphotungstic

acid (PTA) and 5 mmol/L $MgCl_2$ in a standard centrifuge tube (Eppendorf, Hamburg, Germany). After a five-minute incubation and precipitation at room temperature, samples were centrifuged at 5,000 rpm for ten minutes using a centrifugal analyser (Jouan MR 22, Saint Herblain, France).

For the HDL assay, 0.5 ml serum was mixed with 0.05 ml of an HDL-C precipitant solution containing dextran sulphate 10 g/L, magnesium sulphate 0.5 mol/L and 0.025% sodium azide as a non-reactive stabiliser. After a five-minute incubation and precipitation at room temperature, samples were centrifuged at 5,000 rpm for ten minutes using a centrifugal analyser. In principle, the LDL and very low density lipoprotein (VLDL) were precipitated from the serum with both dextran sulphate and magnesium sulphate, and the HDL remained in the supernatant. The supernatant was then removed manually for assays, and HDL-C was determined with an enzymatic end-point assay, by using cholesterol oxidase and then a chromogenic reaction with 4-aminophenazone (CHOD-PAP) on a spectrophotometer (Bayer Express Plus, Tarrytown, NY, USA). TC and TG were determined using the enzyme calorimetric end-point technique on a spectrophotometer.

Noninvasive ambulatory BP monitoring was performed for a minimum 24-hour period with BR-102 monitor (Schiller AG, Baar, Switzerland). This recorder fulfilled the criteria of the British Hypertension Society and the Association for the Advancement of Medical Instruments.⁽²⁰⁾ The BR-102 monitor measures BP by the detection of Korotkoff sounds via a transducer taped over the brachial artery. The study was initiated between 0830 hours and 1000 hours, and the recorder was set to measure BP at 15-minute intervals from 0600 hours to 2200 hours, and at 30-minute intervals from 2200 hours to 0600 hours. 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. Showering, strenuous exercises, sexual intercourse and caffeine intake were not allowed during this period. Each patient was 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 BP readings were included if at least 80% of measurements were acceptable. Data editing was performed if there were impossible values, such as systolic BP (SBP) = diastolic BP (DBP), DBP $>$ SBP, SBP $>$ 240 mmHg or $<$ 50 mmHg, and DBP $>$ 180 mmHg or $<$ 30 mmHg. Average values of awake and sleep periods were calculated based on the patients' diaries.

In this study, arterial compliance was determined

Table I. Clinical characteristics of patients with hyperlipidaemia and the matched controls.

Clinical characteristics	Normolipidaemia	Hyperlipidaemia
Number of subjects	22	22
Age (years)	46 ± 10 (31–65)	44 ± 11 (20–64)
Sex (M:F)	18:4	18:4
BMI (kg/m ²)	25.9 ± 2.7	26.0 ± 3.4
Office blood pressure (mmHg)		
SBP	127 ± 15	129 ± 17
DBP	82 ± 9	84 ± 10
MAP	97 ± 10	99 ± 13
Fasting blood glucose (mmol/L)	5.4 ± 1.3	5.8 ± 41.9
Total cholesterol (mmol/L)	5.6 ± 1.1	6.4 ± 0.6**
High density lipoprotein (mmol/L)	1.5 ± 0.3	1.1 ± 0.1**
Low density lipoprotein (mmol/L)	3.5 ± 1.0	4.1 ± 1.0**
Triglyceride (mmol/L)	1.4 ± 0.8	2.1 ± 0.8**
Total cholesterol: high density lipoprotein ratio	3.8 ± 0.8	6.0 ± 0.9**

Data is expressed as mean ± standard deviation.

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure.

*p < 0.05; **p < 0.01

Table II. The 24-hour ambulatory blood pressure parameters in patients with hyperlipidaemia vs. controls.

Blood pressure parameters	Normolipidaemia	Hyperlipidaemia
24 hours (mmHg)		
SBP	126 ± 15	126 ± 11
DBP	85 ± 10	87 ± 8
MAP	98 ± 11	100 ± 8
Systolic BPV	16.1 ± 4.4	19.9 ± 6.1**
Diastolic BPV	13.9 ± 4.8	16.6 ± 4.7*
Mean arterial BPV	13.3 ± 4.7	16.3 ± 4.9*
Daytime (mmHg)		
SBP	127 ± 15	129 ± 11
DBP	87 ± 10	89 ± 7
MAP	100 ± 11	102 ± 8
Systolic BPV	16.3 ± 4.7	20.3 ± 6.6**
Diastolic BPV	14.0 ± 5.2	17.1 ± 4.7*
Mean arterial BPV	13.3 ± 5.1	16.7 ± 5.1**
Night-time (mmHg)		
SBP	119 ± 17	116 ± 13
DBP	78 ± 11	78 ± 10
MAP	91 ± 12	91 ± 11
Systolic BPV	11.6 ± 5.9	11.4 ± 5.2
Diastolic BPV	8.9 ± 4.3	9.1 ± 4.7
Mean arterial BPV	8.8 ± 4.5	8.7 ± 4.8

Data is expressed as mean ± standard deviation

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; BPV: blood pressure variability.

*p < 0.05; **p < 0.01

by using the HDI/Pulsewave Research Cardiovascular Profiling Instrument (C-VPI) Model CR-200 (Hypertension Diagnostic Inc, Eagen, MN, USA), which uses a noninvasive arterial pulse pressure sensor to obtain waveforms at the radial artery. The tonometer sensor array adjusts itself automatically to obtain the optimal waveform and repeats its calibration until the waveform is stable. The BP waveform derived from the elasticity indices results from the computer-based averaging of

ten consecutive individual arterial BP waveforms that were collected noninvasively during a 30-s period. The elasticity indices are of the large arteries (C₁), which measure the capacitative arterial compliance in ml/mmHg and represent the aorta and major branches, and of the small arteries (C₂), which measure the reflective arterial compliance using the same unit and represent the distal part of the circulation. Both C₁ and C₂ were derived from a third-order four-element modified Windkessel Model.⁽²¹⁾

Table III. The comparison of cardiovascular haemodynamic parameters between hyperlipidaemic patients and normolipidaemic subjects.

Cardiovascular haemodynamic parameters	Normolipidaemia	Hyperlipidaemia
Cardiac ejection time (msec)	324 ± 22	325 ± 28
Stroke volume index (ml/beat/m ²)	44.5 ± 5.6	43.6 ± 6.4
Estimated cardiac output index (L/min/m ²)	3.0 ± 0.3	3.0 ± 0.2
Large artery elasticity index (ml/mmHg × 10) C ₁	15.3 ± 3.9	15.3 ± 5.3
Small artery elasticity index (ml/mmHg × 10) C ₂	6.7 ± 4.1	6.2 ± 2.2
Systemic vascular resistance (dyne·sec/cm ⁵)	1,414 ± 285	1,405 ± 244
Total vascular impedance (dyne·sec/cm ⁵)	126 ± 30	131 ± 37

Data expressed as mean ± standard deviation

Table IV. Relation of large artery compliance to BPV in hyperlipidaemic patients and normolipidaemic subjects.

Variables	Large artery compliance (C ₁) (ml/mmHg × 10)			
	Normolipidaemia (n = 22)		Hyperlipidaemia (n = 22)	
	r-value	p-value	r-value	p-value
24 hours				
Systolic BPV	-0.437	0.042*	-0.007	0.975
Diastolic BPV	-0.377	0.084	0.017	0.941
Mean arterial BPV	-0.393	0.070	0.031	0.891
Daytime				
Systolic BPV	-0.415	0.055	0.016	0.945
Diastolic BPV	-0.391	0.072	0.030	0.894
Mean arterial BPV	-0.402	0.063	0.047	0.836
Night-time				
Systolic BPV	-0.435	0.043	0.201	0.369
Diastolic BPV	-0.335	0.127	0.063	0.779
Mean arterial BPV	-0.390	0.073	0.168	0.455

BPV: blood pressure variability.

*p < 0.05

BPV was defined as the standard deviation (SD) of the mean of SBP, DBP and mean arterial pressure (MAP). All the BP parameters were analysed according to the 24-hour period, daytime period and night-time period. Awake and asleep BP were yielded based on actual times noted in the participants' diaries. Data were given as mean ± SD. Comparison between the groups' means was by dependent/paired *t*-test. The level of significance was 0.05.

RESULTS

22 subjects with hyperlipidaemia and 22 age-, gender- and weight-matched controls completed the study. There were no significant differences in age, gender and body weight among subjects from the two groups (Table I). In the blood chemistry profile, levels of TC, LDL, TG and mean ratio of TC:HDL-C were significantly higher in the hyperlipidaemic subjects as compared to the matched controls (6.0 ± 0.9 vs. 3.8 ± 0.8). There was significantly lower HDL levels in hyperlipidaemic subjects as compared

to the matched controls. There was no significant difference in fasting blood sugar and clinic-measured BP in hyperlipidaemic subjects, as compared to the matched controls (Table I). Subjects with hyperlipidaemia have significantly higher systolic, diastolic and mean arterial BPV in the 24-hour and daytime ambulatory BP monitor (ABPM) analyses, despite normal BP readings. There was no significant difference in the BPV during night-time ABPM analysis (Table II).

There were no significant differences in arterial compliances and other vascular parameters measured in both hyperlipidaemic and the control subjects (Table III). There were no significant correlations between 24-hour, daytime or night-time BPV and C₁ in hyperlipidaemic subjects. In normolipidaemic subjects, there were significant negative correlations between 24-hour systolic BPV and C₁ (Table IV and Fig. 1). There were no significant correlations found between C₂ and all the 24-hour BPV, daytime BPV and night-time BPV analyses in subjects of both groups (Table V).

Table V. Relation of small artery compliance to BPV in hyperlipidaemic patients and normolipidaemic subjects.

Variables	Small artery compliance (C ₂) (ml/mmHg × 100)			
	Normolipidemia (n = 22)		Hyperlipidemia (n = 22)	
	r-value	p-value	r-value	p-value
24 hours				
Systolic BPV	-0.265	0.234	0.037	0.869
Diastolic BPV	0.009	0.968	0.123	0.585
Mean arterial BPV	-0.083	0.714	0.108	0.633
Daytime				
Systolic BPV	-0.192	0.392	0.049	0.827
Diastolic BPV	0.062	0.785	0.128	0.263
Mean arterial BPV	-0.015	0.946	0.115	0.610
Night-time				
Systolic BPV	-0.317	0.150	0.096	0.670
Diastolic BPV	-0.071	0.754	0.187	0.405
Mean arterial BPV	-0.201	0.371	0.198	0.376

BPV: blood pressure variability.

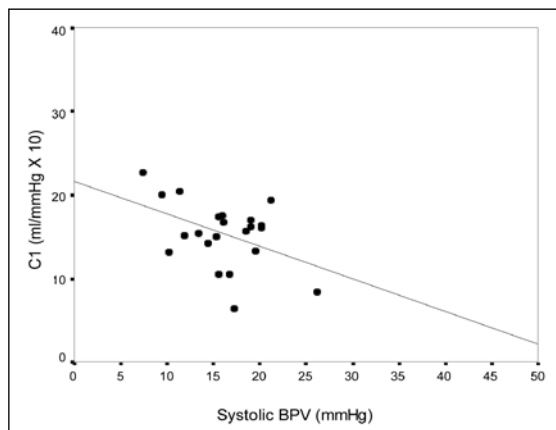


Fig. 1 Scatterplot shows the correlation between C₁ and 24-hour systolic BPV in normolipidaemic subjects.

DISCUSSION

This study demonstrated that hyperlipidaemic patients, as defined by a TC:HDL-C ratio > 5.0, have higher BP fluctuations as compared to the normal subjects. The higher BPV in hyperlipidaemia, however, could not be explained by the role of arterial compliance. A number of studies have also examined the relationships between plasma TC, HDL and LDL to arterial compliances, and they reported contradictory results of no relationship,⁽²²⁻²⁵⁾ increased arterial compliances⁽²⁶⁻²⁸⁾ or reduced arterial compliances⁽²⁹⁻³¹⁾ with elevated levels of TC or HDL-C or LDL-C. These differences could be due to the different types of measurements used or the definition criteria for hyperlipidaemia.

Using a similar diastolic pulse wave analysis to measure arterial compliance, reduced arterial compliance in subjects with high cholesterol has been reported by Grey et al,⁽³¹⁾ but the status of hyperlipidaemia were reported

only by the subjects themselves. This non-rigorous nature of the classification may not reflect the true plasma cholesterol concentration. Syeda et al, on the other hand, found no difference in the C₁ and C₂ values between patients with and without hypercholesterolaemia.⁽²⁵⁾ In a more recent study, Dart et al used a range of arterial pulse wave assessments which included aortic distensibility, augmentation index and systemic arterial compliance.⁽³²⁾ Their associations with TC and HDL in a cohort of elderly hypertensive subjects were assessed. The study found that by multiple regression analyses, there were no significant differences between these pulse wave analyses and TC or HDL-C, or the TC:HDL-C ratio.

High BPV as seen in hyperlipidaemic subjects in the present study may be explained by the involvement of baroreflex (BR) mechanism. Loss of BR sensitivity (BRS) activity in hyperlipidaemia has been reported in both animal and human studies. In an animal study, rabbits fed with a high cholesterol diet developed atherosclerotic lesions in the carotid sinus, which were associated with decreased BRS. Furthermore, the decreased BRS activity was inversely correlated with plasma cholesterol concentration.⁽³³⁾ Pikkujamsa et al had demonstrated that TG was an independent risk factor for decreased heart rate variabilities, which was linked to a reduction in the BRS.⁽³⁴⁾ Recently, Gadegbeku et al had demonstrated that an acute elevation of blood lipids, by raising plasma lipids systemically with an infusion of intralipid and heparin, impaired BRS in healthy normotensive and in obese insulin-resistant subjects.⁽³⁵⁾

Another possibility would be the change in autonomic discharge, which can directly cause extreme variability in BP through the bouts of discharge, or through the impairment of BRS. Enhanced sympathetic and an impaired parasympathetic activities have been observed

in several studies involving animals and humans fed on a high-fat diet studies.⁽³⁶⁻³⁹⁾ A randomised, open-labelled clinical trial found that subjects with combined hyperlipidaemia had increased sympathetic tone and decreased BRS as compared with normolipidaemic subjects of corresponding age.⁽⁴⁰⁾

The present study seemed to suggest that the physiological correlation between BPV and arterial compliance only exist at a low level of circulating plasma lipid in normolipidaemic subjects. It may suggest that the contribution of arterial compliance to BPV or vice versa, in a hyperlipidaemic state in a normal BP setting, is an indirect or a minor one. This study illustrates that the TC:HDL-C ratio is useful as a marker to detect subjects with a high risk of coronary heart disease. Bowman et al suggested that TC, HDL and TG were not significantly associated with an increased risk of ischaemic stroke, but there was an increased risk of ischaemic stroke in those in the highest quartile of TC:HDL-C ratio.⁽⁴¹⁾ In a meta-analysis review, Beswick and Brindle are of the opinion that more specific measures, such as TC:HDL-C ratio or HDL in the scoring charts, would improve the sensitivity for identification of individuals at high risk of coronary heart disease.⁽⁴²⁾

In conclusion, hyperlipidaemic subjects as defined by a ratio of TC to HDL-C of more than 5.0 showed a higher 24-hour and daytime BPV. There was however no significant difference in arterial compliance between hyperlipidaemic and normolipidaemic subjects. There was a weak correlation between 24-hour systolic BPV and large arterial compliance in normolipidaemic subjects, suggesting a physiological correlation at a low level of circulating plasma lipid.

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