The Correlation of Left Ventricular Hypertrophy with the Severity of Atherosclerosis and Embolic Events+

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+ This study was presented in XXIII Congress of European Society of Cardiology in Stockholmes, Sweden, September 2, 2001
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Objective: *The study was undertaken to assess the correlation between the presence and degree of aortic atheroma with degree of Left ventricular (LV) mass index and subsequent clinical outcomes.*
Material and Method: *The authors studied the clinical profiles of 87 patients with aortic atherosclerosis and controls, who had undergone TEE between 1995 and 2000.*
Results: *Mean LV mass index was 116gram/m^2 in atherosclerosis group compared to 81gram/m^2 in the control group ($p < 0.009$). In the atherosclerotic group, there was a close correlation between LV mass index score and severity of the plaque in the aortic arch and descending aorta ($p < 0.001, 0.001$). The presence of large ulcerated plaque had a significant correlation with stroke ($p < 0.002$).*
Conclusion: *1) LV mass index correlates with the severity of aortic atheroma. 2) Smoking, elevated mean arterial blood pressure and a high LV mass index score are significantly correlated with large ulcerated plaque and stroke. 3) These findings may in part explain the higher cardiovascular risk in patients with increased left ventricular mass.*

Keywords: *Left ventricular mass index, Aortic atheroma, Stroke, Transesophageal echocardiography*

J Med Assoc Thai 2005; 88(2): 156-61
Full text. e-Journal: *http://www.medassocthai.org/journal*

Increased LV mass is recognized as a powerful independent risk factor for all cardiovascular disease; stroke, coronary events, morbidity and mortality[1-5]. There is a stepwise increase in the risk of transient ischemic attack and stroke by quartiles of left ventricular mass indexed by height independent of blood pressure, serum lipids and smoking history in both men and women[5]. The association between cardiac hypertrophy and aortic atheroma has not been established. The purpose of this report was to present the correlation between the degree of aortic atheroma by transesophageal echocardiography with the degree of LV mass index and their relationship to clinical outcomes.

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Material and Method

Study population

All patients with a severe degree of atherosclerosis (grade 3 or more in either the ascending, descending aorta or the aortic arch) seen in the echocardiographic laboratory between January 1995 and December 2000 were included. Exclusion criteria included the presence of aortic stenosis, hypertrophic cardiomyopathy, coarctation of aorta or congenital heart disease. The study group consisted of 56 consecutive patients who met these criteria. Thirty-one age-matched patients who underwent transesophageal echocardiography and had minimal aortic atherosclerosis (grade 0-1 in the ascending, descending aorta and the aortic arch) were enrolled consecutively and served as controls. Medical records were reviewed for clinical variables. Clinical data including age, sex, history of cerebral or peripheral embolic events, peripheral vascular disease, coronary artery disease

(history of myocardial infarction, angioplasty, or coronary bypass grafting), diabetes, hypertension, and current smoking were obtained. Medications recorded which included aspirin, clopidrogel, an HMGco A reductase inhibitor, and an angiotensin converting enzyme inhibitor.

Transesophageal Echocardiography

Transesophageal echocardiography was performed using a 5-MHz omniplane or biplane transducer. Imaging was obtained with commercially available ultrasound instruments and probes that included Hewlett-Packard Sonos 1000, 1,500 or the Acuson®. The aorta was imaged in both transverse and longitudinal views. The aortic arch was defined as the portion of aorta between the curve at the take off on the inominate and the origination of the left subclavian artery. The presence, location, and degree of aortic atheroma were graded as follows: grade 1: intimal thickening < 1mm, grade 2: diffuse intimal thickening, grade 3: smooth or ulcerated plaque < 5mm, grade 4: atheroma or ulcerated plaque > 5mm, and grade 5: mobile debris. Large atheroma was defined as plaque > 5mm.

Left Ventricular Mass Index

Left ventricular measurements were made at the midpapillary level in the transgastric short axis[6]. The largest LV internal dimension at end-diastole (LVIDd) at this level was chosen for measurement. Measurements of interventricular septal thickness (IVST) and posterior wall thickness (PWT) and of LVID were made at end-diastole(d) and end-systole(s) as recommended by the American Society of Echocardiography (ASE)[6]. Left ventricular mass index was calculated by the Penn-Cube formula[7]: $(1.04 \times [(IVSTd + LVIDd + PWTd) \times 3 - LVID] \times 3 - 13.6) \div BSA$ (Body surface area).

Clinical outcomes

Comparisons of the study group with the control group with regard to clinical variables such as the presence of stroke, peripheral emboli, coronary artery diseases, were made. In addition comparisons were made with regard to the echocardiographic findings such as the mean dimensions of interventricular septal thickness (IVST), posterior wall thickness (PWT), mean LV mass and LV mass index in the atherosclerotic and the control groups.

Subgroup analysis was made among the group with atheroma. Clinical and echocardiographic variables between the atheromatous group with and without large ulcerated plaque were compared.

Statistics

Between groups, comparisons were performed using Pearson's chi-square or Fisher's Exact test statistical analysis for categorical variables and unpaired t tests for numerical data. A stepwise multiple logistic regression was calculated to determine possible predictors of arterial embolism. Spearman's correlation test was used to investigate the relation between the presence and degree of aortic atheroma by transesophageal echocardiography with the degree of LV mass index. SPSS for Windows version 9.05 (SPSS Inc) was used to perform statistical calculations.

Results

Patient characteristics

The Atheromatous group consisted of 56 patients. The mean age $\pm$ SD of the subjects was 74.2 $\pm$ 8 years, and 50% were men. There was a history of stroke in 19 of 56 (33.9%), peripheral emboli in 6 of 56 (10.7%), peripheral vascular disease in 9 of 56 (16.4%) patients, coronary artery disease in 35 of 56 (63.6%), diabetes mellitus in 17 of 56 (30.9%), hypercholesterolemia (as defined by NCEP guideline) in 19 of 56 (34.5%), current smokers in 11 of 56 (20.4%), and 36 patients (65.5%) were hypertensive (as defined in JNC-VI report).

The control group consisted of 31 patients with a mean age of 72.1 $\pm$ 8.3 years. Four of the 31 patients had clinical evidence of stroke, but none had evidence of peripheral embolic events. The rest of the clinical characteristics were similar between the two groups as listed in Table 1.

Table 1. Percent of baseline clinical characteristics in the Atheromatous and Control groups

Variables	Atheroma (n = 56)	Control (n = 31)	p-value
Age (year)	74.2±7.6	72.1±8.3	0.23
Sex (% male)	50.0	64.5	0.26
Stroke	33.9	12.9	0.04
Emboli	10.7	0.0	0.08
Congestive Heart failure	34.5	22.5	0.61
Coronary heart disease	63.6	29.0	0.01
Peripheral vascular disease	16.4	6.4	0.48
Diabetes mellitus	30.9	25.8	0.99
Hypertension	65.5	45.2	0.34
Hypercholesterolemia	34.5	9.6	0.03
Smoking	20.4	9.6	0.33

Relation of echocardiographic variables to aortic atheroma

Echocardiographic assessment of the left ventricular variables in the atheromatous and control groups, are presented in Table 2. The mean dimensions of the interventricular septal thickness (IVST) and posterior wall thickness (PWT) were significantly higher in the atheromatous group ($p < 0.001$ and $p < 0.001$). Mean LV mass index was 116 gram/m^2 in the atheromatous group and 81 gram/m^2 in the control group ($p < 0.009$).

There was a close correlation between the LV mass index score and the severity of plaque in the arch, ascending, and descending aorta ($p < 0.001$, 0.06 and 0.001 respectively).

Table 2. Mean values ± SD of echocardiographic findings encountered in the atheromatous and control groups

Variables	Atheroma (n = 56)	Control (n = 31)	p-value
LV end-diastolic diameter (cm)	3.7±0.6	4.0±1.24	0.09
Septal Thickness (cm)	1.5±0.3	1.1±0.2	0.001
Posterior wall thickness (cm)	1.5±0.3	1.1±0.2	0.001
LV mass (gram)	210.0±83.5	155.0±108.3	0.008
LV mass index (gram/m^2)	116.4±51.3	81.8±66.3	0.009

Correlation of the presence and degree of aortic atheroma and degree of LV mass index

Univariate analyses of clinical variables of patients with and without large ulcerated plaque in atheromatous group are shown in Table 3. In the atheromatous group, the presence of large ulcerated plaque had a significant correlation with stroke ($p < 0.002$, OR = 5.19) as well as with current smoking ($p < 0.002$, OR = 4.9) (Fig. 1). The presence of large ulcerated plaque also had a significant correlation with systolic arterial blood pressure (0.019), mean arterial blood pressure (0.014), serum creatinine (0.029), LV mass (0.04) and LV mass index (0.02). The presence of large ulcerated plaque had a higher mean of LV mass index (147.3 ± 69.3) compared to the patients without ulcerated plaque (108.8 ± 43.6) ($p < 0.02$). Other clinical variables such as coronary artery disease, peripheral vascular disease, diabetes, hyperlipidemia, medication (HMGco A reductase inhibitor, angiotensin converting enzyme inhibitor, and aspirin) did not.

Multivariable analysis

Stepwise linear regression identified current smoking, elevated mean arterial blood pressure and LV mass index as significant independent variables correlated with large ulcerated plaque ($p = 0.009$, 0.019 and 0.06 respectively).

Table 3. Univariate analysis of baseline variables of patients with and without large ulcerated plaque in an atheromatous group (n = 56)

Variables	Atheroma with large ulcerated plaque (n = 11)	Atheroma without large ulcerated plaque (n = 45)	p-value
Age	73.2±7.6	74.5±7.6	0.62
Sex (male by%)	4 (36.4%)	24 (53.3%)	0.31
Stroke	8 (72.7%)	11 (24.4%)	0.002
Emboli	1 (9.1%)	5 (11.1%)	0.85
Congestive heart failure	2 (18.2%)	17 (37.8%)	0.20
Coronary artery disease	7 (63.6%)	28 (62.2%)	1.00
Peripheral vascular disease	2 (18.2%)	7 (15.6%)	0.85
Diabetes	3 (27.3%)	14 (31.1%)	0.77
Hypercholesterolemia	4 (36.4%)	15 (33.3%)	0.88
Smoking	6 (54.4%)	5 (11.1%)	0.002
Aspirin	9 (81.8%)	27 (60.0%)	0.20
ACE-Inhibitors	1 (9.1%)	12 (26.7%)	0.20
Statin	4 (36.4%)	14 (31.1%)	0.77
Systolic BP (mmhg)	150.9±21.4	132.9±19.8	0.019
Diastolic BP (mmhg)	77.7±11.0	68.2±16.5	0.09
Mean arterial BP	102.1±10.6	90.0±13.5	0.014
Serum urea nitrogen	24.0±15.2	28.7±15.7	0.38
Serum creatinine	4.3±7.2	1.6±1.5	0.029
LV mass (gram)	256.8±109.9	199.7±72.9	0.04
LV mass index (gram/m2)	147.4±69.4	108.9±43.6	0.02

Parameters	Atheroma with large ulcerated plaque	Atheroma without large ulcerated plaque	p value
Stroke	72.7%	24.4%	0.002
Smoking	54.4%	11.6%	0.002
SBP	63.6%	33.3%	0.06
MBP	45.5%	15.6%	0.03

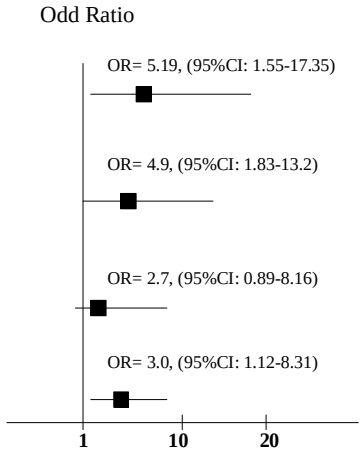

Fig. 1 Clinical Predictors for Large Athroma (plaques > 5 mm)

Discussion

The major findings in the study are as follows: (1) LV mass index correlates significantly with the severity of aortic atheroma; (2) there is a close correlation between LV mass index score and the severity of plaque in the arch, ascending, and descending aorta; (3) smoking, mean arterial blood pressure and a high LV mass index score are significantly correlated with large ulcerated plaque and embolic events which may explain the higher cardiovascular risk such as stroke, coronary events, morbidity, and mortality.

Relation of left ventricular mass to aortic atheroma

The relation between arterial hypertension and left ventricular mass is well recognized. The increase in myocardial wall thickness serves to reduce the wall stress imposed by increased blood pressure[8]. Both atherosclerosis and left ventricular hypertrophy are recognized as a consequence of the long-standing hypertension. Roman et al[9] have previously demonstrated that subjects with left ventricular hypertrophy were twice likely to have carotid atheromas. The present study highlights the correlation between cardiac hypertrophy and aortic atherosclerosis. This finding may contribute to explain the high incidence of vascular events that is well documented in patients with left ventricular hypertrophy.

Clinical predictors for large ulcerated plaque and embolic events

By multivariate analysis, smoking, mean arterial blood pressure and a high LV mass index score are significant predictors for large ulcerated plaque and embolic events. Cigarette smoking has been considered a major stroke risk factor. Davis et al have demonstrated a direct toxic effect of cigarette smoking on human endothelium associated with an increase in the number of endothelial cells with nuclear damage in the circulating blood[10]. Celermajer et al have shown that there is a dose-dependent impairment of endothelial dysfunction in asymptomatic young smokers[11]. In vitro, cigarette smoking has resulted in a dose dependent increase in monocyte adherence to the endothelium[12]. Nowak reported that tobacco smoke appears to activate platelets, which initiates the release of platelet-derived growth factor (PDGF)[13]. PDGF stimulates smooth muscle cell proliferation. Both monocyte adhesion and smooth muscle cell stimulation are part of the initial steps in the development of atherosclerosis. Cigarette smoking has also resulted in a decrease in circulating HDL and an increase in circulating LDL in a dose dependent manner[14]. Most studies have shown that LDL from smokers is more susceptible to oxidation[15]. Cigarette smoking, thus, leads to increased lipid peroxidation and endothelial dysfunction, which leads to atherosclerosis.

Hypertension and aging are the most common factors leading to arterial stiffness. The arteries stiffen as the result of progressive degeneration of arterial media with fractures and fragmentation of elastic lamellae, increased collapse and calcium content, and dilatation and hypertrophy of large arteries and the aorta[16]. Such alterations are more pronounced in the central (thoracic aorta, carotid) than the peripheral

(femoral) arteries[17]. These functional and structural modifications to the arterial wall have important effects on the cardiovascular system such as, increasing the incidence of fracture, rupture, and aneurysm formation in the arteries and, potentially, the development of atherosclerosis. Besides being the result of arterial stiffening after such changes, the increase in systolic and pulse pressure increase the fatigue of arteries walls, accelerating the arterial damage, thus creating a vicious cycle.

The elevated serum creatinine also was correlated with large ulcerated plaque and embolic events by univariate analysis. Patients with chronic uremia have multiple risk factors predisposing to the development of atherosclerosis. The majority of patients who undergo dialysis have diabetes and hypertension as the etiology of their end stage renal disease (ESRD). The prevalence of hypertriglyceridemia in chronic renal disease is higher than in general population especially in patients treated by hemodialysis[18]. Elevated total plasma homocysteine level of greater than 14 mmol/L occurs in approximately 90% in patients with ESRD, compared with 5% of general population[19]. C-reactive protein level is known to be elevated in both ESRD and in pre-dialysis patients[20]. Diamond et al reported the similarities between pathogenesis of atherosclerosis and glomerulosclerosis[21]. Moreover, atherosclerosis and ESRD may be both outcomes of the same underlying disease as proposed by Sarnek et al[22].

Clinical Implication

The present study indicates that LV mass index correlates significantly with the severity of aortic atheroma. In patients with unexplained stroke who have a high LV mass index, and particular those who smoke and also have an elevated mean arterial blood pressure should undergo transesophageal echocardiography to look for the presence of large ulcerated atheromas.

Limitations

This is a retrospective review study. The authors included only patients undergoing transesophageal echocardiography, and therefore a selection bias for a high risk group of stroke and other cardiovascular diseases may have been included in the present study. The study population is not large enough to exclude contribution of other risk factors in predicting large ulcerated plaque in the aorta.

Conclusion

These data provide evidence that LV mass index correlates with the severity of aortic atheroma. Smoking, elevated mean arterial blood pressure and a high LV mass index score were significantly correlated with large ulcerated plaque and stroke. These findings may in part explain the higher cardiovascular risk in patients with increased left ventricular mass.

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ความสัมพันธ์ระหว่างภาวะกล้ามเนื้อหัวใจหนากับระดับความรุนแรงของ atherosclerosis ของหลอดเลือดแดงใหญ่และภาวะการเกิดลิ่มเลือดอุดตัน

ณัฐวุฒิ วงษ์ประภารัตน์, สิริน อภิยสวัสดิ์, สุราจ มาราจ, แลรี่ เจคอบ, มอริส คอทเลอร์

วัตถุประสงค์: เพื่อศึกษาความสัมพันธ์ระหว่างระดับความรุนแรงของ atherosclerosis ในหลอดเลือดแดงใหญ่กับระดับความรุนแรงของดัชนีน้ำหนักของกล้ามเนื้อหัวใจห้องล่างซ้าย (Left ventricular mass index) และผลของการเกิดภาวะการเกิดลิ่มเลือดอุดตัน

วัสดุและวิธีการ: คณะผู้วิจัยได้ทำการศึกษาย้อนหลังในผู้ป่วยโรค atherosclerosis ของหลอดเลือดแดงใหญ่และกลุ่มเปรียบเทียบจำนวนทั้งหมด 87 ราย ที่มารับการตรวจวิเคราะห์โรคหัวใจด้วยคลื่นเสียงสะท้อนทางหลอดอาหาร (transesophageal echocardiography) ระหว่างปีพ.ศ. 2538-2543

ผลการศึกษา: ผลการศึกษาพบว่าค่าเฉลี่ยดัชนีน้ำหนักของกล้ามเนื้อหัวใจห้องล่างซ้าย อยู่ที่ 116 กรัมต่อลูกบาศก์เมตรในกลุ่มผู้ป่วยที่มี atherosclerosis ของหลอดเลือดแดงใหญ่เปรียบเทียบกับ 81กรัมต่อลูกบาศก์เมตรในกลุ่มเปรียบเทียบ ($p < 0.009$) ในกลุ่มผู้ป่วยที่มี atherosclerosis ของหลอดเลือดแดงใหญ่พบมีความสัมพันธ์อย่างสูงระหว่างดัชนีน้ำหนักของกล้ามเนื้อหัวใจห้องล่างซ้ายกับระดับความรุนแรงของ atherosclerosis ของหลอดเลือดแดงใหญ่ส่วน aortic arch และ descending aorta ($p < 0.001$ และ $p < 0.0001$) นอกจากนี้ยังพบว่าการมี ulcerated plaque ขนาดใหญ่ของหลอดเลือดแดงใหญ่มีความสัมพันธ์อย่างสูงกับการเกิดอัมพาตจากลิ่มเลือดอุดตัน ($p < 0.002$)

สรุป: 1) ดัชนีน้ำหนักของกล้ามเนื้อหัวใจห้องล่างซ้ายมีความสัมพันธ์กับความรุนแรงของ atherosclerosis ในหลอดเลือดแดงใหญ่ 2) การสูบบุหรี่, ค่าเฉลี่ยความดันโลหิต และดัชนีน้ำหนักของกล้ามเนื้อหัวใจห้องล่างซ้ายมีความสัมพันธ์อย่างสูงกับการมี ulcerated plaque ขนาดใหญ่ของหลอดเลือดแดงใหญ่ และการเกิดอัมพาตจากลิ่มเลือดอุดตัน 3) ผลการศึกษานี้อาจช่วยอธิบายอัตราเสี่ยงต่อการเกิดโรคหัวใจและหลอดเลือดที่สูงขึ้น ในกลุ่มผู้ป่วยที่มีดัชนีน้ำหนักของกล้ามเนื้อหัวใจห้องล่างซ้ายสูง