Abstract

While hypertension is known to cause left ventricular and vascular hypertrophy, the relationship between alterations of vascular and cardiac structures in patients with hypertrophic cardiomyopathy has not been fully clarified. We measured intima-media thickness of carotid arteries by ultrasonography in patients with hypertrophic cardiomyopathy (n=16), normotensive subjects (n=328), and hypertensive subjects (n=386) in a cohort of 7940 male employees of a bus company. Our object was to determine whether vascular alteration occurs in hypertrophic cardiomyopathy similarly as in hypertension. Hypertrophic cardiomyopathy (wall thickness ≥15 mm, asymmetrical hypertrophy without hypertension) was screened with family history and electrocardiography followed by echocardiography. The intima-media thickness in patients with hypertrophic cardiomyopathy (mean, 0.61 mm) did not differ from that of normotensive subjects (0.60 mm) but was significantly less than that of hypertensive subjects with left ventricular hypertrophy (wall thickness ≥14 mm, n=22, 0.73 mm). In a scatterplot of intima-media thickness versus interventricular septal thickness, these two parameters were significantly correlated in normotensives and hypertensives. The patients with hypertrophic cardiomyopathy distributed outside the 95% confidence range of the normotensive and hypertensive subjects. In summary, the increase in intima-media thickness of the carotid artery paralleled left ventricular hypertrophy in normotensive and hypertensive subjects. Patients with hypertrophic cardiomyopathy had a normal intima-media thickness regardless of the hypertrophied left ventricle. Thus, information on intima-media thickness may be useful in differentiating hypertensive left ventricular hypertrophy from hypertrophic cardiomyopathy (Hypertension. 1997;29(part 2):361-365).

Key Words • risk factor • left ventricular hypertrophy • echocardiography • ultrasound • atherosclerosis • target organ damage

Intima-Media Thickness of the Carotid Artery in Hypertensive Subjects and Hypertrophic Cardiomyopathy Patients

Yusuke Ohya, Isao Abe, Koji Fuji, Kazuo Kobayashi, Uran Onaka, Masatoshi Fujishima

Ultrasoundography allows one to evaluate the structural changes of larger vessels such as carotid arteries. An increased IMT and plaque formation in the carotid arteries have been demonstrated in patients with atherosclerotic disease. Since the increase in IMT has been reported to correlate with various risk factors for atherosclerosis, such as age, BP, diabetes mellitus, hypercholesterolemia, and smoking status, as well as with the presence of coronary heart disease, IMT is considered to represent an early atherosclerotic change of the artery. Patients with hypertension demonstrate increases in IMT and number of plaques as well as a decrease in the ratio of internal diameter to external diameter in carotid arteries compared with normotensive subjects. Several recent studies have shown that the increase in IMT of the carotid artery paralleled the increase in LV wall thickness and LV mass in hypertensive patients. These findings suggest an association between cardiac and vascular hypertrophy in patients with hypertension.

HCM is a myocardial abnormality that is characterized by an asymmetrically hypertrophied and nondilated LV in the absence of any systemic disorder that would cause cardiac hypertrophy. The cause of the myocardial hypertrophy in HCM remains unknown; however, the presence of abnormal myocardial calcium kinetics, abnormal sympathetic stimulation, an abnormally thickened intramural small coronary artery (which may cause myocardial ischemia), and structural abnormalities including crenoid configuration of the septum have been suggested. Recent studies have shown that abnormalities of genes that encode myosin heavy chains and others are associated with HCM. It is possible that some of these etiologies may also stimulate proliferation and hypertrophy of vascular smooth muscle cells and cause vascular hypertrophy. Indeed, it has been reported that the intramural coronary small arteries in patients with HCM demonstrate a marked medial hypertrophy. However, alterations of large arteries have not been fully clarified; only one study examined the carotid artery by ultrasonography in patients with HCM in comparison with a small number of normotensive and hypertensive patients. Since IMT is influenced by various risk factors, a comparison requires a large study population.

Questions to be clarified in the present study were as follows. (1) whether the relationship between vascular and cardiac hypertrophy also exists in a larger population; (2) whether IMT of the carotid artery in HCM patients is normal or increased; and (3) whether the measurement of IMT by ultrasonography provides additional diagnostic information for HCM and hypertensive LV hypertrophy. To answer these questions, we measured IMT of carotid arteries and LV wall thickness echographically in hypertensive and normotensive subjects as well as in patients with HCM in one work-site population.

From the Second Department of Internal Medicine, Kyushu University, Faculty of Medicine, Fukuoka, Japan. Correspondence to Yusuke Ohya, MD, PhD, Second Department of Internal Medicine, Kyushu University, Faculty of Medicine, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-82, Japan. E-mail ohya@ntmed2.med.kyushu-u.ac.jp

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Methods

Subjects

The study group was part of a cohort of 7940 male employees of a bus and railway company in the Fukuoka area, Japan. Females were excluded from the present analysis because they constituted only a small portion of the population. To detect cardiovascular diseases including cardiomyopathy, an annual health check (clinical history, BP measurement, ECG, and chest roentgenogram) was performed in all employees at their offices as the initial screening. Subjects with any chest symptom, ECG change (ST-T change, frequent premature beats, abnormal Q wave, and high voltage), elevation of BP (>150/95 mm Hg, measured at their offices), or a history of cardiovascular disease were invited to the company’s healthcare center for further evaluation by echocardiography, exercise ECG, and Holter ECG, as well as ultrasonography of bilateral carotid arteries (n = 1074). The study protocol was approved by committees in the healthcare center and our department, and informed consent for participation was obtained from these subjects.

Of 1074 subjects who had visited the healthcare center, the following subjects were excluded from the analysis (n = 288): those with coronary heart disease, congestive heart failure, “athlete’s heart,” and valvular heart disease, as well as those with echocardiogram of inadequate quality for estimation of LV parameters.

In the present analysis, cardiomyopathy was diagnosed by two-dimensional B-mode and M-mode echocardiograms and the status of hypertension. HCM was defined by the following criteria: (1) presence of asymmetrical LV wall hypertrophy (ratio of hypertrophied wall thickness to posterior wall thickness ≥ 1.3), (2) hypertrophied LV wall thickness of ≥15 mm, and (3) absence of hypertension (n = 1074). The study protocol was approved by committees in the healthcare center and our department, and informed consent for participation was obtained from these subjects.

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Of 1074 subjects who had visited the healthcare center, the following subjects were excluded from the analysis (n = 288): those with coronary heart disease, congestive heart failure, “athlete’s heart,” and valvular heart disease, as well as those with echocardiogram of inadequate quality for estimation of LV parameters.

Cardiac and Arterial Morphology

To evaluate LV parameters, echocardiography (two-dimensional targeted M-mode) was performed with an ultrasound imager (SSA-160A; Toshiba Medical Co Ltd) with either a 2.5- or 3.5-MHz transducer by expert doctors (Y O, I A, K F, U O, and K K), as has been reported by our group. End-diastolic and end-systolic LV diameters and thickness of interventricular septum and posterior wall were obtained according to the Penn convention. In some HCM patients, measurement was also made from the B-mode image according to the recommendations of the American Society of Echocardiography. Average values from at least three cardiac cycles were used for data analysis. LV mass was calculated using the formula of Devereux and Reichek. Measurements were made by one doctor (Y O) blinded to patient information.

Structure of the common carotid artery was evaluated by ultrasound imaging (SSA-160A) with a 7.5-MHz transducer, as has been reported by our group. Longitudinal B-mode images at the diastolic cardiac cycle were recorded by a single trained technician. The images were magnified and printed using a high-resolution line recorder (LSR 100A, Toshiba). Measurements of IMT were made using fine slide calipers by one technician who was blinded to patient information. The intima-media complex was measured at three points on each side 1 to 3 cm proximal to the carotid bifurcation, where diffuse maximal thickness was observed but no plaque was present. The mean of these six measurements was used as IMT. Measurements were made using fine slide calipers by one technician who was blinded to patient information. The intima-media complex was measured at three points on each side 1 to 3 cm proximal to the carotid bifurcation, where diffuse maximal thickness was observed but no plaque was present. The mean of these six measurements was used as IMT.

Statistical Analysis

Data are expressed as mean ± SD except for IMT. Data for IMT are expressed as means with 95% confidence interval. Statistical analysis was performed by using SAS software, version 6.07. Differences between groups were assessed by ANOVA with multiple comparison test (Scheffe’s test) in an ANOVA procedure. Simple and stepwise regression analyses were performed by CORR and REG procedures, respectively. Adjusted mean values were obtained by analysis of covariance using the GLM procedure.

To obtain Mahalanobis’s generalized distance (D), the following equation was used:

\[ D^2 = (x - \bar{x})^T S^{-1} (x - \bar{x}) \]

where \( r \) is the correlation coefficient, \( \bar{x} \) and \( \bar{y} \) are means, and \( s_x \) and \( s_y \) are standard deviations for the variables, respectively.

A value of \( P < 0.05 \) was regarded as statistically significant.

Results

Clinical characteristics of the five groups are listed in Table 1. Age was higher in the HT1 and HT2 groups than in the normotensive group. Body weight and body mass index in the normotensive group were smaller than those in other groups. Body surface area was smaller in the normotensive group compared with the HCM group. Blood pressure in the normotensive and HCM groups did not
The major findings of the present study are as follows: (1) IMT of patients with HCM was the same as that of normotensive subjects; (2) IMT and LV wall thickness were increased in parallel in non-HCM subjects, and (3) in the scatterplot of IMT versus interventricular septal thickness, patients with HCM distributed outside the 95% confidence ellipse of normotensive subjects.


differ but was lower than that in any hypertensive group. Cholesterol level, creatinine level, and hemoglobin A1c did not differ among the groups. The percentage of smokers was equal in all the groups, but the percentage of ex-smokers was higher in the HCM group.

Table 2 shows the results of echocardiography and carotid ultrasonography. The values for interventricular septal thickness, posterior wall thickness, LV mass, and LV mass index ranked in descending order among non-HCM subjects, HT3, HT2, HT1, and normotensive groups. In the HCM group, interventricular septal thickness was the highest of all groups. The posterior wall thickness in the HCM group was higher than that in the normotensive, HT1, and HT2 groups. LV diastolic dimension in the HT3 and HCM groups was smaller than that in the HT1 group.

IMT was largest in the HT3 group, followed by the HT2, HT1, and normotensive groups. IMT in the HCM group was the same as that in the normotensive group and smaller than that in the hypertensive hypertrophy group. Since age and body mass index among subject groups differed significantly, IMT was adjusted for age and body mass index (Fig 1). Results remained the same even when IMT was adjusted for age and BMI.

The relationship between IMT and interventricular septal thickness for each subject is shown in Fig 2. The IMT and interventricular septal thickness correlated significantly in normotensive and hypertensive subjects without HCM (r = 259 for normotensives, n = 358, P < 0.01, r = 209 for hypertensives, n = 386, P < 0.01, and r = 239 for both, n = 441, P < 0.001). The 95% confidence ellipse of Mahalanobis's ellipse of constant distance was obtained from subjects without HCM was superimposed on the scatterplot. Points for all 16 patients with HCM distributed outside the confidence ellipse.

Relationships among the various clinical parameters, IMT, and interventricular septal thickness were evaluated in the hypertensive and normotensive subjects who were free from antihypertensive, anti diabetic, or cholesterol lowering drugs (n = 589). Simple correlation of parameters with IMT and interventricular wall thickness are shown in Table 3. Age, BP, body mass index, cholesterol level, and hemoglobin A1c were correlated with both interventricular septal thickness and IMT, respectively; however, smoking status was not correlated with either IMT or interventricular septal thickness.

In multiple regression analysis, age, body mass index, and systolic BP were selected as significant determinants of interventricular septal thickness. For IMT, age, systolic BP, total cholesterol, and interventricular septal thickness were selected as significant determinants. This result suggests that the relationship between IMT and interventricular septal thickness remained even after corrected for age, BP, cholesterol level, hemoglobin A1c, and body mass index.

**Table 1. Profiles of Subjects**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Normotensive (n=358)</th>
<th>HT1 (n=213)</th>
<th>HT2 (n=219)</th>
<th>HT3 (n=204)</th>
<th>HCM (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, 7</td>
<td>47±11</td>
<td>52±6*$</td>
<td>53±6†</td>
<td>52±6</td>
<td>47±9</td>
</tr>
<tr>
<td>Height, m</td>
<td>165±6</td>
<td>164±5</td>
<td>165±7</td>
<td>165±6</td>
<td>166±7</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>64±9‡</td>
<td>69±10†</td>
<td>69±9†</td>
<td>72±10†</td>
<td></td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.74±0.13</td>
<td>1.76±0.13</td>
<td>1.80±0.15</td>
<td>1.82±0.11</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>20.8±5.7</td>
<td>24.3±4.7‡</td>
<td>25.3±4.7‡</td>
<td>26.1±4.0§</td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>118±12</td>
<td>142±16‡</td>
<td>148±17‡</td>
<td>152±21§</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>75±8</td>
<td>90±10†</td>
<td>92±10‡</td>
<td>76±7†</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.99±0.88</td>
<td>5.12±0.85</td>
<td>5.10±0.83</td>
<td>5.07±0.85</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.29±0.34</td>
<td>1.32±0.39</td>
<td>1.31±0.42</td>
<td>1.27±0.31</td>
<td></td>
</tr>
<tr>
<td>Creatinine, mmol/L</td>
<td>0.76±0.04</td>
<td>0.79±0.05</td>
<td>0.77±0.04</td>
<td>0.75±0.04</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin A1c, %</td>
<td>5.4±0.8</td>
<td>5.5±0.9</td>
<td>5.6±1.0</td>
<td>5.6±1.0</td>
<td></td>
</tr>
<tr>
<td>Smokers (-/ex/+), %</td>
<td>31/15/54</td>
<td>28/24/47</td>
<td>27/21/51</td>
<td>21/32/47</td>
<td></td>
</tr>
</tbody>
</table>

*P< 0.05, †P< 0.01, ‡P< 0.001 vs NT, §P< 0.05, ††P< 0.01 vs HT1, ‡‡P< 0.001 vs HT2, #P< 0.001 vs HT3

**Table 2. Echocardiographic Parameters for LV and Common Carotid Arteries**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normotensive</th>
<th>HT1</th>
<th>HT2</th>
<th>HT3</th>
<th>HCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septal thickness, mm</td>
<td>10.0±1.7</td>
<td>10.3±1.4*</td>
<td>13.3±3.0*‡</td>
<td>14.8±0.8∥§</td>
<td>19.0±3.6∥§∥</td>
</tr>
<tr>
<td>Posterior wall thickness, mm</td>
<td>9.8±1.6</td>
<td>10.4±1.5*</td>
<td>12.0±1.4*</td>
<td>13.5±0.9*‡</td>
<td>12.0±2.0*§</td>
</tr>
<tr>
<td>Diastolic dimension, mm</td>
<td>47.6±4.4</td>
<td>48.6±4.5</td>
<td>47.1±3.9</td>
<td>45.3±4.2†</td>
<td>45.0±5.4†</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>70.7±7.4</td>
<td>70.0±7.7</td>
<td>69.8±8.0</td>
<td>70.0±7.3</td>
<td>70.0±9.4</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70±16</td>
<td>72±11</td>
<td>71±11</td>
<td>68±12</td>
<td>66±8</td>
</tr>
<tr>
<td>Mass, g</td>
<td>194±45</td>
<td>218±46*</td>
<td>273±45*‡</td>
<td>306±46‡</td>
<td>ND</td>
</tr>
<tr>
<td>Mass index, g/m²</td>
<td>111±24</td>
<td>124±25*</td>
<td>152±23*‡</td>
<td>168±25*‡</td>
<td>ND</td>
</tr>
</tbody>
</table>

**Cardiovascular**

| IMT, mm (95% confidence range) | 0.59 (0.43-0.81) | 0.65 (0.47-0.89)* | 0.68 (0.49-0.93)* | 0.72 (0.50-1.05)† | 0.60 (0.48-0.76)‡ |

*P< 0.001 vs normotensive subjects, †P< 0.05, ††P< 0.001 vs HT1, ‡P< 0.01 vs HT2, ‡‡P< 0.001 vs HT3

ND indicates not determined Data are mean±SD
The prevalence of HCM, as determined by echocardiography in a general population and in a work-site population, has been reported. In the CARDIA (Coronary Artery Risk Development in Adults) study, the prevalence was 0.26% in men and 0.09% in women in a young general population. The prevalence in the Framingham cohort was 0.17%. Another study showed the prevalence in adult workers in Japan to be 0.3%. Our prevalence of HCM in adult male workers was 0.3%, but when apical hypertrophy was included, the prevalence became 0.5%. Thus, prevalence of HCM in the present study did not differ from previous studies. However, the prevalence in our study may still be underestimated. This is because the criteria of the present study were relatively strict, and our screening might miss HCM patients who lack either an ECG abnormality or family history.

IMT in HCM patients was the same as that in normoten- sive subjects. In contrast, IMT in hypertensive subjects with LV hypertrophy was greater than that in normoten- sive subjects and hypertensive subjects without LV hypertrophy. These results remained the same after IMT was adjusted for age and BMI. Since cholesterol level and hemoglobin $A_g$ did not differ among groups, the difference in IMT was not due to the difference in these risk factors. Difference in etiologies of cardiac hypertrophy between HCM and hypertension would explain differences in IMT among groups. Whatever caused the abnormal cardiac hypertrophy in HCM patients did not stimulate vascular structural change. In contrast, factors that are associated with hypertension would increase both IMT and LV wall thickness.

The distributions of HCM and non-HCM subjects were different in the scatterplot of IMT versus interventricular septal thickness. Since HCM patients distribute outside of the 95% confidence ellipse of non-HCM subjects, use of carotid ultrasonography together with echocardiography should provide benefit in the differential diagnosis between HCM and hypertensive LV hypertrophy.

It has not been fully clarified what factor mediates LV hypertrophy and vascular hypertrophy in non-HCM subjects. Since age and BP showed significant correlation with both carotid IMT and LV wall thickness, age and hyper- tension may mediate the relationship. In hypertension, an increased hemodynamic load due to hypertension would cause both vascular and cardiac hypertrophy. Since this correlation between IMT and LV wall thickness existed even after correction for age, BP, cholesterol level, hemoglobin $A_g$, and body mass index, factors other than these risk factors (eg, angiotensin II, insulin and other growth factors, and some genetic factors) might also be involved in the relationship. Recent studies showed that insulin resistance and hyperinsulinaemia are associated with LV structural change, as well as with increased IMT. It has been also reported that the polymorphism of the angiotensin-converting enzyme gene is associated with LV hypertrophy and increased IMT.

The limitations of the present study are as follows. First, we studied only male employees who had been selected from one work site. While this is relatively general compared with hospital patients, it does not represent a general population. Thus, the conclusion may not be applicable to female subjects or a general population. Second, our diagnosis of HCM depended on echocardiographic observations. Studies using genetic diagnosis are required to confirm the present observation.

In conclusion, we have shown that the IMT of patients with HCM is normal regardless of the hypertrophied LV. In contrast, carotid IMT and LV wall thickness increase in parallel in hypertension. Thus, information about the IMT of the carotid artery may be useful in the diagnosis of hypertensive LV hypertrophy and HCM.
References


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