Original Article

Difference in Coronary Blood Flow Dynamics between Patients with Hypertension and Those with Hypertrophic Cardiomyopathy

Katsushi MISAWA, Yutaka NITTA, Takao MATSUBARA, Kotaro OE*, Masaru KIYAMA*, Masami SHIMIZU*, and Hiroshi MABUCHI*

We studied twelve patients with hypertensive left ventricular hypertrophy (LVH), 10 patients with hypertrophic cardiomyopathy (HCM) and 10 control subjects to examine the differences in coronary blood flow (CBF) dynamics between patients with hypertensive LVH and those with HCM. All subjects had normal coronary arteriograms. Measurements of CBF using Doppler Flo-Wire were performed at rest, and after infusions of acetylcholine and papaverine. The baseline CBF was significantly increased in both hypertensive LVH patients and HCM patients compared to that noted in control subjects (64.1 ± 36.9, 80.0 ± 38.1, 32.3 ± 8.0 ml/min, respectively, p < 0.01). Coronary flow reserve and endothelium-dependent vasodilatation were significantly lower in hypertensive LVH patients and HCM patients than in control subjects, but there was no significant difference between the hypertensive LVH and HCM patients themselves. In contrast, the diastolic/systolic velocity ratio at baseline was significantly lower in hypertensive LVH patients than in HCM patients (1.53 ± 0.40, 6.31 ± 7.50, p < 0.05). Although CBF and coronary flow reserve correlated positively and negatively, respectively, with left ventricular mass index (r = 0.51, 0.59, respectively), the diastolic/systolic velocity ratio at baseline did not show a significant correlation to left ventricular mass index. In conclusion, the diastolic/systolic velocity ratio differed between hypertensive LVH and HCM patients, independent of left ventricular mass. These results suggest that the difference of phasic pattern of CBF may be essential for coronary circulation in patients with hypertensive LVH and in those with HCM.

(Hypertens Res 2002; 25: 711–716)

Key Words: left ventricular hypertrophy, hypertrophic cardiomyopathy, hypertension, coronary circulation

Introduction

In patients with left ventricular hypertrophy (LVH), it has been reported that myocardial ischemia may occur in the absence of epicardial coronary artery disease (1–5). It has been suggested that an imbalance between oxygen supply and demand due to the greatly increased myocardial mass might be a mechanism for myocardial ischemia (6). Recently, inadequate coronary flow reserve has been proposed to play an important role in the development of myocardial ischemia in hypertrophic cardiomyopathy (HCM) (7–9) and in hypertensive LVH (10, 11). Moreover, in patients with hypertensive LVH, coronary blood flow (CBF) has been reported to be the most potent predictor of left ventricular function (12), and impaired endothelium-dependent vasodilatation in response to acetylcholine has also been reported to be a cause of ischemia (5).

Hypertension and HCM are the most common causes of LVH. However, the differences in CBF dynamics between...
patients with hypertensive LVH and HCM have not been investigated fully. The purpose of this study was to examine the differences in CBF dynamics between such patients.

Methods

Study Patients

Thirty-two subjects who underwent coronary angiography and CBF measurements for cardiac examinations and who had normal coronary arteriograms were included in this study. They consisted of 10 patients with HCM (7 men and 3 women; mean age: 59.9 years), 12 patients with hypertension (7 men and 5 women; mean age: 57.8 years) and 10 control subjects (7 men and 3 women; mean age: 51.0 years). The diagnosis of HCM was based on the echocardiographic demonstration of a non-dilated, hypertrophied left ventricle in the absence of other cardiac or systemic causes for the left ventricular hypertrophy (13). Hypertension was defined as blood pressure over 140/90 mmHg on at least three measurements taken in the supine position. LVH was defined as left ventricular wall thickness over 13 mm, as estimated with echocardiography. Patients with the obstructive type of HCM or diabetes mellitus were excluded from this study. In addition, no control subjects had hypertension, diabetes mellitus, or hypercholesterolemia.

Echocardiographic Study

All subjects underwent standard M-mode and two-dimensional echocardiography. Left ventricular dimensions and the thicknesses of the septum and the posterior walls were measured at the level of the tips of the mitral valve leaflets. Left ventricular mass was calculated from the obtained measurements by the formula of Devereux et al. (14). The left ventricular mass index was defined as the ratio of left ventricular mass to body surface area.

Cardiac Catheterization and Coronary Flow Velocity Measurements

Written informed consent to participate in the study was obtained from all subjects before cardiac catheterization. This study was approved by the institutional committee for clinical research at Toyama Red Cross Hospital. All medications, including β-blockers, isosorbide dinitrate, and calcium antagonists, were discontinued at least 24 h before cardiac catheterization. The patients received 4 mg of oral diazepam for sedation.

All subjects underwent catheterization by the standard femoral percutaneous approach. Coronary angiography with multiple views was performed to confirm the absence of epicardial coronary artery disease. Next, coronary blood flow velocity was measured with a Doppler-tipped guidewire. A 0.014-inch Doppler guidewire (Flo-Wire; Cardiometrics, Los Angeles, USA) was advanced into the proximal portion of the left anterior descending artery or into the left circumflex artery. The placement of this device was optimized using Doppler signals. The Doppler guidewire was connected to a photographic multi-channel recorder (Flo-Map; Cardiometrics) in order to display phasic and mean velocity waveforms. All measurements were recorded under steady waveforms, and the position of the Doppler guidewire was not changed during the measurements.

Serial intracoronary infusions of acetylcholine and papaverine were administered via the catheter in the following sequence: three 2-min infusions of acetylcholine to achieve estimated final blood concentrations of $10^{-8}$, $10^{-7}$, and $10^{-6}$ mol/l (based on assumed left anterior descending coronary artery blood flow of 80 ml/min), and a bolus injection of 10 mg papaverine. Coronary angiography was performed at the end of each infusion. Throughout each infusion, the heart rate, blood pressure, coronary flow velocity and electrocardiogram (leads I, aVF, V5) were monitored continuously, and all measurements were recorded under steady-state conditions.

Quantitative Coronary Angiography

Coronary angiography was performed using an optimal view so that overlapping of branches and foreshortening of the region of interest were minimized. The angiograms were recorded on 35-mm cinefilm (30 frames/s) using a cineangiographic system (Toshiba, Tokyo, Japan). An optimal end-diastolic cineangiographic frame was selected. Furthermore, coronary artery diameter was measured at the site of the Doppler velocity measurements using a validated videodensitometric analysis system (CCIP-310, Cathex, Tokyo, Japan), and the cross-sectional area was obtained. The diameter of the catheter was used for calibrating the arterial diameter in mm.

Coronary Flow Velocity Analysis

Before and just after the end of drug infusion, the average peak velocity and diastolic/systolic velocity ratio were measured. The ratio of the diastolic average peak velocity to the systolic average peak velocity was defined as the diastolic/systolic velocity ratio. CBF was estimated as the product of the average peak velocity and the cross-sectional area of the arterial segment. The increase in CBF after papaverine infusion was defined as the coronary flow reserve. The maximum increase in CBF after acetylcholine infusion was defined as endothelium-dependent vasodilatation.

Statistical Analysis

Values are expressed as the mean ± SD. Comparisons between groups were performed using a one-way analysis of variance (ANOVA) followed by Scheffe’s method. Categorical data
were compared using \( \chi^2 \) analysis. Possible correlations were assessed by linear regression analysis and Pearson’s correlation coefficient. To evaluate the contribution of left ventricular mass to coronary blood flow at rest, multiple regression analysis was used. Value of \( p < 0.05 \) were considered to indicate statistical significance.

## Results

### Clinical Characteristics

The clinical characteristics of the patients are summarized in Table 1. In the hypertensive LVH group, one patient with primary aldosteronism was included, while the rest of the patients had essential hypertension. Age, gender and heart rate at baseline were not significantly different among the 3 groups. Systolic and diastolic blood pressures were significantly higher in patients with hypertensive LVH than in those with HCM or in the control subjects. The thicknesses of the interventricular septal wall and left ventricular posterior wall were significantly higher in patients with hypertensive LVH and in those with HCM than in control subjects. The left ventricular mass index was increased in the following order: HCM, hypertensive LVH, and controls (207.5 \( \pm \) 58.2, 163.2 \( \pm \) 26.5, 104.1 \( \pm \) 16.4 g/m\(^2\), respectively).

### CBF Velocity

The results of CBF velocity measurements are summarized in Table 2. CBF at baseline was significantly increased in patients with hypertensive LVH and with HCM compared to control subjects, but did not differ between hypertensive LVH and HCM groups themselves. Coronary flow reserve and endothelium-dependent vasodilatation were significantly decreased in patients with hypertensive LVH and in those with HCM compared to control subjects; again, however, these parameters did not differ between the two experimental groups. In contrast, the diastolic/systolic velocity ratio at baseline was significantly smaller in patients with hypertensive LVH than in those with HCM, and this ratio did not differ between hypertensive LVH patients and control subjects. Representative recordings of phasic CBF velocity in each group are presented in Fig. 1. Systolic coronary flow was significantly decreased in patients with HCM, but increased in patients with hypertensive LVH. The same differences in diastolic/systolic velocity ratio were found after infusion of

### Table 1. Clinical and Echocardiographic Characteristics of Patients with Hypertrophic Cardiomyopathy, Patients with Hypertensive Left Ventricular Hypertrophy, and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>HCM (n = 10)</th>
<th>HT-LVH (n = 12)</th>
<th>Control (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.9 ( \pm ) 11.0</td>
<td>57.8 ( \pm ) 12.8</td>
<td>51.0 ( \pm ) 7.0</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>7/3</td>
<td>7/5</td>
<td>7/3</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>71.2 ( \pm ) 15.4</td>
<td>69.5 ( \pm ) 4.9</td>
<td>70.2 ( \pm ) 10.7</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120 ( \pm ) 13</td>
<td>165 ( \pm ) 12*</td>
<td>119 ( \pm ) 12</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72 ( \pm ) 9</td>
<td>91 ( \pm ) 12*</td>
<td>67 ( \pm ) 14</td>
</tr>
<tr>
<td>SWT (mm)</td>
<td>18.0 ( \pm ) 4.2*</td>
<td>16.1 ( \pm ) 1.7*</td>
<td>10.8 ( \pm ) 1.1</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>14.0 ( \pm ) 3.3*</td>
<td>12.8 ( \pm ) 1.5*</td>
<td>10.1 ( \pm ) 1.2</td>
</tr>
<tr>
<td>LVMI (g/m(^2))</td>
<td>208 ( \pm ) 58*</td>
<td>163 ( \pm ) 27*</td>
<td>104 ( \pm ) 16</td>
</tr>
</tbody>
</table>

HCM, hypertrophic cardiomyopathy; HT-LVH, hypertensive left ventricular hypertrophy; SBP, systolic blood pressure; DBP, diastolic blood pressure; SWT, septal wall thickness; PWT, posterior wall thickness; LVMI, left ventricular mass index. * \( p < 0.01 \) vs. control; † \( p < 0.01 \) vs. HCM.

### Table 2. Coronary Blood Flow Velocity in Patients with Hypertrophic Cardiomyopathy, Patients with Hypertensive Left Ventricular Hypertrophy, and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>HCM (n = 10)</th>
<th>HT-LVH (n = 12)</th>
<th>Control (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF at baseline (ml/min)</td>
<td>80.0 ( \pm ) 38.1**</td>
<td>64.1 ( \pm ) 36.9**</td>
<td>32.3 ( \pm ) 8.0</td>
</tr>
<tr>
<td>CBF after acetylcholine (ml/min)</td>
<td>112.0 ( \pm ) 49.8</td>
<td>94.5 ( \pm ) 58.0</td>
<td>79.0 ( \pm ) 30.0</td>
</tr>
<tr>
<td>CBF after papaverine (ml/min)</td>
<td>166.6 ( \pm ) 63.8</td>
<td>168.6 ( \pm ) 93.6</td>
<td>151.7 ( \pm ) 52.6</td>
</tr>
<tr>
<td>DSVR at baseline</td>
<td>6.31 ( \pm ) 7.50</td>
<td>1.53 ( \pm ) 0.40*</td>
<td>2.62 ( \pm ) 0.68</td>
</tr>
<tr>
<td>DSVR after acetylcholine</td>
<td>2.50 ( \pm ) 0.95</td>
<td>1.45 ( \pm ) 0.34*</td>
<td>1.88 ( \pm ) 0.54</td>
</tr>
<tr>
<td>DSVR after papaverine</td>
<td>3.01 ( \pm ) 1.70</td>
<td>1.57 ( \pm ) 0.22*</td>
<td>1.92 ( \pm ) 0.29</td>
</tr>
<tr>
<td>CBF reserve (%)</td>
<td>135 ( \pm ) 138**</td>
<td>188 ( \pm ) 143**</td>
<td>396 ( \pm ) 228</td>
</tr>
<tr>
<td>Endothelium-dependent vasodilatation (%)</td>
<td>51.0 ( \pm ) 56*</td>
<td>51.0 ( \pm ) 56*</td>
<td>163 ( \pm ) 135</td>
</tr>
</tbody>
</table>

HCM, hypertrophic cardiomyopathy; HT-LVH, hypertensive left ventricular hypertrophy; CBF, coronary blood flow; DSVR, diastolic/systolic velocity ratio. * \( p < 0.05 \) vs. control; ** \( p < 0.01 \) vs. control; † \( p < 0.05 \) vs. HCM.
acetylcholine or papaverine.

**Relationship between CBF Velocity and Left Ventricular Mass**

CBF at baseline showed a significant correlation with left ventricular mass index \( (Y = 0.33X + 6.5, r = 0.49, \text{and } p < 0.01) \), as shown in Fig. 2. No significant correlation was found between CBF after acetylcholine or papaverine infusions and the left ventricular mass index. Table 3 shows the results of multivariate analysis among 9 variables related to CBF at rest. Age, left ventricular mass index and smoking were significant independent predictors of CBF at rest, and left ventricular mass index was the most powerful predictor. Coronary flow reserve showed a significant negative correlation with the left ventricular mass index \( (Y = -2.00X + 670, r = 0.52, \text{and } p < 0.01) \). There was no significant correlation between endothelium-dependent vasodilatation and the left ventricular mass index. There was no significant correlation between the diastolic/systolic velocity ratio and the left ventricular mass index.

**Discussion**

This study demonstrates that CBF reserve and endothelium-dependent vasodilatation are decreased in patients with hypertensive LVH and HCM. Furthermore, these decreases are dependent upon increases in left ventricular mass. This study also demonstrates that the diastolic/systolic velocity ratio in patients with hypertensive LVH is different from that in HCM patients, and that this index is independent upon an in-
increase in left ventricular mass.

CBF Reserve in Hypertensive LVH and HCM

In this study, CBF reserve was significantly decreased in patients with hypertensive LVH and in those with HCM compared to control subjects. A decreased CBF reserve has previously been reported in patients with HCM (6–9), hypertensive LVH (5), and aortic stenosis (4). As a possible cause of decreased CBF reserve in patients with hypertensive LVH, increased CBF at baseline has been proposed (5). On the other hand, it has been reported that the reduced arteriolar lumen and inadequate capillary density in relation to the increased myocardial mass are causes of decreased coronary flow reserve in HCM patients (8, 15). In our study, the CBF at baseline was increased in both the group with hypertensive LVH and the one with HCM dependent upon left ventricular mass. In contrast, the maximum CBF after papaverine infusion was not different among the three groups. As a result, the CBF reserve in hypertensive LVH and HCM patients was decreased in a dependent fashion with respect to left ventricular mass. Accordingly, we hypothesize that the decreased CBF reserve in the hypertrophied heart (hypertensive LVH and HCM) may be due to an increased CBF at baseline that is dependent upon an increase in left ventricular mass and due to a constant maximum CBF. It is possible that the maximum CBF could not increase dependently with respect to the increase in left ventricular mass because of the histopathological changes as mentioned above.

Endothelium-Dependent Vasodilatation in Hypertensive LVH and HCM

It has been reported that endothelium-dependent vasodilatation is impaired even in younger patients with hypertensive LVH (15). In our study, endothelium-dependent vasodilatation, as well as CBF reserve, was decreased more in patients with hypertensive LVH than in control subjects. Advanced endothelial injury caused by mechanical stress may be a cause of this change. However, the precise mechanism by which the endothelial injury leads to impairment of endothelium-dependent vasodilatation remains controversial.

Diastolic/Systolic Velocity Ratio in Hypertensive LVH and HCM

The diastolic/systolic velocity ratio at baseline was significantly lower in patients with hypertensive LVH than in those with HCM, in contrast to CBF reserve and endothelium-dependent vasodilatation. Decreased, or sometimes reversed, systolic CBF has been reported in patients with obstructive (7) and non-obstructive HCM (16) and aortic stenosis (17). The following have been proposed as possible causes: asymmetrical LVH, compression of intramural coronary arteries, and poor capacitance of the epicardial coronary arteries (18). Moreover, the markedly disordered myocardial architecture specifically seen in HCM (19) may participate in this change. Disordered myocardial fibers might compress the small intramural coronary arteries and decrease systolic CBF, thereby leading to a higher diastolic/systolic velocity ratio.

In contrast to HCM, systolic CBF was restored in patients with hypertensive LVH. The diastolic/systolic velocity ratio did not correlate with left ventricular mass. Therefore, this difference in CBF velocity pattern between patients with hypertensive LVH and those with HCM was not due to the difference in the left ventricular mass. Although our study did not completely address the mechanism responsible for this change in CBF velocity pattern, our results suggest the following possibilities. First, the patients with hypertensive LVH had high systolic blood pressure, which is known to act as a powerful driving force pushing blood into the coronary artery. Thus, high blood pressure may be a cause of a low diastolic/systolic velocity ratio in patients with hypertension (11). Second, the histopathological changes such as myocardial cell disarray are less pronounced in patients with hypertensive LVH than in those with HCM (20). This histopathological difference may affect the difference in CBF velocity patterns for hypertensive LVH and HCM. Further investigations, including histopathological examination, will be needed to clarify this issue.

Our study demonstrates the possibility of differentiating hypertensive LVH from HCM by using the CBF velocity pattern. Due to advances in methodological techniques, CBF characteristics can be evaluated non-invasively by transesophageal echocardiography (21) and other relatively simple techniques. The diastolic/systolic velocity ratio may provide some insight in deciding between a diagnosis of hypertensive LVH and HCM.

In conclusion, CBF reserve and endothelium-dependent coronary vasodilatation are decreased in patients with hypertensive LVH and in those with HCM, and these decreases are dependent upon an increase in left ventricular mass. On the other hand, the diastolic/systolic velocity ratio in patients with hypertensive LVH is significantly different from that in those with HCM. This index may be a useful tool in the differentiation of these patients.

Study Limitation

Although we used echocardiography to estimate left ventricular mass in our study, MRI or CT scan may be better for calculating this variables, science disproportionate LVH is common in patients with HCM. The number of studied patients was small, and the myocardial mass indexes were significantly different between patients with hypertensive LVH and those with HCM. Many more patients with matched myocardial mass indexes will be needed to determine the efficacy of the diastolic/systolic velocity ratio is in diagnosis between hypertensive LVH and HCM.
References


