Original Article

Different Coronary Blood Flow Increase in Left Ventricular Hypertrophy Due to Hypertension Compared to Hypertrophic Cardiomyopathy at Elevated Heart Rate

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Coronary vasodilator reserve (CVR) is reduced in patients with left ventricular hypertrophy (LVH). However, it is not clear whether there is any difference between the coronary blood flow increase in LVH caused by hypertension (HTH) and that caused by hypertrophic cardiomyopathy (HCM) when the heart rate increases. In this study, 16 subjects with HTH, 10 subjects with HCM, and 10 subjects with normotension (NT) were investigated. Average peak velocities at rest, at pacing, and at dilatation were measured using a Doppler catheter placed at the left descending coronary artery to calculate coronary blood flow (CBF) and CVR. CVR at rest was identical in the HTH and HCM groups, and in both cases was lower than the resting CVR in NT subjects. There were significant differences in the CVR values at a pacing rate of 120 beats/min among the groups. These values were lowest in HCM, highest in NT, and intermediary in HTH subjects. And the percent increase in CBF in HCM at that pacing rate was higher than that in HTH ($p < 0.05$) or NT ($p < 0.05$). There was no difference in the percent increase in CBF at this pacing rate between the HTH and NT groups. The effects of elevated heart rate on the percent increase in CBF were different between the HTH and HCM groups. We conclude that cardiac hypertrophy has qualitatively different effects on coronary circulation depending on whether patients have HTH or HCM. (*Hypertens Res* 2003; 26: 789–793)

Key Words: left ventricular hypertrophy, hypertension, hypertrophic cardiomyopathy, coronary blood flow

Introduction

Left ventricular hypertrophy (LVH) is caused by many factors and is one of the most significant complications of hypertension (HT). LVH tends to be associated with a higher cardiovascular morbidity rate and a higher mortality rate (1). Reduced coronary vasodilator reserve (CVR) is one of the causes of these associations, even among patients with angiographically normal coronary arteries (2). Reduction in CVR leads to precipitation of myocardial ischemia and re-

sults in congestive heart failure, arrhythmias, and sudden death (2). It has been reported that the impairment of CVR in hypertensive patients is not necessarily related to the presence or degree of LVH (3–5). Therefore, we must consider how LVH develops.

Patients with hypertrophic cardiomyopathy (HCM) also have LVH. HCM has been thought to be caused by mutations in genes (6, 7). A reduced CVR has been reported in patients with HCM, and this seems to be related to ventricular hypertrophy (8, 9). A reduction in CVR can lead to myocardial ischemia and left ventricular dysfunction, and a high

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mortality rate has been reported in patients with these conditions (6, 7, 10). However, another study has reported that the mortality rate in HCM is not particularly high (11). We should therefore consider the possibility that various factors contribute to this abnormality.

Coronary blood flow (CBF) is increased by an elevation in heart rate, which leads to a shortening of diastolic filling time. Thus, heart rate is an important factor affecting coronary circulation (12). However, it is not known how the disease factor and heart rate factor interact in patients with LVH. The aim of this study was to determine the differences between the coronary circulations in patients with LVH caused by hypertension and those in patients with LVH caused by hypertrophic cardiomyopathy.

Methods

Study Population

The study population consisted of 16 subjects with HT and LVH (HTH), 10 subjects with HCM without outflow obstruction, and 10 subjects with normotension (NT). Exclusion criteria were diabetes mellitus and hypercholesterolemia. None of the subjects with HTH or HCM had a history of chest pain. NT subjects complained of slight chest discomfort. HT was defined as blood pressure of $\geq 140/90$ mmHg (13). None of the hypertensive patients had previously been treated. NT was defined as blood pressure of $< 140/90$ mmHg. None of the subjects had received medication for 1 month before the study, and none received medication during the study. Plasma catecholamine levels were measured by HPLC with ECD. As an index of plasma renin activity (PRA), the amount of angiotension I formed after incubation of plasma was measured by radioimmunoassay. All subjects were confirmed by ECG to have normal sinus rhythm. Our Institutional Review Board approved the study, and informed consent was obtained from all subjects.

Echocardiographic Measurements

Two-dimensional and M-mode echocardiography were carried out using a 2.5-MHz transducer. Left ventricular mass was calculated by the formula of Devereux and Reichek (14). Values were indexed for body surface area to obtain the left ventricular mass index (LVMI). HTH was defined as a posterior wall thickness ≥ 12 mm (15) and as LVMI > 135 g/m² in order for the LV mass in HTH to be the same as that in HCM.

Cardiac Catheterization and Coronary Flow Measurement

All subjects underwent cardiac catheterization; a 6F pigtail catheter was used for measuring aortic pressure and left ventricular pressure, and left ventriculography was performed. Coronary angiography was performed to confirm the absence

of coronary artery disease. Then a cardiac pacing catheter was placed high in the right atrium. A 0.014-inch Flowire Doppler tipped guide wire (Cardiometrics Inc., Mountain View, USA) was advanced into the proximal portion of the left descending artery and placed for optimal Doppler signal quality. At 10 min or more after diagnostic cardiac catheterization, basic coronary blood flow velocity (basic average peak velocity (basic APV)) was measured. Ten mg of papaverine was then injected into the coronary ostium, and the resultant increase in coronary blood flow velocity (maximum average peak velocity (max APV)) was recorded. The flow velocity was then allowed to return to the baseline value. After 3 min of pacing at a rate of 100 beats/min, coronary blood flow velocity (AP100 basic APV) and maximum coronary blood flow velocity following papaverine injection (AP100 max APV) were measured. These velocities were also measured at a pacing rate of 120 beats/min (AP120 basic APV, AP120 max APV). The CVR was calculated as the ratio of mean coronary flow velocity at peak papaverine-induced hyperemia (max APV) to mean resting coronary flow velocity (basic APV) (16). The radius of the proximal portion of the left descending artery was measured using a caliper (Mitsutoyo Inc., Kanagawa, Japan) from the right anterior oblique (RAO) view of the coronary angiogram. CBF was calculated by the formula of Doucette *et al.* (17). Percent increase in CBF was defined as the ratio of the increase in CBF from that at rest to that at a pacing rate of 100 or 120 beats/min to CBF at dilatation multiplied by 100.

Statistical Analysis

All data are expressed as the means $\pm$ SD. One-way analysis of variance (ANOVA) with Scheffe's test was used for comparison among the groups. In order to show the interaction between the effect of the disease and that of moderate elevation in heart rate, the percent increases in CBF were compared by repeated measures ANOVA. Values of $p < 0.05$ were considered to indicate statistical significance.

Results

Subjects' Characteristics

Subjects' characteristics are shown in Table 1. The ages of the subjects were not different among the groups. The systolic blood pressure (SBP) and the diastolic blood pressure (DBP) of subjects with HTH were higher than those in subjects of the HCM or NT groups. There were no differences in heart rate among the three groups.

Left ventricular diastolic dimension and left ventricular systolic dimension were not different among the groups. The thickness of the intraventricular septum (IVS) in the HCM group was greater than that in the other groups. The IVS thickness in the HTH was greater than that in the NT subjects. The thickness of the left ventricular posterior wall

Table 1. Subjects' Characteristics

	Age (years)	SBP (mmHg)	DBP (mmHg)	HR (/min)	LVDd (mm)	LVDs (mm)	IVS (mm)	LVPW (mm)	LVMI (g/m ²)
HTH	60 ± 12	174 ± 19	98 ± 15	73 ± 12	45.7 ± 3.4	28.4 ± 3.8	13.7 ± 2.3	14.0 ± 1.9	183 ± 37
HCM	67 ± 7	139 ± 17	74 ± 14	66 ± 7	42.5 ± 3.0	26.9 ± 3.7	18.2 ± 3.9	14.6 ± 3.6	228 ± 69
NT	62 ± 5	124 ± 14	78 ± 9	74 ± 13	43.7 ± 3.6	26.7 ± 4.2	8.3 ± 1.1	9.5 ± 1.1	94 ± 15

Data are mean ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; HTH, hypertension with left ventricular hypertrophy; HCM, hypertrophic cardiomyopathy; NT, normotension; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; IVS, intraventricular septum; LVPW, left ventricular posterior wall; LVMI, left ventricular mass index. Lines indicate significance between groups. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Fig. 1. Coronary vasodilator reserve in relation to heart rate. As heart rate increased, CVR decreased, especially in the HCM group. ■, HTH: hypertension with left ventricular hypertrophy; ▨, HCM: hypertrophic cardiomyopathy; □, NT: normotension. CVR, coronary vasodilator reserve; AP100, atria pacing at 100 beats/min; AP120, atria pacing at 120 beats/min. Lines indicate significance between groups. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Data are expressed as the means ± SEM.

(LVPW) in the HTH and HCM was greater than that in the NT subjects. There was no difference in LVPW between the HTH and HCM group. LVMI was greater in the HTH and HCM than in the NT group. There were no differences in LVMI between HTH and HCM subjects.

The PRA values in the HTH, HCM, and NT groups were 0.52 ± 0.46 , 0.34 ± 0.31 , and 0.66 ± 0.65 ng/ml/h, respectively (NS). Plasma norepinephrine levels in the HTH, HCM, and NT groups were 192 ± 162 , 241 ± 151 , and 138 ± 64 pg/ml, respectively (NS).

Cardiac Catheterization and Coronary Flow Measurement

CVR at rest was identical in the HTH and HCM groups (Fig. 1), and in both cases was lower than the resting CVR in NT subjects (Fig. 1). Similarly, CVR at a pacing rate of 100

beats/min was also identical between the HTH and HCM groups, and in both cases was lower than that in the NT group. There were also differences among the three groups in CVRs at a pacing rate of 120 beats/min. The CVR values were lowest in HCM, highest in NT, and intermediary in HTH subjects. There were no differences in CBF at rest or at dilatation using papaverine among the three groups (Table 2). There were no significant differences in the percent increase in CBF at a pacing rate of 100 beats/min among the three groups. However, the percent increase in CBF at a pacing rate of 120 beats/min was higher in the HCM than in either the HTH or NT groups. There was no difference in the percent increase in CBF at that rate between HTH and NT. Repeated measures ANOVA showed that percent increases in CBF using cardiac pacing were due to the disease factor ($p < 0.05$) and the heart rate factor ($p < 0.001$), and both of these factors interacted ($p < 0.01$).

Discussion

The heart becomes hypertrophied in response to various factors, such as genetic, mechanical, and neurohumoral factors. In this study, coronary circulations in subjects with genetic or mechanically induced cardiac hypertrophy were compared under the same neurohumoral circumstances, *i.e.*, the same PRA and plasma norepinephrine levels. The values of CVR at rest in the HTH and HCM subjects in our study were lower than that in the NT group. This finding is compatible with the previous reports. The values of CVR at pacing in our study were lowest in the HCM, highest in the NT, and intermediary in the HTH group. Hypertrophied hearts have been demonstrated to have a higher baseline CBF in order to meet their increased metabolic needs. It is also known that heart rate influences CBF. The larger the LV mass is and the higher the heart rate is, the higher is the CBF. Cardiac pacing is a good method for simulating elevation in heart rate, though the degree of increase in coronary blood flow due to elevation in heart rate caused by cardiac pacing is different from that caused by physical exercise, even if the target heart rate is the same (12). Cardiac pacing is also a good method for precise control of heart rate, when the change in CBF due to increase in heart rate is detected.

The values of CBF at rest were not different among the

Table 2. Coronary Blood Flow

	CBF (ml/min) at rest		% increase CBF	
	At rest	Dilatation	AP100	AP120
HTH	58 ± 6	167 ± 16	7 ± 2	9 ± 2
HCM	49 ± 6	137 ± 20	9 ± 2	17 ± 3
NT	42 ± 4	168 ± 20	4 ± 1	7 ± 1

Data are mean ± SEM. HTH, hypertension with left ventricular hypertrophy; HCM, hypertrophic cardiomyopathy; NT, normotension; CBF, coronary blood flow; % increase CBF, ratio of the increase in CBF from that at rest to that at pacing to CBF at dilatation multiplied by 100; AP100, atrial pacing at 100 beats/min; AP120, atrial pacing at 120 beats/min. Lines indicate significance between groups. * $p < 0.05$.

groups in this study. This may have been due to the large individual differences in coronary artery perfusion area and in cardiac mass size among our subjects. The values of CBF during papaverine-induced dilatation were not different among the groups. The percent increases in CBF from a resting state to a pacing rate of 120 beats/min were higher in the HCM than in the HTH and NT groups. The percent increase in CBF was independently influenced by the nature of the disease and the heart rate, and both factors mutually augmented the increase in CBF. This means that HCM would have a higher coronary blood demand within the limited capability of coronary blood supply compared to HTH when heart rate increases. These results suggest that a different mechanism of coronary circulation is active in individuals with HCM.

In patients with HT, an increase in extravascular compressive forces caused by myocardial hypertrophy results in elevated wall stress and impaired relaxation of vessels, which leads to reduced myocardial blood flow. The luminal area of the intramyocardial coronary artery is reduced, a phenomenon known as "vascular remodeling" (18, 19). Arteriolar wall thickening and perivascular fibrosis have also been reported (20). Moreover, the angiogenesis of coronary resistance arteries may be insufficient compared to the magnitude of cardiac hypertrophy (18). And the diameter of the epicardial coronary artery may be insufficient compared to the LV mass (21). These disorders might be linked to endothelial dysfunction in coronary arteries in patients with cardiac hypertrophy due to HT (22). On the other hand, patients with HCM also show myocardial fibrillar disarray, fibrosis, and an increased interstitial connective tissue element, all of which features are different from those in HT. The occurrence of ischemia in HCM has also been reported to cause remodeling of the coronary micro-circulation. Thus, the impaired coronary circulation in patients with HCM might be due not only to increments in extravascular compression but also to arterioles with decreased lumens due to a congenital structural change in the coronary arterial vascular tree (23, 24). These changes might explain the difference in coronary circulation between the HCM and HTH groups in the present study.

Sudden death occurs in HCM patients. It has been shown

that LV mass weight is not a good indicator of the risk of sudden death in such patients (8, 25, 26), though there is some controversy regarding this conclusion (27). Myocardial ischemia is considered to be one of the most important factors in sudden death of patients with HCM. Increase in daily physical activity elevates heart rate (28). Elevation in heart rate further reduces CVR and intensifies the percent increase in CBF in HCM compared to that in HTH. Our findings might offer one possible reason why sudden death occurs more often in patients with HCM than in those with HTH.

In conclusion, both LVH due to HT and LVH due to HCM reduced CVR at rest in subjects of the present study. Patients in the HCM group more readily developed ischemia than those in the HTH and NT groups when the heart rate increased, though there were remarkable individual differences in the degree of percent increase in CBF and of reduction of CVR. There are thus qualitative differences in the coronary circulation of patients with cardiac hypertrophy depending on the etiology of the disease.

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