Original Article

Effects of Coronary Blood Flow on Left Ventricular Function in Essential Hypertensive Patients

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To elucidate the mechanism of left ventricular dysfunction associated with left ventricular hypertrophy in hypertension, coronary blood flow (CBF) and left ventricular mass (LVM) were measured in 62 patients with essential hypertension (mean age, 54 ± 13 years) and 22 normotensive control subjects (mean age, 57 ± 13 years). According to the indicator fractionation principle, CBF/cardiac output (CO), estimated on the basis of the ratio of myocardial uptake/total injected dose of thallium-201 (% cardiac uptake), was measured. CBF and CBF per 100 g of myocardium (unit CBF) were calculated according to the following formulas: $\text{CBF} = \% \text{ cardiac uptake} \times \text{CO}$, and $\text{unit CBF} = (\text{CBF}/\text{LVM}) \times 100$, where CO and LVM are echocardiographically determined. Midwall fractional shortening (FS) and isovolumic relaxation time (IRT) were calculated as the indices of systolic and diastolic functions. CBF was greater in hypertensives than in controls (218.2 ± 74.0 vs. 187.4 ± 40.4 ml/min, $p < 0.05$), though unit CBF was smaller in hypertensives than in controls (99.1 ± 22.0 vs. 141.2 ± 31.6 ml/min/100 g, $p < 0.0001$). Multiple regression analyses showed that unit CBF was the most potent predictor of both midwall FS and IRT. A positive correlation was found between midwall FS and unit CBF ($r = 0.669$, $p < 0.0001$), and a negative correlation between IRT and unit CBF ($r = -0.579$, $p < 0.0001$). In conclusion, myocardial ischemia reflected by the decrease in unit CBF may be closely related to left ventricular dysfunction in patients with essential hypertension.

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Key Words: coronary blood flow, thallium-201 myocardial scintigraphy, left ventricular function, left ventricular hypertrophy, essential hypertension

Introduction

Left ventricular hypertrophy is known to be an independent risk factor for cardiovascular events (1, 2). In fact, a recent study confirmed that the probability of event-free survival was significantly lower in patients with large left ventricular mass (LVM) than in those with normal LVM, and that it was markedly improved by the regression of LVM (3). In addition, it is also well known that left ventricular functions in hypertensive patients are deteriorated in association with the presence of left ventricular hypertrophy (4-9). However, the exact reasons why left ven-

tricular hypertrophy is closely related to cardiac events or left ventricular dysfunction have remained to be determined. Many studies have suggested that myocardial ischemia associated with left ventricular hypertrophy is related to left ventricular dysfunction in patients with hypertension, and that coronary blood flow (CBF) reserve is also reduced in hypertensive patients (10-17). However, because of the complexity and invasiveness of conventional techniques for measurement of CBF, only several studies have quantified CBF in patients with hypertension (10, 11, 14, 17-19). Thus, most studies did not evaluate CBF reserve by measuring absolute volumetric flow, but by measuring flow velocity. In addition, to our knowl-

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edge, very few studies have appeared that focus on the effects of CBF on left ventricular function in patients with hypertension.

Recently, we reported that CBF can be measured non-invasively by using a combination of thallium-201 myocardial scintigraphy and echocardiography (19). In addition, CBF measured by this noninvasive method correlates well with measurement by the invasive method (19). Further, CBF noninvasively determined by our method closely approximates previously reported data, which were determined by the invasive method (20). Thus, the purpose of this study was to elucidate the effects of CBF on left ventricular systolic and diastolic functions in patients with essential hypertension.

Methods

Study Population

The study group was comprised of 84 subjects who were admitted to our clinic, and the subjects were divided into 2 groups: 62 patients with essential hypertension (22 women and 40 men) and 22 normotensive control subjects (8 women and 14 men). Hypertension was defined as systolic pressure ≥ 140 mmHg, diastolic pressure ≥ 90 mmHg, or both, in the outpatient clinic (21). Patients who had secondary hypertension, coronary artery disease, valvular heart disease, congestive heart failure, cardiomyopathy, diabetes mellitus, or bundle branch block were excluded from this study. Fifteen patients in the hypertensive group received cardiac catheterization because of chest pain; their coronary arteriograms showed no significant stenosis and a negative response to vasospastic stimuli. The mean age of the hypertensive group was 54 ± 13 years.

Twenty-two age- and sex-matched normotensive subjects who had no history of hypertension served as controls. This group consisted of 17 patients who had chest pain of unknown etiology, angiographically normal coronary arteries, and no evidence of coronary artery spasm, and 5 patients who had no cardiac symptoms, normal left ventricular function on echocardiography, and no ST-T change during treadmill exercise testing. The mean age of the control group was 57 ± 13 years.

All subjects received a diet containing 7 g of NaCl per day, and all medications taken prior to admission were discontinued. After a one- or two-week stabilization period, echocardiographic and thallium-201 myocardial scintigraphic examinations were performed.

Informed consent to participation in this study was obtained from each patient.

Echocardiographic Measurements

Two-dimensional guided M-mode and pulsed Doppler

echocardiographic studies were performed using an SSD-9000 echocardiograph with a 3.5-MHz transducer (Aloka Inc., Tokyo, Japan). Left ventricular end-diastolic and end-systolic dimensions, interventricular septal thickness, and left ventricular posterior wall thickness were measured in accordance with the recommendations of the American Society of Echocardiography (22). LVM was calculated according to the method of Devereux and Reichek (23), and was divided by body surface area to obtain LVM index. Relative wall thickness and left ventricular endocardial fractional shortening (FS) were calculated by standard formulas. According to the method of Shimizu *et al.* (6) and de Simone *et al.* (9), we calculated the left ventricular midwall FS to obtain a more sensitive evaluation of left ventricular systolic function. As an index of left ventricular diastolic function, isovolumic relaxation time (IRT) was calculated as the time from the closure of the aortic valve to the onset of mitral inflow. In addition, cardiac output (CO) was determined by using the formula of Teichholz *et al.* (24). Echocardiographic studies were performed within 2 days of thallium-201 myocardial scintigraphic studies.

Thallium-201 Myocardial Scintigraphy and CBF Measurements

All subjects underwent resting thallium-201 myocardial scintigraphy as previously reported (19, 25). Myocardial scintigraphic system (GCA 9300; Toshiba, Tokyo, Japan, and Scintipac 2400; Shimadzu, Kyoto, Japan) consisted of a triple-headed digital gamma camera equipped with high-resolution, low-energy, parallel-hole collimators. On the day of thallium-201 myocardial scintigraphy, subjects were instructed to have no breakfast and to continue fasting until the end of the last imaging session. Ten minutes after and 5 h after intravenous injection of thallium-201, early and delayed single photon emission computed tomographic (SPECT) images were obtained, respectively. A region of interest (ROI) was set on the whole heart, and a rectangular ROI, usually 10×20 pixels in size, was placed on the left upper lung in the anterior projection image obtained by the SPECT study.

CBF was determined as reported previously (19). In brief, initial % cardiac uptake, which indicates CBF/CO ratio (26), was calculated by the following formula: % cardiac uptake (%) = (myocardial uptake of thallium-201/total injected dose of thallium-201) $\times 100$. Myocardial uptake of thallium-201 was measured to subtract lung counts from whole heart counts in ROI on the anterior projection image. The subtracted lung counts were calculated using the lung counts in ROI on the anterior projection image and the lateral length of the lung behind the heart. The count of the heart was converted from counts to MBq using the cross-calibration factor. The total injected dose (MBq) in each subject was calculated on the basis of

Table 1. Clinical Characteristics of Study Subjects

Parameters	Normotensive control subjects (<i>n</i> =22)	Essential hypertensive patients (<i>n</i> =62)	<i>p</i>
Age (years)	57±13	54±13	NS
Sex (Male/Female)	14/8	40/22	NS
Body surface area (m ²)	1.63±0.19	1.68±0.20	NS
Body mass index (kg/m ²)	23.7±1.7	24.7±4.1	NS
Total cholesterol (mmol/l)	5.25±0.72	5.25±0.95	NS
HDL cholesterol (mmol/l)	1.21±0.38	1.11±0.33	NS
Triglycerides (mmol/l)	1.49±0.75	1.57±0.75	NS
Smoking (%)	50	55	NS
Heart rate (bpm)	66±10	71±9	<0.05
Systolic BP (mmHg)	122±11	165±21	<0.0001
Diastolic BP (mmHg)	72±7	98±15	<0.0001
RPP (bpm×mmHg)	8,034±1,644	11,706±2,242	<0.0001

Values are mean±SD. HDL, high density lipoprotein; bpm, beats per min; BP, Blood pressure; RPP, rate-pressure product.

Table 2. Echocardiographic and Scintigraphic Data

Parameters	Normotensive control subjects (<i>n</i> =22)	Essential hypertensive patients (<i>n</i> =62)	<i>p</i>
LVDd (mm)	49.6±3.2	50.6±4.6	NS
LVDs (mm)	30.0±3.0	33.2±4.6	<0.001
LVM index (g/m ²)	89±19	135±45	<0.0001
Relative wall thickness	0.32±0.03	0.42±0.10	<0.0001
Endocardial FS (%)	39.4±5.1	34.5±5.5	<0.0005
Midwall FS (%)	21.4±2.3	16.5±3.0	<0.0001
IRT (ms)	76±12	104±16	<0.0001
Cardiac index (l/min/m ²)	3.46±0.63	3.00±0.54	<0.005
% Cardiac uptake (%)	3.59±0.64	4.34±1.16	<0.0005
CBF (ml/min)	187.4±40.4	218.2±74.0	<0.05
Unit CBF (ml/min/100 g)	141.2±31.6	99.1±22.0	<0.0001

Values are mean±SD. LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension.

the difference between the radioactivities of the syringe before and after injection. Next, CBF was determined by the following formula: CBF (ml/min) = % cardiac uptake × CO. In addition, CBF per unit of 100 g of myocardium (unit CBF) was also calculated by the following formula: unit CBF (ml/min/100 g) = (CBF/LVM) × 100.

Statistical Analysis

Data are expressed as mean±SD in the text and tables. A χ^2 analysis was used to detect differences in categorical variables. An unpaired *t*-test was used to assess differences in continuous variables. Correlation coefficients were calculated by linear regression analysis. Multiple regression analysis was applied for analysis of the dependency between variables. A value of *p* < 0.05 was considered statistically significant.

Results

Clinical Profiles of the Subjects

Table 1 shows the clinical characteristics of the study subjects. No significant differences were observed in age, sex, body surface area, body mass index, serum lipid levels, or smoking habits between the two groups. Heart rate was slightly, but significantly, higher in patients with essential hypertension than in normotensive control subjects. Rate-pressure product was significantly higher in hypertensives than in controls.

Echocardiographic and Scintigraphic Data

As shown in Table 2, no significant difference was ob-

Table 3. Multiple Regression Analyses of Independent Variables of Midwall FS and IRT

Independent variables	Midwall FS			IRT		
	Standard coefficient (β)	SE	<i>p</i>	Standard coefficient (β)	SE	<i>p</i>
Age	-0.041	0.018	0.5429	0.220	0.126	0.0097
Heart rate	-0.099	0.024	0.1291	-0.097	0.162	0.2334
Systolic blood pressure	0.129	0.017	0.3123	0.114	0.115	0.4772
Diastolic blood pressure	-0.312	0.025	0.0162	0.381	0.172	0.0190
LVM index	-0.149	0.008	0.1313	-0.083	0.054	0.5007
Relative wall thickness	-0.335	3.496	0.0006	0.220	23.942	0.0647
Unit CBF	0.374	0.008	<0.0001	-0.317	0.057	0.0007

Midwall FS: $R^2=0.724$, $p<0.0001$. IRT: $R^2=0.567$, $p<0.0001$.

Fig. 1. Relationship between midwall FS and unit CBF (upper panel) and relationship between IRT and unit CBF (lower panel).

served in left ventricular end-diastolic dimension between the two groups, though left ventricular end-systolic dimension was greater in essential hypertensive patients than in normotensive control subjects. LVM index and relative wall thickness were significantly greater in hypertensives than in controls. Both endocardial FS and midwall FS were significantly depressed in hypertensives. IRT

was significantly greater in hypertensives than in controls. Cardiac index was significantly smaller in hypertensives than in controls.

Both % cardiac uptake and CBF were significantly greater in hypertensives than in controls, though unit CBF was significantly smaller in hypertensives than in controls. In addition, CBF correlated positively with LVM ($r=0.757$, $p<0.0001$), and unit CBF correlated negatively with LVM ($r=-0.520$, $p<0.0001$).

Multiple Regression Analyses of the Independent Predictors of Left Ventricular Functions

Table 3 indicates the results of multiple regression analyses assessing the association of shown variables with midwall FS and IRT. The most potent predictor of midwall FS was unit CBF, followed by relative wall thickness, then diastolic blood pressure; the other variables had no significant influence. The upper panel of Fig. 1 shows the correlation between midwall FS and unit CBF in all subjects, and a good correlation was found between these two variables. In addition, a positive correlation was found between endocardial FS and unit CBF ($r=0.487$, $p<0.0001$).

As shown in Table 3, the most potent predictor of IRT was unit CBF, followed by age, then diastolic blood pressure. As shown in the lower panel of Fig. 1, a negative correlation was found between IRT and unit CBF.

Discussion

Multiple regression analyses in the present study indicate that unit CBF was the most potent predictor of both left ventricular systolic and diastolic functions in patients with essential hypertension. Thus, a good positive correlation was found between midwall FS and unit CBF, and a good negative correlation between IRT and unit CBF. Diastolic blood pressure was also a significant predictor in both left ventricular systolic and diastolic functions. In left ventricular systolic function, relative wall thickness was

another potent predictor, while in diastolic function age was another potent predictor. However, our findings indicate that myocardial ischemia associated with the progression of left ventricular hypertrophy is mainly responsible for both left ventricular diastolic and systolic dysfunctions in hypertension.

Several methods such as thermodilution (11), gas clearance method (10, 14, 18), coronary Doppler catheter (12, 13), coronary Doppler guide wire (16), and positron emission tomography (17) have been established for measuring CBF reserve. However, most of these methods are invasive (10-14, 16, 18) or not in general use (17). Consequently, it is very difficult to measure CBF in hypertensive patients. Very recently, we reported that a combination of thallium-201 myocardial scintigraphy and echocardiography could exactly quantify CBF noninvasively (19). In the present study, using this method, we studied the relation between CBF and left ventricular function in patients with essential hypertension.

In the previous study, we found that CBF was greater in hypertensive patients than in control subjects, though unit CBF was smaller in hypertensive patients, even at rest, than in control subjects (19). Nichols *et al.* (18) and Johnson *et al.* (27) demonstrated that resting unit CBF was smaller in patients with hypertension and aortic stenosis than in normal controls. Gimelli *et al.* (17) concluded that there was no significant difference in unit CBF determined by positron emission tomography between hypertensive patients and normal controls, but the mean value of unit CBF was about 20% higher in normal controls than in hypertensive patients. Several reports have shown that unit CBF in patients with hypertension is normal (10, 11, 17). In view of the findings that unit CBF decreases according to increase in LVM, the relatively small value of LVM is responsible for the discrepancy. In fact, Pichard *et al.* (28) reported that CBF per 100 g of myocardium in patients with ventricular hypertrophy remained normal, whereas the calculated unit CBF was 116.3 ml/min/100 g in the control group, 92.1 in the mild hypertrophy group, and 83.4 in the severe hypertrophy group.

The increased incidence of ischemic heart disease, left ventricular dysfunction, and congestive heart failure in hypertensive patients with left ventricular hypertrophy is well recognized. Moreover, it is well acknowledged that left ventricular hypertrophy in arterial hypertension is characterized by myocyte hypertrophy, myocardial fibrosis, and structural changes of the intramural coronary arteries (29). These changes suggest that left ventricular hypertrophy associated with hypertension is not simply an adaptive process, but a pathological process. In fact, left ventricular hypertrophy in hypertension is accompanied by marked diastolic dysfunction, and in this regard it differs from left ventricular hypertrophy in athletes (30). The reactive and reparative fibrosis that occurs mainly

with renin-angiotensin-aldosterone system activation seems to contribute much to left ventricular diastolic dysfunction (31). Left ventricular systolic dysfunction may be due to the change of structural and functional factors such as cardiac myocyte growth and death, and impaired endothelial-dependent coronary vasodilation, both of which result in the impairment of CBF reserve.

The present study clearly shows that unit CBF is closely related to left ventricular systolic dysfunction in patients with essential hypertension. Previous studies have shown that endocardial FS was less sensitive to evaluation of left ventricular contractility in hypertension than to that of the midwall FS (6, 9). Thus, in this study, we evaluated both endocardial FS and midwall FS as indices of systolic function. Based on the good positive correlation between midwall FS and unit CBF, left ventricular systolic function appears mainly dependent on the severity of myocardial ischemia. According to a study by Polese *et al.* (32), normotensive controls and hypertensive patients without left ventricular hypertrophy are able to maintain CBF by the maneuver of rapid decrease in coronary perfusion pressure, though CBF in hypertensive patients with left ventricular hypertrophy is markedly diminished. These results suggest that the myocardium in hypertensive patients with left ventricular hypertrophy is vulnerable to treatment-induced relative hypotension. Johnson *et al.* (27) also indicated that a marked decrease in unit CBF associated with left ventricular hypertrophy was closely related to myocardial contractility in patients with aortic stenosis. Thus, persistent myocardial ischemia associated with myocardial hypertrophy may be closely related to the systolic dysfunction in hypertensive patients. Previously, we indicated that midwall FS was less in patients with concentric hypertrophy than in patients with eccentric hypertrophy, despite the same LVM index between the two groups (33). In view of this finding, it is reasonable to assume that relative wall thickness is a significant predictor of midwall FS in hypertension.

In previous studies, we reported that left ventricular diastolic dysfunction in hypertension was more severely damaged in the isovolumic phase than in the rapid filling phase (34), and that IRT prolongation was observed even in hypertensive patients without left ventricular hypertrophy (7). Thus, in this study, we measured IRT as an index of left ventricular diastolic dysfunction. As was observed in the case of systolic function, unit CBF was the most potent predictor of IRT prolongation in hypertensive patients. This finding suggests that myocardial ischemia may be one of the important factors for the increase in fibrillar collagen volume fraction, which is closely related to left ventricular diastolic dysfunction. Though qualitatively different from systolic function, age is another potent predictor of IRT prolongation. We previously reported that LVM index increased according to age (35). In addition, Czernin *et al.* (36) reported that according to

the increase of age, resting CBF increased, while CBF reserve decreased. In view of these findings, aging also seems to accelerate myocardial ischemia.

Our results may explain the chest pain observed in hypertensive patients with normal epicardial coronary arteries, and the fact that LVM can be a strong risk factor of cardiovascular events. In a previous study, we showed that the regression of LVM may be associated with improved unit CBF in hypertension (19). Thus, we must choose antihypertensive drugs that have strong functions not only of lowering blood pressure but also of attenuating myocardial hypertrophy.

The present study has several limitations. First, CBF in our study includes both left and right ventricles, although only muscle mass of the left ventricle was measured. Thus, unit CBF in our study is slightly overestimated. Second, there is a time difference between the determinations of % cardiac uptake by thallium-201 myocardial scintigraphy and CO by echocardiography. However, in view of the fact that % cardiac uptake remains unchanged for at least 40 days after the first measurement (19), this difference is negligible. Third, several studies have reported the improvement of CBF reserve by antihypertensive treatment (13, 14), and 60% of the patients in our series had received antihypertensive therapy before the time of our study. Though Motz and Strauer (14) reported finding no significant change in unit CBF before and after long-term antihypertensive treatment with an angiotensin-converting enzyme inhibitor, unit CBF may have been slightly overestimated in this 60% of the our hypertensive patients.

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