The Influence of Left Ventricular Geometry on Coronary Vasomotion in Patients With Essential Hypertension

Michihito Sekiya, Junichi Funada, Jun Suzuki, Kouki Watanabe, Masao Miyagawa, and Hiroshi Akutsu

The objective of this study was to assess the influence of left ventricular (LV) geometric pattern on coronary vasomotion in patients with essential hypertension. We studied 34 hypertensive patients, who had never been treated, with angiographically normal coronary arteries. Patients were classified into four LV geometric patterns by echocardiography: normal, concentric remodeling, eccentric hypertrophy, and concentric hypertrophy. The responses of coronary vasomotion in left anterior descending artery to vasoactive agents (acetylcholine, isosorbide dinitrate, adenosine triphosphate) were examined using a Doppler guidewire and quantitative coronary angiography. The percent increase in coronary blood flow evoked with acetylcholine (endothelium-dependent vasomotion) showed lowest in concentric hypertrophy, followed by eccentric hypertrophy, concentric remodeling, and normal geometry. The significant linear relationship between acetylcholine-induced coronary blood flow and LV mass was noted. There was no difference in the percent increase in coronary blood flow evoked with isosorbide dinitrate (endothelium-independent vasomotion of conduit vessel) among the four groups. The percent increase in coronary blood flow evoked with adenosine triphosphate (endothelium-independent vasomotion of resistant vessel) was significantly lower in patients with concentric hypertrophy than in the other three groups. The results in this study suggest that coronary vasomotion may be associated with LV geometry in patients with hypertension. The endothelium-dependent vasodilation is impaired progressively as LV hypertrophy advances. The endothelium-independent vasodilation of microvessels is impaired only in concentric hypertrophy. This advanced abnormality of coronary vasomotion may contribute to the high cardiovascular morbidity and mortality in patients with concentric hypertrophy.

KEY WORDS: Coronary vasomotion, hypertension, left ventricular geometry, left ventricular hypertrophy.

The subjects consisted of 34 patients as determined by echocardiography. In addition to blood pressure, circulating hormones such as angiotensin II and catecholamine may also induce not only LV hypertrophy but also an intrinsic abnormality of the coronary vasculature. In the present study, was thus conducted to examine coronary vasomotion in patients with essential hypertension using a Doppler flow-wire technique and quantitative coronary angiography, to assess its association with LV geometry as determined by echocardiography.

**MATERIALS AND METHODS**

**Study Patients** The subjects consisted of 34 patients with essential hypertension aged 49 to 72 years (mean ± SD, 57 ± 7 years) undergoing diagnostic coronary angiography for evaluation of chest pain. All patients had angiographically normal coronary arteries without luminal irregularities and no coronary spasm (≤ 50% decrease in coronary diameter from baseline) during intracoronary infusion of acetylcholine (ACh). Hypertension was defined as systolic blood pressure at the outpatient department of ≥ 160 mm Hg and/or diastolic blood pressure of ≥ 95 mm Hg in the sitting position on at least three separate visits. In addition, hypertension was recently diagnosed in all patients who had never been treated. Twelve age-, gender-, and risk factor-matched normotensive individuals were employed as controls. Patients with secondary hypertension, preexisting cardiac disease, preexisting medical illnesses that affect longevity such as diabetes mellitus, hypercholesterolemia, heavy smoking (defined as smoking ≥ 60 cigarettes daily within 1 month before the study), patients aged ≥ 75 years, and patients without sufficient echocardiographic windows for the measurement of left ventricular mass, were excluded from the analysis. We also excluded patients with hypertrophic cardiomyopathy, defined by a ratio of septal to posterior wall thickness ≥ 1.5, with posterior wall thickness ≥ 1.2 cm. Informed consent was obtained from all subjects before the study. The study was conducted in agreement with the guidelines approved by the ethics committee at our institution. Vasoactive agents were discontinued 12 to 24 h before catheterization. All smokers had quit smoking at least 5 days before the study.

**Echocardiography** M-mode echocardiography was performed with commercially available echocardiography using 2.25- to 3-MHz transducers (Toshiba Inc., Tokyo, Japan). Tracings were recorded under two-dimensional guidance, and measurements were taken at the tip of the mitral valve or just below that point. Measurements were made according to the American Society of Echocardiography guidelines using a leading edge to leading edge convention. LV internal dimension, septal thickness, and LV posterior wall thicknesses were measured at end-diastole, as defined by the onset of the QRS complex. The LV mass was measured at end-diastole by the formula developed by Devereux et al: 0.80 × 1.05 ([LV internal diameter + LV septal thickness + posterior wall thickness]3 – [LV internal diameter]3) + 0.6. The LV mass index was calculated by dividing LV mass by body surface area to adjust for body size. Relative wall thickness (RWT) was measured at end-diastole as the ratio of 2 × (LV posterior wall thickness/LV internal dimensions). A value of ≥ 0.45 was defined as abnormal. The study patients were classified into four types based on the LV mass index and RWT by the cutoffs developed in the Framingham Heart Study: 1) normal (n = 14; LV mass index < 131 g/m² for men; < 100 g/m² for women, RWT < 0.45); 2) concentric LV remodeling (n = 6; LV mass index < 131 g/m² or 100 g/m², RWT ≥ 0.45); 3) concentric hypertrophy (n = 6; LV mass index ≥ 131 g/m² or 100 g/m², RWT ≥ 0.45); and 4) eccentric hypertrophy (n = 8; LV mass index ≥ 131 g/m² or 100 g/m², RWT < 0.45). Echocardiographic readings were made in random order by an investigator who had no knowledge of coronary vasomotion study.

**Protocol** After 15 min of rest after the diagnostic cardiac catheterization for suspected coronary artery disease, a 0.014-inch wire equipped with a Doppler crystal at its tip (Flowire, Cardiometrics, Inc, Mountain View, CA) was introduced into the left anterior descending coronary artery through a coronary angiography catheter and positioned in a straight proximal part. An optimal Doppler signal was obtained by moving the guidewire slightly within the vessel lumen and adjusting the range gate control. Doppler signals were recorded at rest and during hyperemia on videotape and by a videoprinter, along with an electrocardiogram and aortic pressure tracing. Frequency analysis of the Doppler signals was carried out in real time by fast-Fourier transform using a velocimeter (FloMap, Cardiometrics, Inc.). At baseline, mean arterial pressure and coronary flow velocity were recorded. Coronary arteriography was performed with
cinearteriography. The preliminary study was performed before the present study. ACh was assessed at 0.5, 5.0, 50, and 100 μg/min for induction of increase in coronary blood flow in normal subjects. Maximum induction of increase in blood flow was attained at 50 μg/min with ACh. According to previous studies in a Japanese population and our preliminary study, ACh was infused subselectively into study vessel at a rate of 50 μg/min for 1 min. Next, when hemodynamic variables returned to baseline values, isosorbide dinitrate was infused through the coronary catheter at a dose of 30 mg/min for 1 min. Finally, adenosine triphosphate (ATP) at a dose of 50 μg/min was introduced. Throughout each infusion, mean arterial pressure and coronary flow velocity were monitored continuously, and all measurements were recorded in steady-state conditions. Coronary angiograms were done 30 s after inducing maximal flow increases by injection of each agent. Analysis of coronary arterial dimension was made quantitatively at the portion corresponding to the tip of the Doppler guidewire where flow velocity was recorded, using a coronary arteriographic analysis system (DAR-2400; Shimazu Corp., Kyoto, Japan). To estimate volumetric coronary blood flow, coronary blood flow (mL/min) was calculated by the following formula: 0.5 × average peak velocity (cm/sec) × cross-sectional area (cm²). By setting the baseline coronary blood flow at 100%, maximal percent increase for intracoronary infusion of each stimulant was determined (maximal blood flow/baseline blood flow × 100). The measurements of diameter and blood flow velocity at the segment of interest were performed by two observers blinded to the study protocol.

### Statistical Analysis

The data are expressed as means ± SD. The statistical comparisons were performed by two-way analysis of variance followed by Tukey’s multiple range test. The statistical significance was defined as P < .05.

### RESULTS

The clinical characteristics of study patients are shown in Table 1. The arithmetic mean of the last two measurements of blood pressure was calculated. Systolic and diastolic blood pressures were significantly higher in hypertensive patients with concentric or eccentric hypertrophy than in those with normal morphology and concentric remodeling, but there were no significant differences in age, gender, body structure, serum total cholesterol, and other risk factors among the four groups. The echocardiographic data of the study patients with hypertension are listed in Table 2. The LV cavity size was significantly smaller in concentric remodeling and larger in eccentric hypertrophy than in normal geometry. The LV septal and posterior walls were significantly thicker in concentric remodeling, eccentric, and concentric hypertrophy than in normal geometry. The LV mass index showed higher in hypertensive patients with concentric or eccentric hypertrophy than in those with normal morphology.
controls, but decreased by 2*P, 5
Pre-CBF
Acetylcholine 24%, and response to ACh increased by 2 three groups. The epicardial coronary diameters in with concentric hypertrophy than those in the other
evoked with ATP was significantly lower in patients among the four groups. The percent increase in CBF increases in CBF evoked with isosorbide dinitrate linear relation between this percent increase and LV hypertrophy. There was a significant
ing, and normal geometry. There was a significant
troph subjects than in hypertensive patients. The percent
‡P

TABLE 2. ECHOCARDIOGRAPHIC DATA OF STUDY PATIENTS

<table>
<thead>
<tr>
<th>Patients Groups</th>
<th>Normal Geometry (n = 14)</th>
<th>Concentric Remodeling (n = 6)</th>
<th>Eccentric Hypertrophy (n = 8)</th>
<th>Concentric Hypertrophy (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>65 ± 9</td>
<td>68 ± 10</td>
<td>62 ± 8</td>
<td>64 ± 7</td>
</tr>
<tr>
<td>LVDD, mm</td>
<td>47 ± 4</td>
<td>42 ± 3*</td>
<td>52 ± 3†</td>
<td>46 ± 3§</td>
</tr>
<tr>
<td>LVDs, mm</td>
<td>30 ± 3</td>
<td>27 ± 4*</td>
<td>32 ± 3†</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>IVST, mm</td>
<td>8.5 ± 1.5</td>
<td>10.2 ± 1.6*</td>
<td>10.4 ± 1.0*</td>
<td>12.4 ± 1.6§§</td>
</tr>
<tr>
<td>PWT, mm</td>
<td>8.0 ± 1.5</td>
<td>10.6 ± 1.2*</td>
<td>10.3 ± 1.0†</td>
<td>12.0 ± 1.0§§</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>89 ± 12</td>
<td>98 ± 14†</td>
<td>135 ± 16*</td>
<td>145 ± 17†</td>
</tr>
<tr>
<td>RWT</td>
<td>0.34 ± 0.07</td>
<td>0.50 ± 0.03*</td>
<td>0.38 ± 0.04‡</td>
<td>0.52 ± 0.04**</td>
</tr>
<tr>
<td>EF, %</td>
<td>68 ± 7</td>
<td>69 ± 8</td>
<td>66 ± 7</td>
<td>65 ± 10</td>
</tr>
<tr>
<td>%FS, %</td>
<td>36 ± 5</td>
<td>36 ± 4</td>
<td>37 ± 5</td>
<td>35 ± 5</td>
</tr>
</tbody>
</table>

HR = heart rate; LVDD = left ventricular diastolic dimension; LVD = left ventricular systolic dimension; IVST = interventricular septal thickness; PWT = posterior wall thickness; LVMI = left ventricular mass index; RWT = relative wall thickness; EF = ejection fraction; %FS = fractional shortening.

* P < .01, † P < .05 v normal geometry; ‡ P < .01, || P < .05, v concentric remodeling; ** P < .01, §§ P < .05, v eccentric hypertrophy.

Acetylcholine was significantly higher in normal control subjects than in hypertensive patients. The percent increases in CBF evoked with ACh in hypertensive patients were lowest in concentric hypertrophy, followed by eccentric hypertrophy, concentric remodeling, and normal geometry. There was a significant linear relation between this percent increase and LV mass (Fig. 1). There were no differences in the percent increases in CBF evoked with isosorbide dinitrate among the four groups. The percent increase in CBF evoked with ATP was significantly lower in patients with concentric hypertrophy than those in the other three groups. The epicardial coronary diameters in response to ACh increased by 2 ± 7% in normal controls, but decreased by -3 ± 2%, -5 ± 3%, -10 ± 4%, and -15 ± 5% in hypertensive patients with normal geometry, concentric remodeling, eccentric hypertrophy, and concentric hypertrophy, respectively. Those in response to isosorbide dinitrate or ATP showed no significant differences among the four hypertensive groups.

DISCUSSION

The results in this study suggest that the regulatory functions of coronary vasomotion may be associated with LV geometry in patients with hypertension. The endothelium-dependent vasodilation is impaired progressively as LV hypertrophy advances. Nonetheless, endothelium-independent vasodilation of the coronary microvessel was impaired only in patients with concentric hypertrophy. Thus, the severe coronary endothelial dysfunction and abnormality of coronary mi-

TABLE 3. RESPONSES OF CORONARY BLOOD FLOW IN PATIENTS WITH HYPERTENSION

<table>
<thead>
<tr>
<th>Patients Groups</th>
<th>Normal Geometry (n = 14)</th>
<th>Concentric Remodeling (n = 6)</th>
<th>Eccentric Hypertrophy (n = 8)</th>
<th>Concentric Hypertrophy (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>59.2 ± 10.0</td>
<td>57.8 ± 12.0</td>
<td>56.6 ± 10.2</td>
<td>56.2 ± 11.8</td>
</tr>
<tr>
<td>Increase in CBF, %</td>
<td>302 ± 20</td>
<td>258 ± 15*</td>
<td>208 ± 17**†</td>
<td>125 ± 15**†§§</td>
</tr>
<tr>
<td>Isosorbide dinitrate:</td>
<td>59.6 ± 9.8</td>
<td>58.6 ± 11.2</td>
<td>58.0 ± 11.2</td>
<td>57.8 ± 10.8</td>
</tr>
<tr>
<td>Increase in CBF, %</td>
<td>332 ± 32</td>
<td>326 ± 40</td>
<td>318 ± 38</td>
<td>322 ± 32</td>
</tr>
<tr>
<td>Adenosine triphosphate:</td>
<td>60.6 ± 10.8</td>
<td>59.0 ± 11.8</td>
<td>58.8 ± 9.0</td>
<td>58.2 ± 12.2</td>
</tr>
<tr>
<td>Increase in CBF, %</td>
<td>312 ± 28</td>
<td>285 ± 38</td>
<td>302 ± 28</td>
<td>219 ± 26**†§§</td>
</tr>
</tbody>
</table>

Pre-CBF = coronary blood flow before the infusion of each vasoactive agent.

* P < .05, ** P < .01 v normal geometry; † P < .05, ‡ P < .01 v concentric remodeling; § P < .05, §§ P < .01 v eccentric hypertrophy.
Crovascular dilatation coexist in hypertensive patients with concentric hypertrophy. This advanced abnormality of coronary vasomotion may contribute to the high cardiovascular morbidity and mortality in concentric hypertrophy.

The endothelium has been shown to exert its vasoregulatory action by releasing a substance (nitric oxide) that induces smooth-muscle relaxation by increasing the production of intracellular cyclic guanosine monophosphate. Vasodilation in response to ACh is considered to represent normal endothelial function, and constriction or reduced dilation to be a sign of dysfunctional endothelium. The coronary endothelial function was progressively impaired as LV hypertrophy advanced, and might depend mainly on LV mass rather than RWT. The cardiac hypertrophy in hypertension was promoted pathologically by blood pressure as well as by neurohormonal factors such as the tissue renin-angiotensin system and sympathetic nerve function. Such hormones generate superoxide anion (oxidative stress) through stimulation of the NADH/NADPH oxidase at the coronary endothelium, which can degrade nitric oxide from endothelial cells. Shigematsu et al reported that the renin-angiotensin system was most activated in hypertensive Japanese patients with concentric hypertrophy. Kuwabara et al. indicated that cardiac sympathetic nerve function might be stimulated as LV hypertrophy increased in Japanese patients with hypertension. Thus, the renin-angiotensin system as well as sympathetic nerve function might be stimulated strongly in concentric hypertrophy, resulting in advanced endothelial dysfunction. Impaired endothelial function is intimately involved in the pathogenesis of atherosclerosis, and contributes to vasospasm, myocardial ischemia, and rupture of plaque, resulting in cardio-vascular events. Thus, patients with LV geometry with concentric hypertrophy might be at the highest risk for coronary artery disease.

The effect of isosorbide dinitrate produces vasodilation by direct activation of guanylate cyclase in vascular smooth-muscle cells (endothelium-independent vasodilator) of epicardial artery. This action showed no differences among the patient groups. Accordingly, the endothelium-independent vasodilator of epicardial artery might be not affected by the LV geometry pattern. Different from isosorbide dinitrate, ATP is metabolized rapidly and its degradation product, adenosine, can induce coronary vasodilation of resistant vessel (microvessel) through activation of purine receptors (A1 and A2 membrane adenosine receptors). The CBF response to ATP is accepted to be reflected by microvessel vasodilator capacity, that is, coronary flow reserve. Microvessel vasodilation was affected mainly by extrinsic vascular compression and inadequate microvascular growth relative to increased LV mass. In this study, coronary flow reserve was reduced in patients with concentric hypertrophy, but preserved in those with the other types of LV geometry despite the presence of LV hypertrophy. Previous reports have demonstrated that LV hypertrophy is associated with a limitation in coronary flow reserve. This might be due to the following reason. ATP causes vasodilation of the microvessel, resulting in augmentation of coronary blood flow. As the epicardial coronary endothelium produces nitric oxide in response to augmentation of coronary blood flow (shear stress), endothelial dysfunction fails to make adequate increase of coronary blood flow. Therefore, the coronary flow reserve of patients in previous reports was apparently reduced by endothelial dysfunction. In this study protocol, as the evaluation of CBF response to ATP was done after the administration of isosorbide dinitrate, endothelial dysfunction of epicardial vessel might be abolished. Thus, despite LV hypertrophy, microvessel vasodilator capacity may really be preserved in concentric remodeling or eccentric hypertrophy. Houghton et al reported that there was no statistically linear relation between LV mass index and coronary flow reserve, suggesting that the relationship is more complex and that coronary flow reserve was affected by myocardial structure or function. All patients in this study showed normal LV function, so myocardial structure might be one cause of reduced coronary flow reserve. Tadaoka et al also reported that the coronary flow reserve decreased with RWT and its possible mechanisms were excessive extravascular compression and delayed early diastolic inflow. In concentric remodeling, CBF response to ATP was preserved despite the same RWT as concentric hypertrophy. Therefore, increased RWT accompanied by

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**FIG. 1.** Regression line between percent increase of CBF with ACh (%) and LV mass index (g/cm²). There was a significant linear relation (r = 0.85, P < .01). CBF = coronary blood flow; ACh = acetylcholine; LV = left ventricular.
large LV mass might reduce the response to ATP (coronary flow reserve).

The limitation of this study is the small number of patients enrolled. Further studies with large numbers of subjects are required.

In conclusion, the regulatory function of the coronary circulation was severely impaired by coronary endothelial dysfunction, as well as reduction of microvessel vasodilator capacity, in hypertensive patients with concentric hypertrophy, compared with hypertensive patients with other morphologies. This may in part be the cause of the high likelihood of dying or having a cardiovascular event in patients with concentric hypertrophy.

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