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Homogeneously Reduced Versus Regionally Impaired Myocardial Blood Flow in Hypertensive Patients: Two Different Patterns of Myocardial Perfusion Associated With Degree of Hypertrophy

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Objectives. **The aim of this study was to quantitatively measure regional and global myocardial blood flow and coronary reserve in hypertensive patients without coronary artery disease and to assess the correlation with left ventricular mass.**

Background. **The effect of left ventricular hypertrophy on regional vasodilating coronary capability in arterial hypertension is controversial, and no quantitative method has been applied to assess a possible correlation.**

Methods. **Positron emission tomography was performed in 50 untreated hypertensive patients and 13 normotensive subjects. Blood flow at baseline and after dipyridamole was globally and regionally measured by using nitrogen-13 ammonia; coronary reserve and resistance were calculated. Left ventricular mass was assessed by two-dimensional echocardiography.**

Results. **In hypertensive patients, flow at baseline was similar to that of normotensive subjects ($p = 0.21$), but values were reduced after pharmacologic vasodilation ($p < 0.05$). This impairment of maximal coronary flow was not correlated with left ventricular mass ($p = 0.13$). Among hypertensive patients, we identified a group with a homogeneous distribution of perfusion and a group with a heterogeneous flow pattern. Flow was globally reduced in the former group, but it was abnormal only at the site of perfusion defects in the latter. Patients with regional defects showed the highest likelihood of having an increased left ventricular mass.**

Conclusions. **In arterial hypertension, left ventricular mass is not correlated with global myocardial blood flow. Nevertheless, patients with ventricular hypertrophy are likely to show a heterogeneous flow pattern with regional defects and almost normal blood flow in nonaffected regions. In hypertensive patients with a homogeneous perfusion pattern during stress, myocardial blood flow frequently shows a diffuse reduction.**

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The presence of an abnormal coronary vasodilator reserve despite angiographically normal coronary arteries in patients with essential hypertension has been demonstrated by various experimental and clinical studies (1–3). To explain this observation, several works attributed this finding to the effects of left ventricular hypertrophy induced by hypertension. Possible mechanisms included an increase in extravascular compressive forces caused by hypertrophy and resulting in elevated systolic/diastolic wall stress and impaired relaxation or structural alterations such as myocyte hypertrophy, interstitial fibrosis and rarefaction of coronary microvasculature leading to reduced myocardial blood flow (MBF) (2).

More recently, it has been shown (1,4) that the impairment of coronary flow reserve in hypertensive patients is not necessarily related to the presence or degree of left ventricular hypertrophy. Vogt et al. (4), by using the argon washout technique and echocardiography, observed in a group of hypertensive patients that myocardial mass and overall minimal coronary vascular resistance were not directly correlated. These data indicated that the impairment of coronary reserve is mainly caused by a reduction in the vasodilating capacity of the coronary resistance vessels rather than by effects linked to hypertrophy alone. This effect may be due to "vascular remodeling," such as media thickening, perivascular fibrosis or functional alterations linked to endothelial dysfunction (5–7).

Houghton et al. (8) performed measurements of coronary flow reserve by Doppler technique in combination with exercise thallium scintigraphy in hypertensive patients. Despite the absence of a linear relation, left ventricular mass index (LVMI) was significantly higher in patients with stress-induced perfusion abnormalities than in patients with a negative thallium study result. Additionally, patients with thallium-201

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Abbreviations and Acronyms

ECG = electrocardiogram, electrocardiographic
LVMI = left ventricular mass index
MBF = myocardial blood flow
PET = positron emission tomography

defects had lower coronary vasodilator reserve. This observation suggests that stress-induced heterogeneity of perfusion is caused by an abnormal vasodilating capacity and leads to a mismatch between oxygen supply and demand in hypertrophic hearts. Nevertheless, the lack of spatial correspondence between intracoronary Doppler flow measurements and the results of thallium-201 scintigraphy, as well as the absence of absolute MBF measurements, hampered the conclusions on the relation among perfusion defects, regional coronary flow reserve and LVMI in that study.

To date, no published studies have evaluated the correlation among absolute regional MBF, impaired coronary flow reserve and LVMI in hypertensive patients, with emphasis on regional flow inhomogeneities. Evaluating regional aspects of flow impairment may help to further elucidate the causes of this phenomenon and thus contribute to a better understanding of the relation between myocardial hypertrophy and regional perfusion. Therefore, aim of the study was to investigate in patients with essential hypertension the relation between absolute MBF, quantified by positron emission tomography (PET), and LVMI as assessed by echocardiography. Additionally, regional aspects of blood flow were examined.

Methods

Study patients. The study group comprised 50 patients (mean age ± SD 56 ± 8 years, range 43 to 76) with a first diagnosis of mild to moderate arterial hypertension in the absence of coronary artery disease. Coronary artery disease was ruled out by the presence of normal coronary angiographic results in 34 patients, and by negative findings on both maximal stress exercise testing and high dose dipyridamole stress echocardiography (9) in the remaining 16 patients.

Hypertensive patients had a casual diastolic blood pressure reading, as measured by mercury manometer, ≥95 mm Hg. None had ever received antihypertensive medical treatment; thus, pharmacologic effects on hemodynamics, function or ventricular hypertrophy could be ruled out. Patients who had evidence of secondary hypertension or valvular, coronary or primary myocardial disease were excluded. Thirteen normotensive subjects, enrolled as a control group, were evaluated with the same protocol. They were referred for coronary angiography to exclude an organic cause of their atypical chest pain. All had normal findings on physical examination, rest electrocardiogram (ECG), echocardiogram, exercise stress test, coronary angiography and left ventriculography. Age, gender and race were similar in normotensive and hypertensive subjects.

All patients were informed about the partially investigative nature of the study and gave written informed consent to participate. The study protocol was approved by the local Ethical Committee on Human Studies.

PET study. A positron emission tomograph (ECAT III, Siemens/CTI) providing three simultaneous cross sections of the heart (two from the primary planes and one from the interplane) was used. Regional MBF was assessed by N-13 ammonia at rest and during pharmacologic vasodilation with dipyridamole. All patients were studied after an overnight fast; caffeine and theophylline were withheld for ≥12 h before imaging. Transmission scans of 60 million counts were acquired and subsequently served to generate attenuation correction factors. Correct positioning was maintained throughout the study by a light beam and indelible marks on the patient's torso. Thereafter, 7.4 MBq/kg body weight (0.2 mCi/kg) of N-13 ammonia was infused as a slow bolus over 10 to 20 s. Dynamic data acquisition started simultaneously with tracer injection; 28 frames were acquired over 8 min (16 frames × 3 s, 11 × 12 s and 1 × 300/s).

After acquisition of the baseline study, a period of 50 min was allowed for the physical decay of N-13 ammonia. Thereafter, dipyridamole (0.56 mg/kg over 4 min) was infused intravenously under continuous ECG monitoring. This protocol was adopted because it has been shown (10) to induce maximal vasodilation. The second N-13 ammonia flow study was started 2 to 3 min after the end of dipyridamole infusion with the same protocol as the baseline study. To antagonize the effects of dipyridamole, aminophylline (120 to 240 mg) was injected 3 min after N-13 ammonia injection in all patients.

MBF analysis. MBF was calculated according to a previously validated method (11,12). Briefly, only the transversal plane visualizing the left ventricle at its best was analyzed. Into each of the three walls—i.e., septal, anterior and posterolateral—two small regions of interest (25 to 30 voxels) were drawn to calculate regional ammonia uptake, resulting in six regions for each patient. The time curve of N-13 ammonia activity in the arterial blood was computed with a small region of interest placed in the left ventricular cavity.

Data values were corrected for decay and dead time loss. A dedicated program was used to perform automatic edge detection of the left ventricular wall to measure myocardial thickness and to correct for the partial volume effect (11). Regional MBF times N-13 ammonia extraction (rMBFe) was calculated as

$$rMBFe = Cm \times 60/\int_0^{\infty} Cb(t) \times dt,$$

where Cm and Cb are N-13 ammonia activity concentrations in the myocardium in the last frame and in the arterial blood at each time t, respectively. The Cb(t) curve was fitted by a gamma variate function for integration. The rMBFe values were then divided by tissue gravity (1.08 g/ml) to obtain the real values in ml/min per g. Actual MBF values were calculated from rMBFe by using the experimental relation between ammonia uptake and microsphere-determined flow observed in animal preparations (11).

To assess individual regional heterogeneity, percent values for all regions of every patient were calculated. The 100% reference value was assigned to the region with maximal flow. To identify those regions with a perfusion defect during maximal vasodilation, the average percent differences between the minimal and the maximal flow for all six regions and its relative standard deviations were calculated in the normal study patients. Any region in the hypertensive patients having an individual percent value lower than this difference plus 1 SD was considered to have a perfusion defect.

Two-dimensional echocardiography. Two-dimensional echocardiograms were performed in all patients by expert sonographers using commercially available echocardiographs with 2.5- to 3-MHz transducers. Left ventricular end-diastolic and end-systolic cross-sectional diameters as well as septal and posterolateral wall thickness were derived from M-mode images according to conventional criteria. Left ventricular volumes were estimated from the end-diastolic and end-systolic dimensions by using the formula of Teichholz et al. (13). LVMI was calculated in end-diastole according to the Penn convention (14). Patients were considered to have ventricular hypertrophy when LVMI was >150 g/m^2 in men and >120 g/m^2 in women (15). Accordingly, the hypertensive group was subdivided into patients with normal LVMI and patients with ventricular hypertrophy.

Because echocardiography permits reliable measurement of only the wall thickness of the septal and posterolateral walls, only those values were used to compare regional flow data with echocardiographic data, resulting in the best possible spatial match between echocardiographic and PET data. Relative wall thickness was measured at end-diastole as the ratio of 2 × posterior wall thickness/left ventricular end-diastolic diameter. The presence of concentric or eccentric hypertrophy was evaluated by using relative wall thickness and left ventricular mass as previously described (16).

Statistical analysis. Data are presented as mean value ± SD. For comparison of differences, the appropriate test for independent or paired samples was employed. Comparison of patients and normotensive subjects and comparison of blood flow values in hypertensive patients with and without left ventricular hypertrophy were performed by using analysis of variance (ANOVA) and Newman-Keuls procedure for multiple comparison. Chi-square analysis was performed to determine the significance in rate of occurrence. Least square linear regression analysis was used to test the correlation between dipyridamole flow and LVMI. The difference between correlations was examined by one-way analysis of covariance. For all comparisons, a p value < 0.05 was considered significant.

Results

Clinical findings. No serious side effects occurred as a result of the study. In the hypertensive group, dipyridamole injection caused chest pain in nine patients; ST segment depression was observed in six. During dipyridamole infusion, no significant changes were observed in blood pressure (systolic/diastolic blood pressure: 144/88 ± 22/14 mm Hg vs. 145/92 ± 21/13 mm Hg at baseline, p = 0.18). By contrast, dipyridamole increased heart rate significantly from 68 ± 12 beats/min at baseline to 93 ± 16 beats/min during pharmacologic vasodilation ($p < 0.01$). Other clinical and demographic data are reported in Table 1.

Table 1. Demographic Characteristics*

	Normotensive Subjects (n = 13)	Hypertensive Patients (n = 50)
Age (yr)	55 ± 10	56 ± 8
Body surface area (m^2)	1.9 ± 0.3	1.9 ± 0.4
Body mass index (kg/m^2)	26.5 ± 4.5	26.4 ± 5.1
Gender (male/female [no.])	11/2	40/10
Cholesterol (mg/dl)	170 ± 11	175 ± 8
Diabetes (%)	0	0
Atypical angina (%)	0	3
End-diastolic diameter (mm)	48 ± 9	50 ± 8

*p = NS for all comparisons. Data presented are mean ± SD, unless otherwise indicated.

Echocardiographic findings. Mean LVMI in all hypertensive patients was 149 ± 33 g/m^2 in men and 140 ± 27 g/m^2 in women. Of the 50 hypertensive patients, 22 were classified as without hypertrophy and 28 as with hypertrophy. In patients without hypertrophy, mean LVMI was 125 ± 15 g/m^2 in men and 106 ± 5 g/m^2 in women. In patients with hypertrophy, LVMI was 173 ± 23 g/m^2 in men and 155 ± 16 g/m^2 in women; mean diastolic thickness of the septal and posterolateral walls was 13 ± 2.4 mm and 12 ± 1.4 mm, respectively. Regional wall motion abnormalities, cavity dilation, left ventricular ejection fraction <50% or valvular disease was not observed in any patient.

Global MBF, coronary reserve, coronary resistance and correlation with LVMI in normotensive subjects and hypertensive patients. In normotensive subjects, rest MBF was 1.09 ± 0.2 ml/min per g and increased significantly after dipyridamole (3.57 ± 1.0 ml/min per g, $p < 0.01$). Coronary reserve was 3.35 ± 1.03, coronary resistance was 89 ± 15 mm Hg/ml per min per g at baseline and 27 ± 8 mm Hg/ml per min per g after pharmacologic vasodilation ($p < 0.01$).

In hypertensive patients, rest MBF was similar to the baseline MBF of normal subjects (0.89 ± 0.22 ml/min per g, p = 0.21), but after dipyridamole the increase in MBF was significantly lower (2.18 ± 0.75 ml/min per g, $p < 0.05$) than the increase in normal subjects. Coronary reserve (2.51 ± 0.88) as well as coronary resistance (rest 134 ± 33 mm Hg/ml per min per g, minimal 57 ± 19 mm Hg/ml per min per g) were significantly different from values in normotensive subjects ($p < 0.05$). In hypertensive patients with normal or elevated LVMI, the increase in MBF after pharmacologic vasodilation, coronary reserve, baseline and minimal coronary resistance were significantly different from values in normotensive subjects (all $p < 0.05$), whereas no difference was found in baseline MBF (p = 0.15) (Fig. 1). LVMI was not correlated with mean basal flow, mean dipyridamole flow (r = −0.22, p =

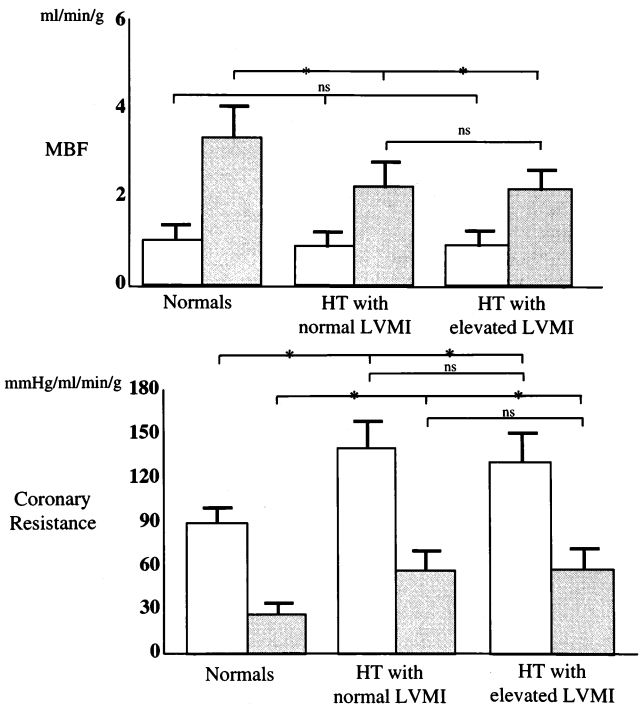

Figure 1. Mean MBF (**upper panel**) and coronary resistance (**lower panel**) in basal conditions (**open bars**) and after dipyridamole (**shaded bars**). HT = hypertensive patients. *p < 0.05.

0.13) (Fig. 2), coronary resistance (p = 0.12 at baseline, p = 0.09 after dipyridamole) or coronary reserve (p = 0.35).

Regional MBF, coronary reserve and coronary resistance. In the control subjects, mean rest and dipyridamole MBF were highest in the septum and lowest in the posterolateral wall. This difference did not reach statistical significance under baseline conditions (p = 0.13) but was significant after dipyridamole (p < 0.05). Coronary reserve as well as baseline and after dipyridamole coronary resistance were not significantly different among the septal, anterior and posterolateral walls (all p = NS).

In hypertensive patients, regional baseline MBF was similar to that in normal subjects in all three ventricular walls, whereas the regional flow values after pharmacologic vasodilation were significantly lower (p < 0.05). The regional disparity was analogous to that in the normotensive subjects, with flow values highest in the septum and lowest in the posterolateral wall (p = 0.11 at baseline, p < 0.05 after dipyridamole). Regional coronary reserve and coronary resistance before and after dipyridamole for all three walls were significantly different from values in the normotensive subjects (p < 0.05). No significant differences in these variables (all p = NS) were found between hypertensive patients with and without left ventricular hypertrophy (Table 2).

Assessment of regional heterogeneity. Of 50 hypertensive patients, 18 (group 1) showed regional flow heterogeneity after dipyridamole, resulting in 29 of 108 regions displaying perfusion defects. In the remaining 32 patients (group 2), 192 of 192 regions showed a homogeneous perfusion pattern. Groups 1 and 2 had similar clinical findings (gender, age, severity of hypertension, chest pain, ECG changes). They also had similar values for mean rest and dipyridamole MBF (0.84 ± 0.18 vs. 0.93 ± 0.94 ml/min per g at baseline [p = 0.11] and 2.17 ± 0.74 vs. 2.19 ± 0.77 ml/min per g after dipyridamole [p = 0.09]). In addition, group 1 and 2 baseline values did not differ significantly for coronary resistance (141 ± 31 vs. 130 ± 34 mm Hg/ml per min per g [p = 0.09], dipyridamole 58 ± 22 vs. 56 ± 18 mm Hg/ml per min per g [p = 0.08]) or coronary reserve (2.66 ± 0.95 vs. 2.42 ± 0.77 [p = 0.08]). In group 1, mean MBF after dipyridamole in the areas with perfusion defects was significantly lower than the mean values in group 2 patients with homogeneous perfusion. Maximal flow in group 1 was similar to the value obtained in the normotensive subjects (p = 0.11), whereas that in group 2 was significantly lower than that in the normotensive group (p < 0.05, Fig. 3).

Of the 29 of 108 regions with an obvious perfusion deficit after dipyridamole, 21 were located in the posterolateral wall and 8 in the anterior wall; none was found in the septum. In the remaining 79 of 108 regions of group 1, mean rest MBF was 0.98 ± 0.3 ml/min per g (p = 0.12 vs. values in normal sub-

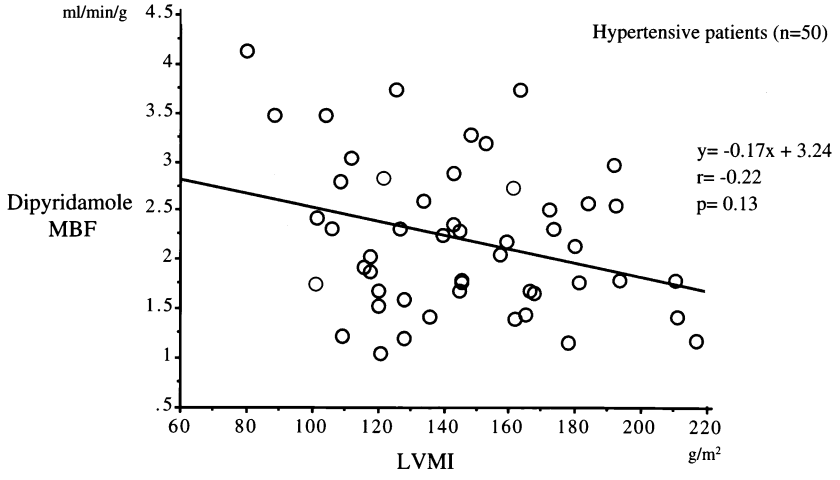

Figure 2. Correlation between LVMI and mean dipyridamole MBF in all hypertensive patients.

Table 2. Regional Values for Myocardial Blood Flow, Coronary Reserve and Resistance

		Hypertensive Patients	
	Normotensive Subjects	With Normal LVMI	With Elevated LVMI
Baseline rMBF			
Septum	1.2 ± 0.3	0.95 ± 0.2	1.15 ± 0.25
Anterior	1.1 ± 0.2	0.82 ± 0.24	0.86 ± 0.24
Posterolateral	1.03 ± 0.17	0.79 ± 0.25	0.84 ± 0.21
Dipyridamole rMBF			
Septum	4.23 ± 1.39	2.47 ± 0.97*	2.53 ± 0.79*
Anterior	3.53 ± 0.87	2.03 ± 0.9*	2.02 ± 0.66*
Posterolateral	3.2 ± 0.89	1.89 ± 0.71*	1.89 ± 0.68*
Coronary reserve			
Septum	3.6 ± 1.3	2.6 ± 1*	2.5 ± 1.1*
Anterior	3.4 ± 0.9	2.5 ± 1*	2.4 ± 0.8*
Posterolateral	3.2 ± 0.9	2.4 ± 0.7*	2.4 ± 1*
Coronary resistance (mm Hg/ml per min per g)			
Baseline			
Septum	82 ± 16	123 ± 26†	113 ± 27†
Anterior	87 ± 13	148 ± 41†	140 ± 37†
Posterolateral	93 ± 16	155 ± 49†	144 ± 40†
Dipyridamole			
Septum	24 ± 9	50 ± 19†	49 ± 16†
Anterior	26 ± 6	62 ± 24†	61 ± 21†
Posterolateral	29 ± 7	65 ± 24†	68 ± 29†

*$p < 0.05$, †$p < 0.01$ versus normotensive subjects. Data presented are mean value ± SD. LVMI = left ventricular mass index (g/m^2); rMBF = regional myocardial blood flow (ml/min per g).

jects) and increased significantly after dipyridamole (2.8 ± 0.9 ml/min per g, $p = 0.09$ vs. values in normal subjects).

LVMI in patients with regional perfusion heterogeneity was significantly higher than that obtained in patients with a homogeneous perfusion pattern (156.2 ± 37.7 vs. 141.4 ± 26.6 g/m^2, $p < 0.05$). Seven group 1 patients showed the most severely elevated LVMI (>180 g/m^2). Echocardiographic wall thickness was not significantly different between the posterolateral and septal walls in group 1 patients (11.5 ± 1.9 and 12.8 ± 2.7 mm, respectively, $p = 0.33$), and no significant differences were observed between groups 1 and 2 with respect to this variable. End-diastolic diameter was similar in groups 1 and 2 (50 ± 5 mm vs. 49 ± 6 mm, respectively, $p = 0.23$). Relative wall thickness was 0.48 ± 0.06 in group 1 and 0.51 ± 0.07 in group 2 ($p = 0.13$). Fifty-five percent of patients with regional flow heterogeneity and 45% of patients with a homogeneous perfusion pattern exhibited concentric hypertrophy ($p = 0.11$).

Discussion

In this study, an accurate method to measure specific MBF (i.e., flow per unit of weight) was applied with the aim of exploring the relation between LVMI and maximal coronary vasodilating capability in hypertensive patients with normal coronary arteries. Regional coronary resistance and coronary reserve were also assessed.

Our results demonstrate that the vasodilating capability of the coronary microvasculature in hypertensive patients with normal coronary arteries is significantly impaired in comparison with that of a control group of normotensive subjects. This global impairment is not directly linked to the presence or degree of left ventricular hypertrophy as assessed by echocardiography.

Different patterns in the spatial distribution of this impairment of vasodilating capability were elucidated when regional aspects were analyzed. Two groups were identified among hypertensive patients: In group 1, patients had heterogeneous perfusion after dipyridamole, whereas patients in group 2 had homogeneous MBF after pharmacologic vasodilation. In patients with perfusion defects, dipyridamole flow was within the normal range in the scintigraphically normal territories. In contrast, patients with homogeneous perfusion without regional deficits demonstrated global flow impairment. In the homogeneous group, 4 patients had severely reduced MBF

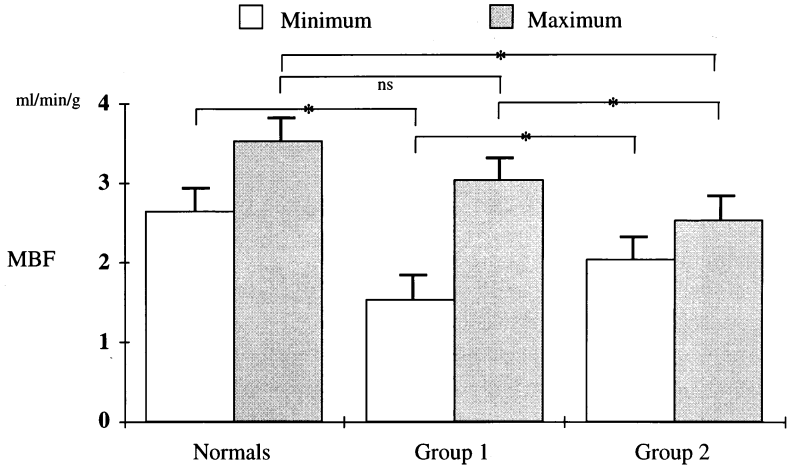

Figure 3. Maximal and minimal dipyridamole MBF in normal subjects and in group 1 and 2 hypertensive patients. Group 1 patients (heterogeneous flow pattern) show abnormal flow values only in territories with perfusion defects (minimal flow) during dipyridamole with respect to findings in control subjects. Group 2 patients (homogeneous flow pattern) show homogeneously reduced flow values with respect to findings in normal subjects. Mean maximal flow values are also significantly lower than those observed in group 1. *$p < 0.05$.

after dipyridamole in all six regions analyzed, 11 had moderately reduced MBF and the remaining 3 had flow within the normal range.

No differences were found between patients with homogeneous and heterogeneous MBF by analyzing other variables such as age, gender, severity of hypertension, heart rate under basal conditions and after dipyridamole infusion, ischemic ECG alterations or symptoms. In contrast, LVMI was significantly higher in patients with regional hypoperfusion during stress, thus indicating a link between the occurrence of regional inhomogeneity and the degree of hypertrophy.

Mechanism for abnormal vasodilating capability in hypertensive hearts. Several causes for the impairment of coronary reserve in patients with arterial hypertension have been postulated (2,17–21). One may be a structural remodeling of the coronary microvasculature and the accumulation of fibrillar collagen in the myocardium (5,6). Vascular remodeling might increase minimal resistance since it is associated with a reduction of arteriolar lumen (5). Maximal flow inhomogeneities could indicate a different degree of remodeling in the myocardial walls. Structural changes are associated with increased expression of growth factors (22), matrix proteins (23) and matrix proteinases (24). With respect to media thickening or perivascular fibrosis, it is conceivable that these alterations are not homogeneously distributed throughout the myocardium.

In addition, an increase in the extravascular component of coronary resistance due to an augmentation of myocardial tissue pressure during diastole (2,17) may contribute to impaired reserve, as suggested by previous study (18). A third possible mechanism may be related to the effects of myocardial hypertrophy (19–21). In concentric left ventricular hypertrophy, rest MBF in the epicardial vessel is increased to supply the hypertrophied myocardium. A decreased capillary density and a reduced flow reserve can be observed. It is conceivable that MBF regulation in hypertrophied hearts might be affected by various factors such as changes in oxygen consumption, vascular wall remodeling and changes in the extravascular component of coronary resistance. The data of the present study show that myocardial hypertrophy is associated with regional flow heterogeneity; however, we observed no significant effect of concentric hypertrophy on specific flow (i.e., flow per gram of tissue) either at rest or during maximal vasodilation. In fact, a reduced maximal flow capacity was also observed in nonhypertrophied hearts, while the correlation between left ventricular mass and minimal resistance was not present.

Finally, a functional increase in the tone of the coronary resistance vessels could be responsible for the decreased coronary reserve. In the last years the endothelium has been recognized as a major regulator of vascular tone and growth. Both acute and chronic experimental hypertension are associated with reduced endothelium-dependent relaxation in response to acetylcholine, adenosine diphosphate and, in large vessels, thrombin (25). Human studies support these experimental data (7,26). Furthermore, duration and severity of hypertension may have an important effect on coronary flow reserve (27). All of these theories represent possible explanations for the reduced vasodilating capability in hypertensive patients and the absence of correlation with left ventricular hypertrophy. Nevertheless, none sufficiently clarifies the relation between myocardial hypertrophy and an abnormal vasodilating capability.

The presence of left ventricular hypertrophy does represent an indicator for those hypertensive patients who may show stress-induced heterogeneous MBF. In a study by Geltman et al. (28) in patients with angina and normal coronary arteries, no regional MBF disparities were observed. Of their 17 study patients, 7 were hypertensive but only 1 patient had left ventricular hypertrophy. This discrepancy emphasizes the role of hypertrophy for the development of regional heterogeneity. In our study, hypertensive patients with homogeneous flow had a high likelihood of displaying a diffuse reduction of maximal flow after pharmacologic vasodilation. The pathophysiologic mechanisms of this observation remain largely hypothetical. In patients with heterogeneous regional MBF, the flow impairment seems to affect only a few areas, whereas others seem to be unaffected. In contrast, in patients with homogeneous MBF, the whole myocardium displays a reduced vasodilating capability, thus possibly indicating a more advanced stage of the disease.

Local functional alterations (such as hemodynamic pressure overload) and local vasoactive substances (angiotensin II, endothelin, prostaglandins), may play an important role in the genesis of regional perfusion abnormalities. Molecular and cellular biologic support for the important role of these substances was offered recently (29,30) by the demonstration of the "on switch" for cellular events that mediate cell growth by proto-oncogenes. Functional alterations may display spatial heterogeneity throughout the heart, thus affecting the microvascular response regionally. These changes are associated with structural alterations, such as endothelial dysfunction, as evidenced by decreased endothelium-dependent relaxation (7). To elucidate the role played by the mechanisms described, studies that pay particular respect to regional rather than only global effects of hypertension and hypertrophy on the coronary microvasculature are warranted.

Comparison with previous studies. Published studies have elucidated only a few aspects of the complex interactions among hypertension, hypertrophy and regional MBF. Vogt et al. (4), applying the argon method to examine the correlation between MBF and myocardial hypertrophy, were able to assess global MBF in basal conditions and during maximal vasodilation and to calculate vascular resistance and coronary flow reserve for the entire heart. They found no significant correlation between flow data and echocardiographically assessed LVMI. Because the argon method does not allow regional flow evaluation, they could not clarify the regional aspects of flow impairment in hypertensive patients. In contrast, Houghton et al. (8) demonstrated that regional aspects may play an important role. In agreement with Vogt et al. (4) they (8) found, using Doppler catheter-derived coronary flow measurements, no linear relation between flow reserve and the degree of left ventricular hypertrophy. Nevertheless, they showed that hyper-

tensive patients displaying thallium-201 perfusion defects had a significantly lower coronary flow reserve and higher LVMI than did with patients with negative scan results. They then speculated that myocardial ischemia or hypoperfusion secondary to an effect of hypertrophy may be the basis for positive thallium-201 findings. They concluded that although there is no linear correlation between the decrease in coronary flow reserve and the severity of left ventricular hypertrophy, the presence of hypertrophy predicts those patients with a high likelihood for positive thallium scan results. Because the Doppler catheter technique permits assessment of flow velocity only in the territory of the catheterized coronary artery, these authors also could not compare regional thallium-201 defects with regional flow measurements in the affected and adjacent regions. Because of these methodologic drawbacks, this group was unable to explain the paradoxic finding that patients with hypertrophy show a higher incidence of positive thallium findings despite the lack of a correlation between ventricular mass and coronary flow.

Our results may explain this observation. As demonstrated, there is a regional impairment of perfusion that is correlated with ventricular mass and therefore may be the basis for positive thallium findings in these patients. This regional flow impairment can be identified only by assessing regional aspects of MBF. The presence of "physiologic flow" during dipyridamole infusion in some regions in patients with regional heterogeneity results in a perfusion abnormality enhancement with detectable perfusion defects. By contrast, a diffuse reduction in MBF in patients with a homogeneous perfusion pattern results in an apparently normal flow distribution. Calculation of mean maximal flow (such as measurement of Doppler flow velocity not necessarily linked to the site of perfusion abnormalities) would not permit appreciation of differences between these two perfusion patterns.

Clinical implications. The increased incidence of sudden cardiac death and arrhythmias in hypertensive patients with myocardial hypertrophy is well recognized. The findings of the present study may offer a possible explanation for this phenomenon. Spatial flow heterogeneity during pharmacologic coronary vasodilation, most often observed in hypertrophic hearts, may be the pathophysiologic mechanism underlying malignant arrhythmias. It is possible that regional abnormal vasodilating capability may predispose to abnormal patterns of myocardial electrical depolarization and repolarization or regional myocardial ischemia, or both, during increased cardiac demand; these abnormal patterns might create a nidus for the genesis of clinically important arrhythmias. If our results are confirmed in future studies (which might even provide de facto demonstration of regional ischemia), this observation may warrant a different pharmacologic approach to the treatment of hypertensive patients with myocardial hypertrophy, normal coronary arteries and regional flow heterogeneity.

Another important effect of different perfusion patterns could be their contribution to the modulation of left ventricular geometry. In a previous study (16), concentric remodeling or eccentric hypertrophy was described as the effect of essential hypertension. In the present study, regional MBF heterogeneity was associated with left ventricular hypertrophy; however, we could not establish whether MBF heterogeneity is the cause or the effect of left ventricular hypertrophy and of the concentric remodeling. According to Ganau et al. (16), ventricular chamber size and stroke volume may be influenced by factors like blood volume, venous return, afterload and diastolic or inotropic properties. The endothelial surface is particularly suited to play a prominent part in the vascular and ventricular remodeling; in fact, it is constantly exposed to humoral factors and physical forces. Thus, the endothelium is strategically located to serve as a sensory cell assessing hemodynamic and humoral signals, as well as an effector cell eliciting biologic responses that may eventually affect the structure of the vessels. These observations suggest that the differences in regional vasodilating capability in hypertrophied hearts identified in this study may have an effect on the diastolic or inotropic properties of the ventricle and thus contribute to the development of ventricular remodeling.

Limitations of the study. One possible limitation of this study is the use of N-13 ammonia as a flow tracer, because it has been shown (31) that N-13 ammonia tends to underestimate regional blood flow in the lateral wall even in normal subjects. In fact, blood flow values in the lateral wall in our patients were lower than in the remaining two ventricular walls. The approach chosen to identify regions with severe flow deficits should exclude effects of this technical limitation on the results. However, the possible underestimation of lateral blood flow in our study should not affect the calculation of regional flow reserve, and therefore should not affect our results. Another study limitation is that no follow-up data are available in our patients, thus preventing assessment of the link between reduced MBF and future events as well as of differences in the prognosis of patients with homogeneous or heterogeneous perfusion patterns during pharmacologic stress.

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