Original articles

Impact of myocardial diastolic dysfunction on coronary flow reserve in hypertensive patients with left ventricular hypertrophy

Maurizio Galderisi, Silvana Cicala*, Luigi De Simone*, Pio Caso*, Antonio Petrocelli, Ilaria Pietropaolo, Aldo Celentano, Nicola Mininni*, Oreste de Divitiis

*Division of Emergency Medicine, Department of Clinical and Experimental Medicine, "Federico II" University of Naples, *Division of Cardiology, Monaldi Hospital, Naples, Italy*

Key words:
Arterial hypertension; Coronary flow reserve; Diastolic dysfunction; Dobutamine.

Background. **The aim of the study was to assess the possible association, in hypertensive patients, between left ventricular myocardial diastolic dysfunction and coronary flow reserve (CFR) in relation to the presence of left ventricular hypertrophy (LVH).**

Methods. **Twenty-eight untreated hypertensives (22 males, 6 females, mean age 53.1 years), free of coronary artery disease, were enrolled in the study. Standard Doppler echocardiography, color Doppler tissue imaging of the posterior septum during dobutamine stress and second harmonic Doppler of the distal left anterior descending coronary vessel, at baseline and after maximal hyperemia induced by dipyridamole, were performed. CFR was estimated as the ratio between hyperemic and baseline diastolic velocities. Hypertensives were divided into two groups according to the left ventricular mass index: 15 without LVH (left ventricular mass index < 51 g/m$^{2.7}$) and 13 with LVH (left ventricular mass index > 51 g/m$^{2.7}$). The two groups were comparable for sex prevalence, age, body mass index, baseline heart rate and blood pressure.**

Results. **Color Doppler tissue imaging did not show any significant difference of both the baseline and high-dobutamine septal systolic peak velocities between the two groups. The ratio between myocardial early and atrial peak velocities (E_m/A_m ratio) was lower in patients with LVH, either at baseline ($p < 0.01$) or at high-dose dobutamine ($p < 0.0001$). Also, CFR was lower in the presence of LVH ($p < 0.01$). After adjusting for age, body mass index, left ventricular mass index, diastolic blood pressure and high-dose dobutamine heart rate by a multiple linear regression analysis, the high-dose dobutamine E_m/A_m ratio was an independent contributor of CFR in the overall hypertensive population ($\beta = 0.65$, $p < 0.0001$) (cumulative $r^2 = 0.38$, $p < 0.0001$).**

Conclusions. **The combined use of second harmonic Doppler and color Doppler tissue imaging identifies, in arterial hypertension, an association between myocardial diastolic properties and CFR, independent of the presence of LVH. In hypertensive patients free of coronary artery stenosis, left ventricular myocardial diastolic dysfunction may be a determinant in the impairment of the coronary microvessel vasodilation capacity or a marker of silent ischemia involving the microvascular circulation.**

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Dr. Silvana Cicala is performing a Ph Doctorate in Medical-Surgical Pathophysiology of the Cardiopulmonary and Respiratory System and Associated Biotechnologies, Second University of Naples, Italy.

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Address:

Dr. Maurizio Galderisi

Laboratorio di Ecocardiografia Cattedra di Medicina d'Urgenza Dipartimento di Medicina Clinica e Sperimentale Università degli Studi "Federico II" Via S. Pansini, 5 80131 Napoli E-mail: mgalderi@unina.it

Introduction

Left ventricular hypertrophy (LVH) is a recognized independent risk factor for subsequent cardiovascular disease events[1-3]. The main pathologic consequence of LVH leading to increased cardiovascular morbidity and mortality is the development of congestive heart failure and of coronary artery disease including myocardial infarction[4-6]. In particular, LVH determines an impairment of left ventricular (LV) diastolic function, which alone may produce a congestion of the pulmonary veins[7,8] as well as a reduction in coronary flow, even in the absence of overt coronary artery stenosis[9,10]. Because coronary blood flow occurs predominantly during the diastolic phase of the cardiac cycle, it may be interesting to investigate the relations existing between the LV myocardial diastolic properties and the microvessel coronary circulation in hypertensive patients affected by LVH.

On these grounds, the aim of the present study was to assess the possible association between LV myocardial diastolic dysfunction and coronary flow reserve (CFR) in hypertensive patients with and without LVH, by the combined non-invasive use of color Doppler tissue imaging (DTI) off-line quantitative analysis during dobutamine stress echocardiography and second harmonic Doppler echocardiography during dipyridamole infusion.

Methods

Study population. This study was approved by the Institutional Committee of the "Federico II" University of Naples (Italy). By an initial screening, 135 patients affected by newly diagnosed arterial hypertension (WHO/ISH grade 1-2) were studied at the outpatient clinic of the Division of Emergency Medicine, Department of Clinical and Experimental Medicine of the "Federico II" University between September 1998 and December 2000. The exclusion criteria were: antihypertensive therapy, coronary artery disease (based on the presence of angina pectoris and of negative findings at both the maximal stress exercise test and at effort myocardial perfusion scintigraphy), diabetes mellitus, congestive heart failure, valvular heart disease, atrial fibrillation, and echocardiograms of inadequate quality. Thus, 103 patients were excluded: 59 because of coronary artery disease, 19 because of diabetes mellitus, 5 because of congestive heart failure, 6 because of valvular heart disease, 2 because of chronic atrial fibrillation, and 12 because of inadequate echocardiograms. By this selection, 32 hypertensive patients underwent both dipyridamole infusion for CFR evaluation and dobutamine stress echocardiography, after having given their informed consent. Of these, 2 patients did not complete the dobutamine test because of the occurrence of severe ventricular arrhythmias while the visualization of coronary flow was not adequate in 2 other patients. Thus, the final study group comprised 28 hypertensive patients (22 males, 6 females, mean age 53.1 years). They were divided into two groups: 13 with LVH (LV mass index > 51 g/m$^{2.7}$ according to the Cornell criteria[11]) and 15 without LVH.

Procedures. Hypertensive patients underwent transthoracic echocardiography, color DTI dobutamine stress echocardiography and CFR determination by the dipyridamole test.

Transthoracic echocardiography. Standard echocardiographic examinations were performed using a System FiVe, Vingmed Sound AB machine (GE, Horten, Norway) inclusive of a 2.5 MHz transducer equipped with second harmonic capability. All patients were examined in the left lateral decubitus position. M-mode echocardiographic analysis was performed according to the criteria of the American Society of Echocardiography[12]. The LV mass was calculated according to the Penn Convention[13] and indexed for body height powered to 2.7 (Cornell adjustment[11]). The relative diastolic wall thickness was estimated as follows: (septal wall thickness + posterior wall thickness)/LV end-diastolic diameter.

Color Doppler tissue imaging dobutamine stress echocardiography. Color DTI dobutamine stress echocardiography was recorded using the same System FiVe Vingmed machine and employing the standard setting for Doppler tissue imaging. The dobutamine stress protocol was performed according to standard methods[14]. The ECG was monitored continuously during the test. Blood pressure and a 12-lead ECG were recorded at rest and at the end of each stage. Wall motion analysis was performed by two experienced readers who were blinded to the other data and who evaluated the dobutamine stress echocardiography (super VHS) recording completely. Color DTI acquisition of the posterior septal wall was performed in real time and superimposed on two-dimensional images both at rest and at the end of high-dose dobutamine infusion. Color DTI was stored in digital format and color DTI analysis was performed off-line on a color DTI cineloop[15]. The region of interest was the middle segment of the posterior septal wall where the myocardial velocity profile was obtained at rest and at high-dose dobutamine. The choice of the middle posterior septum for color DTI measurements was based on the assumption that the perfusion of this myocardial segment is provided by a branch of the left anterior descending coronary artery (LAD). CFR was also determined at the distal LAD. In addition, because of a reduced heart translation movement, optimal imaging and analysis of the color DTI septal pattern is obtainable in apical 4-chamber views. Figure 1 shows the color DTI of the posterior septal wall at baseline and at high-dose dobutamine: a systolic velocity (S_m) and two diastolic velocities – early (E_m) and late (A_m) – are detectable. All color DTI measurements were analyzed without knowledge of the patients' clinical data. The reproducibility of color DTI measurements was tested, in a sample of 10 randomly selected patients, by two readers (MG and AP). The intra and interobserver variability was < 3% and < 6% respectively for all the measurements, both at baseline and at high-dose dobutamine.

Coronary flow reserve determination. CFR assessment was performed by a Acuson Sequoia ultrasound system (Acuson Corporation, Mountain View, CA, USA), inclusive of a transducer with second harmonic capability 1.7 MHz transmitting and 3.5 MHz receiving. The methods employed by our laboratory for the measurement of coronary blood flow have been previously reported[16]. The distal portion of the LAD was visualized by means of a modified foreshortened 2-chamber view obtained by sliding the transducer on the upper part and medially from an apical 2-chamber view in order to achieve the best alignment to the interventricular sulcus[16-19]. The contrast agent (Levovist®, SHU-508A, Schering AG, Berlin, Germany) 300 mg/ml and an infusion rate of 1 ml/min[17]), administered by an infusion pump into the right cubital vein, was used in case of suboptimal color Doppler imaging (3 patients). By placing the sample volume on the color signal of the LAD, spectral Doppler of the LAD flow showed the characteristic biphasic flow pattern with a larger diastolic and a smaller systolic component. Coronary blood

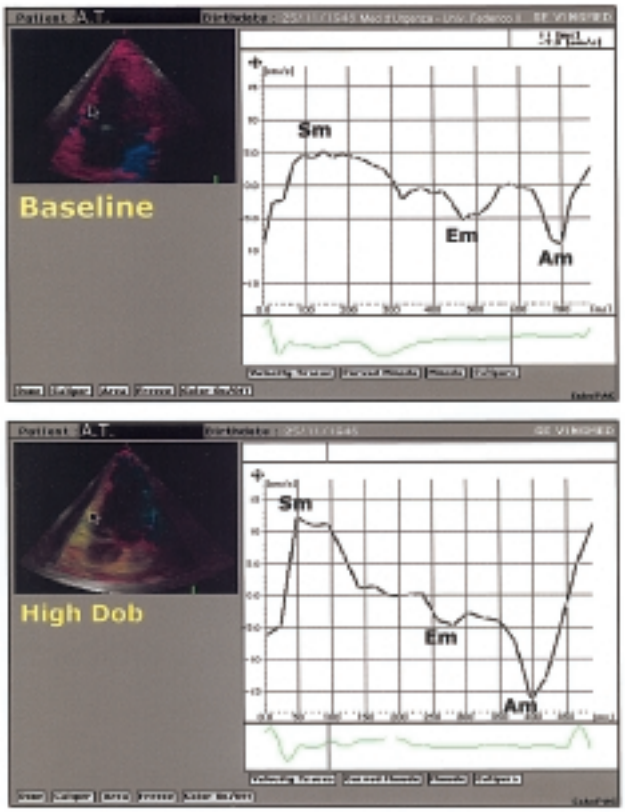

Figure 1. *Color Doppler tissue imaging of the posterior septum at baseline* (upper panel) *and at high-dose dobutamine* (lower panel) *in a hypertensive patient. From baseline to high-dose dobutamine, we can observe a great increase in the S_m and A_m peak velocities while the E_m peak velocity remains almost unchanged. A_m = myocardial atrial velocity, E_m = myocardial early diastolic velocity, S_m = myocardial systolic velocity.*

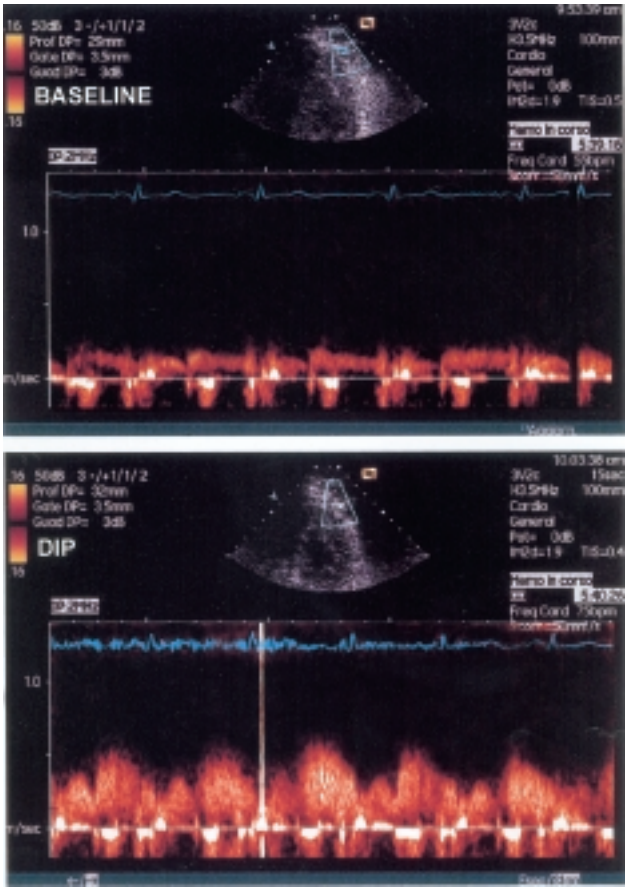

Figure 2. *Coronary blood flow both at baseline* (upper panel) *and after dipyridamole infusion* (lower panel) *in a hypertensive patient with a normal coronary flow reserve. The ratio between the hyperemic and baseline coronary blood flows is* > 2.

flow velocities were recorded under color-guided pulsed-wave Doppler at baseline and after dipyridamole administration (0.56 mg/kg over 4 min). Figure 2 shows the coronary blood flow both at baseline and after dipyridamole-induced hyperemia. The diastolic peak velocities were measured at baseline and after dipyridamole, by averaging the highest three spectral Doppler signals for each measurement. CFR was defined as the ratio of hyperemic to basal diastolic peak velocities. All images were recorded on a magneto-optical disk and subsequently analyzed by two observers blinded to the standard Doppler echo and color DTI data. Measurements were made off-line by use of the built-in calculation package of the ultrasound machine. CFR reproducibility was tested by two observers (LDS and SC) on a sample of 10 patients. The intraobserver variability was 1.9% (LDS) and 3.2% (SC) respectively; the interobserver variability was 4.2%.

Statistical analysis. The analyses were performed using SPSS for Windows release 8.0 (Chicago, IL, USA). Data are presented as mean values ± SD. The Student's t test for unpaired data was used to assess intergroup differences. Linear regression analyses and the partial correlation test using Pearson's method were performed in order to assess univariate relations between CFR and potential determinants. Prediction of CFR was obtained by stepwise, forward, multiple regression analysis that included potential confounding variables not obviously related to each other. Differences were considered statistically significant at $p < 0.05$.

Results

Clinical characteristics and stress response of the two study groups. The clinical characteristics and both the baseline and high-dose dobutamine heart rate and blood pressure of the two study groups are listed in table I. Only systolic blood pressure at high-dose dobutamine was higher in hypertensive patients with LVH. No patient complained of chest discomfort and no ischemic ST-segment changes occurred during either dobutamine or dipyridamole stress.

Doppler echocardiographic analysis. The comparison of the Doppler echocardiographic measurements between the two groups is reported in table II. The septal and posterior wall thickness as well as the relative

diastolic wall thickness were significantly higher in hypertensive patients with LVH than in those without LVH. Except for the transmitral E peak velocity, the other Doppler indexes of LV global diastolic function were all significantly impaired in patients with LVH.

Dobutamine test and color Doppler tissue imaging analysis. No wall motion abnormality was observed in both the study groups. The color DTI analyses at baseline and at maximal dobutamine infusion are summarized in table III. No S_m difference was found between the two groups both at baseline and at high-dose dobutamine. The E_m/A_m peak velocity ratio was significantly lower in hypertensive patients with LVH at baseline ($p < 0.01$) and, more significantly ($p < 0.001$), at high-dose dobutamine. This was due at baseline mainly to a lower E_m peak velocity, and at high-dose dobutamine to a higher A_m peak velocity (both $p < 0.05$).

Coronary flow reserve analysis. CFR was significantly different between the two groups, being 1.8 ± 0.3 in patients with LVH and 2.2 ± 0.8 in those without LVH ($p < 0.05$). This was due to a lower hyperemic diastolic peak velocity in the LVH group compared to that in the control group (0.48 ± 0.07 vs 0.58 ± 0.12 cm/s, $p < 0.01$) while the difference in the baseline diastolic peak velocities was not significant (0.29 ± 0.08 vs 0.27 ± 0.04 cm/s, p = NS).

Relationship between coronary flow reserve and color Doppler tissue imaging measurements. In the overall hypertensive population, CFR was not related to Doppler standard diastolic measurements. On the other hand, CFR was positively related to the color DTI E_m peak velocity at baseline ($r = 0.45$, $p < 0.01$) while the relation with the other color DTI measurements at baseline (with A_m: $r = -0.10$, with E_m/A_m: $r = 0.25$, with S_m: $r = 0.12$) was not significant. Among color DTI measurements at high-dose dobutamine, the E_m peak velocity ($r = 0.39$, $p < 0.05$), the A_m peak velocity ($r = -0.41$, $p < 0.05$) and the E_m/A_m peak velocity ratio ($r = 0.60$, $p < 0.0001$) (Fig. 3) were significantly related to the CFR at univariate analysis while the relation between the S_m peak velocity and the CFR ($r = 0.10$) was not significant.

Table I. Characteristics of the study population.

Variable	Hypertensives without LVH (n=15)	Hypertensives with LVH (n=13)	p
Sex (M/F)	12/3	10/3	NS
Age (years)	52.9 ± 5.8	53.3 ± 5.8	NS
Body mass index (kg/m^2)	26.8 ± 2.3	27.6 ± 2.7	NS
Baseline SBP (mmHg)	146.7 ± 9.6	150.4 ± 13.3	NS
Baseline DBP (mmHg)	99.3 ± 1.8	100.8 ± 4.5	NS
Baseline HR (b/min)	75.8 ± 6.5	73.8 ± 6.6	NS
Dobutamine SBP (mmHg)	159.3 ± 7.8	172.3 ± 15.9	< 0.01
Dobutamine DBP (mmHg)	98.3 ± 3.1	99.6 ± 5.8	NS
Dobutamine HR (b/min)	134.3 ± 7.2	134.5 ± 5.5	NS

DBP = diastolic blood pressure; HR = heart rate; LVH = left ventricular hypertrophy; SBP = systolic blood pressure.

Table II. Standard Doppler echocardiographic analysis.

Variable	Hypertensives without LVH (n=15)	Hypertensives with LVH (n=13)	p
Septal wall thickness (mm)	10.2 ± 0.2	12.3 ± 0.2	< 0.001
Posterior wall thickness (mm)	7.9 ± 0.2	9.7 ± 0.1	< 0.01
LV internal diastolic diameter (mm)	50.5 ± 1.3	54.5 ± 0.5	NS
LV internal systolic diameter (mm)	32.1 ± 1	36.8 ± 0.4	NS
Endocardial fractional shortening (%)	30.9 ± 4.6	32.2 ± 5.5	NS
Relative diastolic wall thickness	0.37 ± 0.06	0.42 ± 0.07	< 0.01
LV mass index (g/m$^{2.7}$)	43.6 ± 4.1	63.0 ± 6.5	< 0.00001
Peak E velocity (m/s)	0.58 ± 0.12	0.56 ± 0.10	NS
Peak A velocity (m/s)	0.55 ± 0.14	0.65 ± 0.12	< 0.01
Peak E/A ratio	1.05 ± 0.25	0.86 ± 0.15	< 0.001
E wave deceleration time (ms)	170.7 ± 54	210.1 ± 40	< 0.01
Isovolumic relaxation time (ms)	72 ± 17	106.7 ± 37	< 0.02

LV = left ventricular; LVH = left ventricular hypertrophy.

Table III. Color Doppler tissue imaging analysis at baseline and at high-dose dobutamine.

Variable	Hypertensives without LVH (n=15)	Hypertensives with LVH (n=13)	p
Baseline			
E_m velocity (cm/s)	6.95 ± 1.8	5.78 ± 1.7	< 0.05
A_m velocity (cm/s)	7.02 ± 1.5	7.40 ± 1.4	NS
E_m/A_m ratio	0.99 ± 0.25	0.80 ± 0.37	< 0.01
S_m velocity (cm/s)	5.0 ± 0.5	5.3 ± 0.7	NS
High-dose dobutamine			
E_m velocity (cm/s)	7.70 ± 1.8	6.12 ± 2.2	NS
A_m velocity (cm/s)	9.11 ± 1.8	10.90 ± 2.4	< 0.05
E_m/A_m ratio	0.95 ± 0.24	0.63 ± 0.21	< 0.001
S_m velocity (cm/s)	10.6 ± 1.6	11. 8 ± 2.1	NS

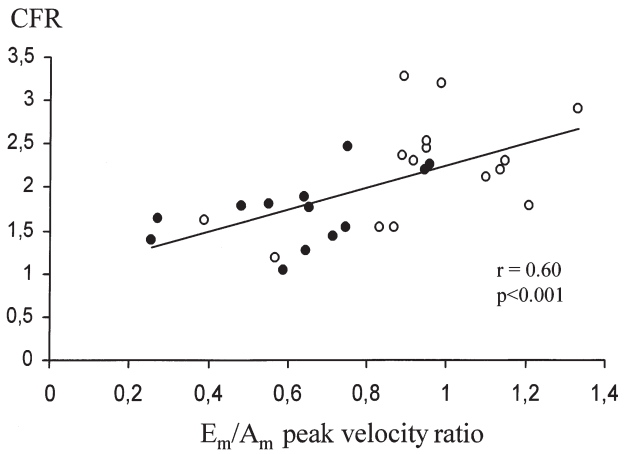

Figure 3. *Scatter plot and regression line of the positive association between the high-dose dobutamine color Doppler tissue imaging-determined E_m/A_m peak velocity ratio and the coronary flow reserve (CFR) in the overall hypertensive population.* Empty circles *are hypertensives without left ventricular hypertrophy;* filled circles *are hypertensives with left ventricular hypertrophy.*

CFR was also negatively related to both high-dobutamine heart rate (r = -0.41, p < 0.05) and diastolic blood pressure (r = -0.40, p < 0.05) as well as to the LV mass index (r = -0.42, p < 0.02) while the relations with age (r = -0.32) and body mass index (r = -0.14) did not reach statistical significance.

On the grounds of all these univariate relations, a stepwise forward multiple regression analysis was performed to identify the independent contributors to CFR. After adjusting for age, LV mass index and both high-dose dobutamine heart rate and diastolic blood pressure, the high-dobutamine E_m/A_m ratio was an independent determinant of CFR (standardized β coefficient = 0.65, p < 0.001) (cumulative $r^2 = 0.38$, p < 0.0001).

Discussion

In arterial hypertension, abnormalities of myocardial perfusion are very frequent, even in the absence of overt coronary artery stenosis. This yields a low specificity for myocardial perfusion scintigraphy[20,21]. This is mainly due to microvessel coronary alterations which may be detected by a CFR reduction in the distal LAD. Thus, in hypertensive patients the identification of the determinants of CFR is crucial. In order to investigate this issue, we selected a homogenous population in which patients with myocardial scintigraphic perfusion defects were excluded by selection. By using off-line quantitative color DTI analysis and non-invasive Doppler CFR assessment, the present study underscores an important association between LV myocardial diastolic function and CFR in arterial hypertension. According to the levels of the LV mass, hypertensive patients with LVH have a reduced CFR as well as a myocardial diastolic dysfunction which is evident at baseline and, more significantly, at high-dose dobutamine. In the overall hypertensive population however, CFR was positively associated with the high-dose dobutamine E_m/A_m peak velocity ratio, independently of the effect of clinical confounders and of the presence of LVH.

Myocardial diastolic dysfunction in patients with left ventricular hypertrophy. In accordance with previous reports[22-24], the main indexes of the Doppler-derived diastolic function in the present study were impaired in the presence of LVH. Color DTI off-line analysis provided additional information about myocardial diastolic function even during dobutamine stress. Of note, standard Doppler transmitral inflow cannot allow reliable recording of the relationships existing between the E and A velocities during dobutamine infusion since they overlap at the highest heart rate. The DTI-determined E_m peak velocity may be considered a reliable index of energy-dependent myocardial relaxation while the A_m peak velocity reflects atrial activity and probably the intrinsic distensibility of LV myocardial fibers. Thus, the E_m/A_m ratio is a good index of LV myocardial compliance. Changes in LV relaxation in arterial systemic hypertension may be de-

termined either by increased afterload or by changes in the LV structure[25,26]. In the present study, the color DTI-derived E_m/A_m ratio of the posterior septum was lower in patients with LVH at baseline, where it was due to an impairment of myocardial relaxation. At high-dose dobutamine, the reduction in the E_m/A_m ratio was further evident in the LVH group, being mainly due to the A_m peak velocity increase while the reduction in the E_m peak velocity had a marginal role.

Coronary flow reserve reduction in patients with left ventricular hypertrophy. Hypertensive patients with LVH had a significantly lower CFR, mainly due to the reduction in the dipyridamole diastolic peak velocity. Several mechanisms are involved in the development of coronary flow impairment in the presence of LVH: microvessel alterations, increased coronary resistance, increased LV cavity pressures and wall stress, greater systolic compression index, and an impaired vasodilator function[27-30]. Worthy of note, the LV myocardial diastolic impairment itself has been suggested as a possible determinant of CFR reduction in hypertensive LVH[31].

Independent association between color Doppler tissue imaging E_m/A_m ratio and coronary flow reserve. In the overall hypertensive population of the present study, CFR was inversely related with the color DTI E_m peak velocity at baseline, indicating how an impairment of myocardial relaxation may, even at rest, negatively influence the vasodilator capacity of coronary microvessels in arterial hypertension. In addition and more important, we found a strong positive association between color DTI E_m/A_m peak velocity ratio of the posterior septum at high-dose dobutamine and CFR. It is likely that myocardial diastolic dysfunction exerts negative effects on CFR since LV diastolic properties participate in the regulation of the relation between coronary flow and perfusion pressure[32]. The diastolic time fraction has been found to be a determinant of the coronary flow increase when the autoregolatory mechanism is exhausted since the fractional diastolic time at a lower perfusion pressure is longer both in the presence and in the absence of coronary artery stenosis[32]. On these grounds, LV diastolic impairment has been demonstrated to influence the early diastolic coronary flow both in dogs[33,34] and in humans[31]. This mechanism may be active even in hypertensive patients without evidence of coronary artery disease. In addition, microvessel alterations of the hypertensive heart induced by extravascular diastolic compression[35] may not be evident at baseline but become overt during faster heart beating as shown by using cardiac pacing[31].

The association observed between color DTI septal E_m/A_m ratio and CFR was tested by a multiple linear regression analysis adjusting for several confounders. Age, heart rate and diastolic blood pressure were included in the model as possible determinants because of their recognized influence on both the LV diastolic function[24,36,37] and the CFR[38-41]. The role of the LV mass was assessed in view of the adverse effect exerted by LVH on both myocardial flow[42-44] and LV myocardial diastolic properties[23,24]. By this analysis, the association between stress-determined myocardial diastolic function and CFR remained independent of the influence exerted by all these variables. It is remarkable that this association was independent of the effects exerted by the heart rate, that is by the tachycardia usually evident at high-dose dobutamine, and above all of the effects exerted by the different values of LV mass. These findings suggest that LV diastolic dysfunction may itself be responsible for the alterations in the microvessel coronary circulation, probably through the perivascular fibrosis which impairs myocardial oxygen supply and through the deterioration of myocardial diastolic properties which hampers myocardial perfusion, even in the early stages of arterial hypertension. Early changes in both CFR[27,29,45] and LV diastolic function[22-24] have been observed in hypertensive patients before the development of LVH. Alternatively, a reduced CFR may itself exert an influence on LV myocardial diastolic properties. In the ischemic process, LV diastolic dysfunction occurs early, preceding the development of wall motion abnormalities and of LV systolic failure[46]. In such a context, LV diastolic dysfunction itself may be consequent to the reduced CFR and represent a marker of multiple episodes of transient subendocardial ischemia, regardless of the evidence of LVH. The occurrence of LV diastolic abnormalities might then aggravate CFR inducing a vicious circle.

Clinical implications. The present study provides evidence of an association between LV myocardial diastolic function estimated during maximal dobutamine infusion and CFR in arterial systemic hypertension, independent of changes in afterload and LV mass. In hypertensive patients without overt coronary heart disease, the alterations in LV myocardial diastolic properties should be taken into account as determinants of coronary blood flow reduction and possibly to explain angina pectoris or else may themselves be a consequence of microvessel CFR changes. The novel non-invasive technology allows quantification of the relations occurring between the myocardial functional reserve and the hyperemic coronary blood flow supply.

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