Coronary Vasodilator Capacity and Hypertension-Induced Increase in Left Ventricular Mass

Michaela Kozákovà, Giovanni de Simone, Carmela Morizzo, Carlo Palombo

Abstract—An increase in left ventricular mass represents a compensatory response of hypertensive heart to augmented loading conditions. The concept of inappropriate mass has been proposed to define an increase in left ventricular mass higher than needed to compensate for increased workload. To assess whether inappropriate left ventricular mass is associated with more severe impairment of coronary vasodilator capacity, 64 untreated middle-aged hypertensive patients without significant coronary artery stenosis and 14 normotensive volunteers comparable for age and gender were studied by transthoracic and transesophageal echocardiography to evaluate left ventricular mass, geometry, and coronary flow velocity response to adenosine. Thirty-three patients had appropriate and 31 had inappropriate increase in left ventricular mass, whereas all normotensive control subjects had appropriate left ventricular mass. Compared with control subjects, minimum coronary resistance (0.87±0.18 mm Hg per second/centimeter) was increased in both hypertensive subgroups, more in those with inappropriate left ventricular mass (1.34±0.23 versus 1.19±0.23 mm Hg per second/centimeter, P<0.01), who also exhibited lower afterload-corrected midwall shortening and ratio of peak early and peak late velocities of transmitral flow. In hypertensive patients, minimum coronary resistance was related positively to absolute and relative left ventricular wall thickness (r=+0.33 and +0.35, both P<0.01) and negatively to midwall shortening and ratio of peak early and peak late velocities of transmitral flow (r=−0.32 and −0.31, both P<0.02). Thus, in the hypertensive heart, a deviation of left ventricular mass from values compensatory for increased cardiac workload is associated with lower coronary vasodilator capacity, depressed left ventricular wall mechanics, and abnormal left ventricular diastolic filling pattern. (Hypertension. 2003;41:224-229.)

Key Words: hypertrophy ■ hypertension, arterial ■ vasodilation ■ cardiac function ■ echocardiography

Left ventricular (LV) hypertrophy (LVH) represents an adaptive response of the heart to volume and/or pressure overload, aimed to preserve LV chamber function. In arterial hypertension, LVH also stands for a preclinical disease1,2 and is a strong predictor of cardiovascular morbidity and mortality.3,4 Cardiovascular risk in hypertensive LVH has been attributed to several pathophysiologic factors, including impairment in coronary structure and vasodilator capacity,5–12 which can explain increased prevalence of myocardial ischemia, arrhythmias, and sudden death.9,12–15 In previous studies, we have demonstrated a reduced coronary flow velocity response to the downstream arteriolar vasodilation in hypertensive patients either with or without LVH.16–18 One study by positron emission tomography indicated that impairment of coronary reserve in hypertensive patients is relatively independent of LVH.19 Recently, a new concept has been introduced for evaluation of hypertensive heart, discriminating between the increase in LV mass compensatory (or appropriate) and overcompensatory (or inappropriate) for increased cardiac workload.20,21 Prognostic studies have demonstrated that inappropriate LV mass increase predicts cardiovascular outcome in hypertensive patients, even independent of the presence of clear-cut LVH,20,22 and is related to lower LV myocardial contractility.23 The present study was designed to investigate whether inappropriately high LV mass in hypertensive patients is associated with a more severe impairment in coronary vasodilator capacity, as well as the relations between coronary function, myocardial systolic performance, and LV diastolic filling pattern.

Methods

Study Population

The study population consisted of 78 subjects, including 14 healthy normotensive volunteers with normal LV mass (9 men) and 64 untreated patients with systo-diastolic hypertension (39 men). Significant coronary artery disease was excluded on the basis of clinical history, exercise ECG test, atropine-dipyridamole echocardiography, and, when needed, coronary angiography (36 of 64 patients). Forty-five hypertensive patients were newly diagnosed and previously untreated. Nineteen patients had been previously treated but never achieved adequate blood pressure control. Previous therapy had been stopped since at least 2 weeks before the study for diagnostic workup. Only short-acting nitrates, discontinued at least 48 hours before exercise ECG testing and evaluation of coronary
function, were used in hypertensive patients with history of chest pain. The institutional review committee approved the study, and each participant provided informed consent.

**Study Protocol**

All study subjects underwent (1) standard transthoracic, 2-dimensionally targeted M-mode and Doppler echocardiography, (2) transesophageal echocardiography for evaluation of coronary flow velocity response to adenosine.

Transthoracic echocardiograms were performed according to standard protocols, and LV mass and mass index, relative wall thickness, afterload-corrected midwall shortening, and stroke volume were calculated with the use of standard formulas. A relative wall thickness >0.42 has been used as a cutoff value for concentric LVH. In addition, theoretical optimal LV mass was individually computed and the percent deviation of the observed from the theoretical LV mass (%LVM) was calculated as previously described. Inappropriate LV mass was defined as an increase >55% from the theoretical value (ie, ∆%LVM>135%). Pulsed Doppler was used to determine transmitral flow profile by measurement of early peak E-wave flow velocity, late peak A-wave flow velocity, and their ratio (E/A ratio).

Transesophageal Doppler echocardiography was used to record coronary flow velocity profile in the proximal left anterior descending artery (SONOS 2500 and 5500, Philips Technologies) at baseline, during adenosine infusion (700 μg/kg per 5 minutes through an indwelling 18-gauge cannula in an antecubital vein), and for 5 minutes afterward. Coronary flow velocity (CFV) was measured at baseline and during maximal flow response to adenosine, and coronary vasodilator response to adenosine was expressed as coronary flow reserve (CFR) and minimum coronary vascular resistance (MCR, mm Hg per second/centimeter). The accuracy of transesophageal Doppler echocardiography for coronary vasodilator capacity assessment and the reproducibility of measurements has been previously tested.

**Statistical Analysis**

Data are expressed as mean±SD. One-factor ANOVA was used to compare normotensive control subjects and subgroups of hypertensive patients, followed by Scheffé post hoc test when needed. When appropriate, ANCOVA was applied to adjust for significant group differences. χ² distribution and the Fisher exact test were used for categorical variables. Least-squares linear regression analysis was used to assess univariate relations between continuous variables, and correlation matrix was used to evaluate the independence of association of continuous variables that did not exhibit excessive collinearity with each other. Statistical analysis was performed by a commonly available software (StatView 5.0, Abacus Concepts Inc).

**Results**

**Characteristics of Study Population**

All normotensive control subjects had appropriate LV mass, 33 hypertensive patients had appropriate LV mass, and 31 had inappropriate LV mass (Table 1). The age of hypertensive patients with inappropriate LV mass was slightly higher as compared with normotensive control subjects (P<0.07). Body mass index was comparably higher in subgroups of hypertensive patients. Hypertensive patients with inappropriate LV mass exhibited slightly higher blood pressure than patients with appropriate LV mass. All measures of LV geometry, including interventricular septum and posterior wall thickness, relative wall thickness, LV mass index, and ∆%LVM were more abnormally greater in hypertensive patients with inappropriate LV mass (all P<0.01), who also exhibited higher prevalence of traditionally defined LVH. In addition, hypertensive patients with inappropriate LV mass had lower afterload-corrected midwall shortening and E/A ratio (both P<0.01). In the whole hypertensive group, E/A ratio was negatively related to interventricular septum thickness, relative wall thickness, and ∆%LVM (r=-0.37, -0.34, and -0.34, respectively; all P<0.01).

**Baseline Coronary Flow Velocity**

Baseline CFV in the left anterior descending artery was increased in hypertensive patients with inappropriate LV mass (Table 2) compared with normotensive control subjects and patients with appropriate LV mass. In both normotensive control

---

**TABLE 1. Characteristics of the Study Groups**

<table>
<thead>
<tr>
<th>Clinical Profile, LV Geometry and Function</th>
<th>Controls (n=14)</th>
<th>Hypertensive Patients (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51±8</td>
<td>52±7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.2±1.6</td>
<td>25.6±2.7*</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>126±7</td>
<td>167±17**</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>76±8</td>
<td>97±7**</td>
</tr>
<tr>
<td>IVS thickness, cm</td>
<td>0.85±0.07</td>
<td>0.99±0.10**</td>
</tr>
<tr>
<td>Posterior wall thickness, cm</td>
<td>0.84±0.08</td>
<td>0.98±0.10**</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.35±0.03</td>
<td>0.40±0.07*</td>
</tr>
<tr>
<td>LVM, g/m²</td>
<td>37±6</td>
<td>47±12*</td>
</tr>
<tr>
<td>Prevalence of LVH, %</td>
<td>108±12</td>
<td>113±15</td>
</tr>
<tr>
<td>Afterload-corrected MS, %</td>
<td>108±4</td>
<td>103±10</td>
</tr>
<tr>
<td>E/A Ratio</td>
<td>1.31±0.17</td>
<td>0.94±0.18**</td>
</tr>
</tbody>
</table>

LVM indicates left ventricular mass; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; IVS, interventricular septum; LVMI, left ventricular mass index; MS, midwall shortening.

*P<0.05, **P<0.01 vs Controls; †P<0.05, ††P<0.01 vs appropriate LVM.
subjects and hypertensive patients, baseline CFV was related positively to simultaneously measured rate-pressure product and, in hypertensive patients, also to age, interventricular septum thickness, and Δ%LVM (Table 2). After adjustment for blood pressure, baseline CFV remained related to rate-pressure product and Δ%LVM. Interventricular septum thickness has been considered because septum represents the perfusion region of the left anterior descending artery, where CFV is measured by transesophageal Doppler echocardiography.

Coronary Flow Velocity Response to Adenosine

CFR was lower and MCR higher in both hypertensive subgroups than in normotensive control subjects, but this impairment was significantly more severe when LV mass was inappropriate (Table 3), even after adjusting for blood pressure. In normotensive control subjects, CFR decreased and MCR increased with age. In hypertensive patients, CFR decreased with age, whereas MCR was not influenced by age. Relative wall thickness, interventricular septum thickness, and Δ%LVM negatively influenced CFR; the inverse relation between CFR and relative wall thickness remained significant after adjusting for age and blood pressure. MCR increased with relative and absolute wall thickness, whereas afterload-corrected midwall shortening and E/A ratio decreased with increasing MCR (Table 3). After adjustment was made for blood pressure, MCR remained positively related to absolute and relative wall thickness and inversely to midwall shortening.

LVH and CFV Response to Adenosine

A separate assessment of coronary flow characteristics was performed in 42 hypertensive patients with clear-cut LVH.

### TABLE 2. Coronary Flow Velocity at Baseline and Its Relationship to Age, Rate-Pressure Product, and LV Geometry

<table>
<thead>
<tr>
<th>Coronary Flow at Baseline</th>
<th>Controls</th>
<th>Hypertensive Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Appropriate LVM</td>
<td>Appropriate LVM</td>
</tr>
<tr>
<td>Comparison</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline CFV, cm/s</td>
<td>26.9±4.2</td>
<td>29.6±7.5</td>
</tr>
<tr>
<td>Baseline RPP, mm Hg per bpm</td>
<td>10099±2432</td>
<td>13721±3009**</td>
</tr>
</tbody>
</table>

**Correlations**

<table>
<thead>
<tr>
<th>Baseline CFV</th>
<th>RPP (r=+0.73, P&lt;0.01)</th>
<th>Age (r=+0.30, P&lt;0.02)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RPP (r=+0.38, P&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IVS Thickness (r=+0.25, P&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Δ%LVM (r=+0.25, P&lt;0.05)</td>
</tr>
</tbody>
</table>

RPP indicates rate-pressure product. **P<0.01 vs Controls; ††P<0.01 vs appropriate LVM.

### TABLE 3. Coronary Flow Velocity Response to Adenosine and Its Relationship to Age, LV Geometry, Function, and Diastolic Filling

<table>
<thead>
<tr>
<th>Coronary Response to Adenosine</th>
<th>Controls</th>
<th>Hypertensive Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Appropriate LVM</td>
<td>Appropriate LVM</td>
</tr>
<tr>
<td>Comparison</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosine CFV, cm/s</td>
<td>93.1±19.3</td>
<td>79.3±20.4*</td>
</tr>
<tr>
<td>Adenosine MBP, mm Hg</td>
<td>79±8</td>
<td>91±11**</td>
</tr>
<tr>
<td>CFR</td>
<td>3.48±0.62</td>
<td>2.72±0.40**</td>
</tr>
<tr>
<td>MCR, mm Hg per s/cm</td>
<td>0.87±0.18</td>
<td>1.19±0.23**</td>
</tr>
</tbody>
</table>

**Correlations**

<table>
<thead>
<tr>
<th>CFR</th>
<th>Age (r=−0.53, P&lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (r=−0.30, P&lt;0.02)</td>
</tr>
<tr>
<td></td>
<td>IVS Thickness (r=−0.33, P&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td>RWT (r=−0.36, P&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td>Δ%LVM (r=−0.27, P&lt;0.05)</td>
</tr>
<tr>
<td>MCR</td>
<td>Age (r=+0.67, P&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td>IVS Thickness (r=+0.33, P&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td>RWT (r=+0.35, P&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td>MS (r=−0.32, P&lt;0.02)</td>
</tr>
<tr>
<td></td>
<td>E/A ratio (r=−0.31, P&lt;0.02)</td>
</tr>
</tbody>
</table>

CFV indicates coronary flow velocity; CFR, coronary flow reserve; MCR, minimum coronary vascular resistance; MBP, mean blood pressure; RWT, relative wall thickness; and MS, afterload-corrected midwall shortening. *P<0.05, **P<0.01 vs Controls; ††P<0.01 vs appropriate LVM.
Twenty-nine of them had inappropriately high LV mass, and 24 had concentric LVH. Within patients with inappropriate LV mass, 22 (76%) had concentric LVH, whereas within those with appropriate LV mass, 11 (85%) had eccentric LVH. Patients with inappropriately high LV mass had lower CFR and higher MCR (2.36 ± 0.41 and 1.33 ± 0.23 mm Hg per second/centimeter) as compared with those with appropriate LV mass (2.74 ± 0.40 and 1.12 ± 0.23 mm Hg per second/centimeter, both P < 0.01). Relations between CFR and relative or absolute wall thickness (r = −0.48 or −0.33, P < 0.01 or 0.05), as well as those between MCR and relative wall thickness, interventricular septum thickness, E/A ratio, and midwall shortening (r = +0.43, +0.35, −0.49, −0.33, P < 0.05) also remained significant when analyzing the sole subgroup with LVH.

Discussion
This study indicates that in patients with essential hypertension, an increase in LV mass higher than needed to compensate for increased cardiac workload at a given body size is associated with more severe reduction of CFR and increase in MCR as compared with the condition of a purely compensatory increase in LV mass. This observation is evident in the whole hypertensive population as well as in the subset of patients with clear-cut LVH. Coronary vasodilator capacity appears to deteriorate mainly in relation to increasing LV wall thickness, both absolute and relative.

Although increase in LV mass is considered a compensatory mechanism finalized to cope with abnormal loading conditions and to preserve pump function, it is also clear that at some point of the evolution of cardiovascular disease, this mechanism becomes dangerous. Hypertensive LVH is related to myocardial ischemia, heart failure, and sudden death and represents the most important predictor of cardiovascular risk other than age. Thus, understanding when increasing LV mass ceases to be a compensatory mechanism and deviates toward the progression of cardiovascular risk, and what are the major pathophysiologic alterations underlying this risk, can be an important clinical goal.

The simple, traditional normalization of LV mass for body size does not account for the increased workload imposed on the heart by systemic hypertension. In contrast, a study investigating the age-related increase in LV mass and the age-related changes in cardiac workload in a reference population of healthy normotensive, normal-weight individuals demonstrated that up to 82% of LV mass variance can be explained when body size, gender, and stroke work at rest are considered together. This observation allowed differentiating between compensatory or appropriate and overcompensatory or inappropriate increase in LV mass in pathologic conditions affecting hemodynamic load. A study in a population of 294 hypertensive patients demonstrated that an increase in LV mass >35% of the value predicted for gender, body height, and stroke work is an independent predictor of cardiovascular risk, both in the whole population and in the subset of patients with clear-cut LVH. This finding has been recently confirmed in a larger population from a multicenter study. Coronary microvascular abnormalities might be one possible pathophysiological explanation for the prognostic value of inappropriate LV mass. The present study provides evidence that detectable differences in coronary function can be highlighted in relation with the presence of excess LV mass, even in a subgroup selected on the basis of the presence of clear-cut LVH.

Even though indexes of coronary function are tightly interrelated, each of them may provide distinct insight on coronary hemodynamics. CFR indicates the ability of coronary flow to increase above resting levels to meet any augmentation of myocardial oxygen demand, whereas MCR reflects the decline of vasomotor tone up to the maximally vasodilated state. In the hypertensive heart, in the absence of significant epicardial artery stenosis, increase in MCR is a consequence of structural and functional changes in coronary circulation that result in the reduction of maximal cross-sectional area of the coronary microvasculature. Morphometric studies in various animal models suggest that growth of the coronary microvascular bed is not adequate to the magnitude of the myocardial growth, and a relative decrease in microvascular density occurs in hypertensive LVH. The parallel increase in MCR and LV wall thickness observed in our hypertensive patients may therefore reflect inadequate neangiogenesis. Accordingly, hypertensive patients with higher absolute and relative wall thickness, that is, those with inappropriate LV mass, had significantly higher MCR. Furthermore, with increasing wall thickness and LV mass as a percentage deviation from its theoretical value, baseline coronary flow velocity also increased, and the amplitude of relative flow velocity increment, that is, CFR, decreased. Altogether, these data indicate that in hypertensive patients with inappropriate LV mass, the ability of coronary flow to increase during conditions of high myocardial oxygen demand may be restricted both by impaired vasodilator capacity as well as high baseline flow. Observed alterations in coronary hemodynamics seem to be mainly related to increase in LV wall thickness.

In our study, LV diastolic filling pattern (grossly estimated by E/A ratio) and myocardial systolic performance (assessed as afterload-corrected midwall shortening) deteriorated with increasing MCR, whereas MCR and LV diastolic filling worsened with wall thickness. Theoretically, the relation between LV functional impairment and coronary dysfunction may be a reciprocal one. Hypertension-induced LVH is characterized not only by myocyte hypertrophy but also by collagen deposition within the ventricular wall and around the coronary vessels. Myocardial fibrosis increasing stiffness of the ventricular wall impairs ventricular relaxation, which, in turn, and together with perivascular collagen deposition, may interfere with coronary hemodynamics, and diminishes systolic function. The impairment in coronary vasodilator capacity is likely to initiate and maintain a process of myocardial malperfusion and malnutrition, which can provoke functional depression of myocardial performance and further increase in interstitial fibrosis. Previous clinical studies demonstrated that Doppler indexes of impaired LV relaxation are independently related to LV midwall shortening and that midwall shortening, decreasing with increasing relative wall thickness, represents an independent predictor of cardiovascular risk in arterial hypertension.
Study Limitations

By transesophageal echocardiography, coronary flow velocity can be measured in the left anterior descending artery, whereas vessel diameter can be measured at the left main artery level. Thus, this method does not allow calculation of volumetric flow, and coronary microcirculatory function must be evaluated through the flow velocity response to the downstream arteriolar vasodilation.4 Such an approach could lead to the underestimation of coronary vasodilator capacity if the diameter of epicardial vessel significantly increases in response to arteriolar vasodilator and flow enhancement. In a previous study,17 we have demonstrated that in hypertensive patients, epicardial vessel diameter increased by 6.4±3.3% during the infusion of arteriolar vasodilator. Consequently, changes of epicardial vessel caliber can be neglected in the estimation of coronary microvascular function of hypertensive patients.

Conclusions

In the hypertensive heart, a deviation of LV mass from values predicted for individual body size, gender, and cardiac workload is associated with higher baseline coronary flow velocity, lower coronary flow velocity response to adenosine, impaired LV diastolic filling, and depressed LV myocardial performance. Such a cluster of functional abnormalities may be responsible for an increased susceptibility to myocardial ischemia13–14 and heart failure.15 Current data, together with the previous observation that patients with inappropriate LV mass have higher body mass index and unfavorable metabolic profile with higher fasting glucose levels and lower HDL cholesterol,23 may help to explain the adverse cardiovascular outcome of these subjects.20,22

References


3. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med. 1991;114:345–352.


Coronary Vasodilator Capacity and Hypertension-Induced Increase in Left Ventricular Mass

Michaela Kozáková, Giovanni de Simone, Carmela Morizzo and Carlo Palombo

Hypertension. 2003;41:224-229; originally published online December 30, 2002;
doi: 10.1161/01.HYP.0000049623.25854.B7

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/41/2/224

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/