Cardiac Hypertrophy in Hypertension
Repolarization Abnormalities Elicited by Rapid Lowering of Pressure

MAURO PEPI, MARINA ALIMENTO, ANNA MALTAGLIATI, AND MAURIZIO D. GUAZZI

SUMMARY In hypertension, coronary flow is augmented and oxygen balance is adequate despite an increase in coronary resistance. For the maintenance of flow in the presence of and after regression of ventricular hypertrophy, the ratio of pressure and ventricular mass must remain normal. Coronary reserve would be altered if treatment normalized pressure but not ventricular mass or if pressure were lowered too fast. We investigated 42 patients with primary hypertension. In 28 (Group 1) left ventricular mass index (by ultrasound) was within the mean value + 2 SD (96 + 38 g/m²) of 145 controls and exceeded these values in the remaining 14 patients (Group 2). The diastolic pressure was lowered rapidly to between 85 and 90 mm Hg with two potent vasodilators, nifedipine (sublingually) and nitroprusside, while a 12-lead electrocardiogram was recorded continuously. During both tests, seven patients in Group 2 (responders) showed inversion of normal T waves, in lead I, aVL, and V₃₋₆. These changes waxed and waned in parallel with the pressure fall and recovery and were not attributable to alterations in adrenergic tone, conduction disturbances, variations, or group differences in the QRS axis, QTc interval, heart rate, left ventricular fractional shortening, wall stress, rate of dimension increase in early diastole, or isovolumic relaxation. A "steal phenomenon" or passive collapse in compliant coronary lesions during vasodilatation seems unlikely; in fact, patients were free from coronary symptoms, and the electrocardiographic alterations occurred only in seven patients in Group 2, who had a greater left ventricular mass index and required a larger pressure drop to return the diastolic pressure to normal. These data support the concept that energy supply to the hypertrophied hypertensive heart may depend on coronary perfusion pressure.

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KEY WORDS • coronary perfusion • ventricular mass • coronary reserve • subendocardium

With the development of sustained hypertension and cardiac hypertrophy, several factors, in addition to the progression of coronary artery disease, undermine coronary circulation and the metabolic reserve of the heart: an increase in the vascular and in the myocardial components of the coronary resistance, impairment of the coronary vascular reserve, and enhancement of the myocardial oxygen demand because of the augmented mass or wall stress, or both. In essential hypertensive subjects, coronary oxygen extraction is largely normal and coronary blood flow per unit of weight is increased, so that an adequate oxygen balance is maintained despite a significant increase in coronary vascular resistance. Wicker and Tarazi found that coronary blood flow per gram of tissue was normal in a rat model of left ventricular hypertrophy induced by renal arterial clipping, both during development and following regression of hypertrophy. The maintenance of normality in coronary flow in the presence of ventricular hypertrophy and following its regression was related to the fact that pressure and ventricular mass varied in parallel, so that the ratio of the two variables remained normal at all stages. On this basis, the rise of aortic pressure would appear to have two opposing aspects: an increase of myocardial oxygen demand and a rise of the coronary perfusion pressure adequate to maintain or to raise the coronary blood flow.
These considerations have the important clinical implication that coronary flow reserve after antihypertensive treatment will remain normal if hypertension and hypertrophy regress in parallel. Concern has been expressed regarding the possibility that coronary flow reserve becomes altered if treatment normalizes blood pressure but not ventricular mass. A discrepancy like this would occur with rapid lowering of blood pressure in the presence of an augmented LV mass. Although electrocardiographic changes suggestive of myocardial injury have been reported with the use of diazoxide, hydralazine, and nifedipine for severe hypertension, this problem has so far received little attention despite its obvious clinical importance. Therefore, these aspects were investigated in the present study using noninvasive methods.

Patients and Methods

The study population was composed of 42 hospitalized patients who fulfilled the following requirements: primary hypertension untreated or poorly treated in the past with interruption of any drug therapy at least a month before admission to hospital; age of 60 years or less; willingness to participate in the study; no history or signs of myocardial infarction or valvular, primary, or ischemic heart disease; absence of cerebrovascular disease, diabetes, or renal functional impairment; no urgent need for therapy, as judged from the clinical condition; sinus rhythm with normal intraventricular conduction and normal T waves in the electrocardiogram (ECG); high quality LV echocardiograms.

During the first week after admission, no drug interfering with the cardiovascular function was given, secondary forms of hypertension were excluded through appropriate tests, a 12-lead ECG was recorded daily in the baseline and during adrenergic activation (patients were asked to divide a four-digit number by a two-digit number while under pressure of time) for a reliable evaluation of the baseline appearance and of the possible changes induced by alterations in adrenergic tone, and LV mass was determined through echocardiography (average of measurements on two different days). We then evaluated the pattern of the repolarization phase of the ECG during rapid lowering of blood pressure with nifedipine. The ECG was monitored continuously and 12-lead standard records, at a paper speed of 100 mm/sec. Echocardiograms were digitized using a Kontron computer system (Model Cardio 80, Munich, Germany). Two-dimensional views were used as a quality control check on the accuracy of the M-mode calculations. Records of the LV cavity were taken at the level of the tip of the mitral leaflets showing cusp separation; simultaneous ECGs and phonocardiograms were recorded at the paper speed of 100 mm/sec. Echocardiograms were digitized using a Kontron computer system (Model Cardio 80, Munich, West Germany). The following measurements were obtained: maximum (Dd) and minimum (Ds) LV dimension, and fiber fractional shortening calculated as 100(Dd - Ds)/Dd; thickness of the LV posterior wall at minimum cavity size (PWs) and at the onset of the QRS (PWd); ventricular septal thickness at the onset of the QRS (VS); peak value of normalized rate of dimension (D) increase, calculated as 1/D x DD/dt during early diastole; and isovolumic relaxation period, calculated as the interval between the onset of the first high frequency deflection of the aortic component of the second heart sound to mitral valve opening. LV end-systolic stress was calculated from the following equation: end-systolic stress = 0.98(0.334 x systolic arterial pressure x Ds/PWs [1 + PWs/Ds]) - 2; LV
mass was obtained by using the Penn convention measurements\textsuperscript{15}: Penn-cube LV mass $= 1.04 \left( [Dd + VS + PWd]^3 - Dd^3 \right) - 13.6$ g.

Six patients with atypical chest pain underwent coronary arteriography; in them the ECG recorded during pain did not vary from the baseline appearance.

Analysis of variance for repetitive measurements was used for statistical comparisons, and a $p$ value of less than 0.05 was considered significant. Data are expressed as means $\pm$ SD.

**Results**

**Patient Population**

LV mass index was considered augmented if exceeding the average value $+2$ SD (96 $\pm$ 38 g/m\textsuperscript{2}) of 145 control normal subjects investigated in our laboratory with the same ultrasound methods. By these criteria, LV mass was normal in 28 (Group 1) and augmented in 14 patients (Group 2) of the study population.

The repolarization phase on the ECG remained unchanged during the pharmacological tests in all patients in Group 1 and in seven in Group 2, while seven in this group showed the T-wave alterations described in Patients and Methods. According to this pattern, Group 2 was further divided into Groups 2A and 2B (responders).

Table 1 shows that Groups 1, 2A, and 2B were homogeneous as regards sex and age. LV mass index in Groups 2A and 2B exceeded, by selection, that in Group 1; however, a significant finding was that responders exhibited mass and relative wall thickness (reflected by the ratio of wall thickness and ventricular dimension) significantly greater than those of nonresponders. The ECG pattern of LV hypertrophy occurred in a similar number of patients in the three groups, and the QTc interval was comparable.

**Blood Pressure Variations and ECG Pattern**

Responders were invariably responsive to both nifedipine and nitroprusside treatments, and alterations of the repolarization phase with the two compounds were quite similar. A typical example is shown in Figure 1, which reproduces a 12-lead ECG in the baseline and following nifedipine and nitroprusside treatment: T-wave inversion in lead I, aVL, V\textsubscript{3} and V\textsubscript{6}, and flattening in lead II and aVF are obvious with both drugs. In this particular patient blood pressure was lowered from 215/125 mm Hg to 145/90 mm Hg and to 150/90 mm Hg by nifedipine and nitroprusside, respectively. The clear time relation existing between the blood pressure pattern and that of the T wave is outlined in Figure 2, which reports blood pressure averages of the responder group at baseline, at 20 minutes after nifedipine treatment, at the nadir of the pressure drop, and during recovery; an example of the ECG pattern is also reproduced. From an average of 212/123 mm Hg, pressure was already significantly reduced to 167/94 at 20 minutes, reached 160/88 at 55 minutes, and rose to 188/108 mm Hg at 190 minutes. The T-wave changes waxed and waned in parallel with the blood pressure fall and recovery. The ECGs varied in an impressively similar manner when comparable variations in blood pressure were obtained with the nitroprusside test.

**Adrenergic Activation Tests and ECG Pattern**

Each patient invariably reacted to the mental arithmetic test with activation of the adrenergic system, as reflected by heart rate and blood pressure rises. The T wave did not become inverted and its baseline amplitude did not decrease in any patient.

**Symptoms and Cardiac Enzymes**

Patients remained entirely asymptomatic during the ECG changes, and there was no rise in serum cardiac enzymes.

**Circulatory and Ultrasound Variables**

Systolic and diastolic pressures in Group 2B were somewhat higher than those in the other groups (Figure 3); however, the differences were of marginal statistical significance. No group differences were seen in heart rate at baseline and at maximal pressure fall with either compound or in the blood pressure levels attained during the tests.

Figure 4 shows changes in diastolic pressure produced by nifedipine (vertical axis) and LV mass indexes (horizontal axis) for individual patients, as well as the means for the groups. The vertical line indicates the average $+2$ SD for normal index of LV mass and separates patients in Group 1 from those in Groups 2A and 2B. In Group 2B the diastolic pressure fall from baseline and the LV mass index significantly exceeded those in Group 2A. In other words, compared with nonresponders, responders showed greater indices of LV mass and needed larger pressure fall for the diastolic pressure to return to normal levels.

Among the examined variables reflecting the systolic and the diastolic function of the left ventricle (see Figure 3), baseline fractional shortening and systolic wall stress were comparable in the three groups. The peak rate of dimensional increase during early diastole was lower in Group 2B than in the other groups. The isovolumic relaxation period was significantly prolonged in Groups 2A and 2B compared with that in Group 1. Both drugs reduced systolic wall stress, raised fractional fiber shortening, enhanced early diastolic rate of dimensional increase to a similar level in each group, and curtailed the isovolumic relaxation period in a proportionally greater extent in Groups 2A and 2B, so that differences from Group 1 were abolished.

The QTc interval remained unchanged during the pharmacological tests. Coronary angiography showed only minimal epicardial coronary artery lumen narrowing in four patients and entirely normal vessels in two patients.

**Discussion**

This study confirms the previous observations that short-term treatment of severe hypertension with nifedipine may be associated with the occurrence of tran-
TABLE 1. Clinical, Electrocardiographic and Echocardiographic Data in 42 Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 28)</th>
<th>Group 2A (n = 7)</th>
<th>Group 2B (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>34–60</td>
<td>45–58</td>
<td>31–60</td>
</tr>
<tr>
<td>Mean</td>
<td>52.3 ± 8.7</td>
<td>52.4 ± 9.6</td>
<td>51.8 ± 7.6</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>13:15</td>
<td>5:2</td>
<td>5:2</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>101.5 ± 15.1</td>
<td>148.8 ± 13.5*</td>
<td>179.5±28.1*†</td>
</tr>
<tr>
<td>LV dimension (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>45.5 ± 4.6</td>
<td>50 ± 7.1</td>
<td>47.4 ± 5.5</td>
</tr>
<tr>
<td>Minimum</td>
<td>27.9 ± 3.7</td>
<td>34.3 ± 7.8</td>
<td>32.1 ± 4.2</td>
</tr>
<tr>
<td>Posterior wall thickness (onset of QRS; mm)</td>
<td>9.1 ± 1.3</td>
<td>10.5 ± 1.7*</td>
<td>11.7 ± 1.7*</td>
</tr>
<tr>
<td>Septal thickness (onset of QRS; mm)</td>
<td>10.4 ± 1.6</td>
<td>12.6 ± 2.8*</td>
<td>15.1 ± 2.2*†</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.58 ± 0.13</td>
</tr>
<tr>
<td>Atypical chest pain</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>LV hypertrophy (ECG criteria)</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>QTc interval (msec)</td>
<td>402 ± 22</td>
<td>404.5 ± 23.4</td>
<td>406 ± 41</td>
</tr>
<tr>
<td>Serum uric acid (mg/dl)</td>
<td>5.6 ± 0.7</td>
<td>5.5 ± 0.9</td>
<td>5.1 ± 1</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>211 ± 19</td>
<td>195.2 ± 18.3</td>
<td>190 ± 24.1</td>
</tr>
</tbody>
</table>

Most values are means ± SD. LV = left ventricular.

*p < 0.01, compared with Group 1 values; †p < 0.05, compared with Group 2A values.

Figure 1. Twelve-lead ECG, blood pressure (BP), and heart rate (HR) in a patient who responded to nifedipine and nitroprusside treatment with T-wave inversion in lead I, aVL, V₅, and V₆.
Moore et al.\textsuperscript{17} examined the anatomical and physiological correlations of the T-wave changes in a large series of patients with LV hypertrophy. They found that in pressure overload–induced hypertrophy the ECG “strain” pattern, compared with normal ST segment and T wave, correlated most closely with diastolic abnormalities, such as reduction of the rate of dimensional increase in early diastole and prolongation of isovolumic relaxation. Diastolic alterations similar to these were noticed (see Figure 3) in the basal condition in Group 2A and, more obviously, in Group 2B. These alterations disappeared, however, during the nifedipine and nitroprusside tests in both groups; only Group 2B exhibited the ischemic pattern on the ECG.

Nifedipine\textsuperscript{18, 19} and nitroprusside\textsuperscript{20, 21} are potent coronary artery dilators that may produce myocardial ischemia by dilating vessels of nonischemic myocardium to a greater degree than those of ischemic myocardium or by diverting perfusion from an ischemic coronary vascular bed to a more vasodilated peripheral circulation. Aggravation of underlying myocardial ischemia by nitroprusside\textsuperscript{22} or nifedipine\textsuperscript{23} has been explained through such a “coronary steal” phenomenon. Passive collapse in compliant coronary lesions due to the pressure drop through the stenoses consequent to drug-induced coronary hyperemia\textsuperscript{24} might be an alternative negative effect of the vasodilatation. However, these mechanisms imply the existence of severe coronary lesions. The lack of systematic invasive procedures in our study is an obvious limitation to these interpretations. Although coronary artery disease in this large patient group is not excludes, 1) none of the patients had had any coronary events in the past and all were free from anginal symp-
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**Figure 3.** Hemodynamic variables in the baseline and during the nifedipine and nitroprusside tests in Groups 1, 2A, and 2B. Bars represent means ± SD. BP = blood pressure (systolic and diastolic); HR = heart rate; FFS = fiber fractional shortening; eSS = end-systolic wall stress; IRP = isovolumic relaxation period; PRDI = peak rate of dimension increase during early diastole. Asterisk indicates differences from Group 1 significant at $p < 0.01$. Triangle indicates differences from baseline significant at $p < 0.01$.

A few points are well documented in this study: the ECG changes were induced by rapidly acting pressure-lowering agents in patients in whom hypertension was more severe, the blood pressure drop more marked, and LV mass and hypertrophy greater. The T-wave inversion waxed and waned in parallel with the fall and recovery of blood pressure. The relationship between the two appears even more obvious if it is considered that pressure recovered faster after nitroprusside than after nifedipine treatment, because of the different rate of decay of the vasodilating action, and that T-wave recovery behaved in the same way. These data fit well with the concept that coronary reserve of the hypertensive hypertrophied ventricle is abnormal and that the energy supply and the electrical activity of the hypertrophied heart become dependent on the adequacy of the coronary perfusion pressure. Our observations did not discern whether this pattern is inherent in the hypertrophy process itself or derives from a coronary small vessel disease that develops in parallel with the increasing LV mass. However, our findings...
suggest the possibility that high blood pressure from a pathological elicitor becomes a physiological requirement for the hypertrophied hypertensive heart. The subendocardium tends to suffer from these discrepancies first. By this line of reasoning, a link may be established between the repolarization abnormalities elicited by rapid lowering of pressure and the strain pattern in aortic regurgitation. The latter, in fact, has been shown to be more likely to occur in the presence of increased ventricular mass and internal dimension, reduction in coronary flow reserve, and decreased aortic diastolic pressure.

If these interpretations are correct, we support the practice of assessing LV mass in severe hypertension before the initiation of treatment. This seems especially pertinent in hypertensive crisis situations in which prompt lowering of pressure becomes crucial to the prevention of disabling or even lethal complications. A cautious use of rapid-acting drugs in patients with augmented LV mass may result in clinical benefit for those with underlying coronary insufficiency. Prospective studies are needed to define whether the application of one of these vasodilators would be appropriate for differentiating between hypertensive patients with and without coronary risk.

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