Coronary Reserve Is Depressed in Postmyocardial Infarction Reactive Cardiac Hypertrophy

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After a myocardial infarction (MI), the remaining myocardium undergoes a compensatory reactive hypertrophy. Although coronary perfusion to the surviving myocardium can be an important determinant of cardiac function in this setting, there are no available data regarding myocardial blood flow in reactive hypertrophy. Accordingly, we measured coronary blood flow and reserve using radioactive microspheres in rats 4 weeks after indution of an MI by ligation of the left coronary artery. Maximal coronary dilation was induced by Carbochrome, a potent coronary vasodilator, infused at a rate of 0.45 mg/kg/min up to a total dose of 12 mg/kg. Sham-operated rats served as controls. All animals in the infarct group had a large MI affecting 30–51% (average, 41%) of the left ventricle. Left ventricular end-diastolic pressure was significantly elevated (30±6.5 vs. 8.0±2.5 mm Hg in sham-operated rats, \( p<0.01 \)) and baseline hemodynamic indexes of cardiac performance were significantly (\( p<0.01 \)) reduced in this group. Myocyte cross-sectional area measurements were used as an index to quantify the degree of reactive hypertrophy and indicated that the infarcted animals had, on average, a 30% hypertrophic response of the surviving left ventricular myocardium. In the infarcted animals, both coronary flow and vasodilator reserve in the surviving myocardium were depressed. Maximal coronary blood flow in the remaining myocardium was significantly lower than that measured in the sham-operated animals (839 and 1,479 ml/min/100 g, respectively; \( p<0.001 \)). Similarly, minimal coronary resistance was significantly higher in the MI group as compared with the sham group (0.12 vs. 0.07 mm Hg/ml/min/100 g, respectively; \( p<0.001 \)). There was a significant correlation between minimal coronary resistance and myocardial cross-sectional area (\( r=0.65, \ p<0.01 \)) or between minimal coronary resistance and left ventricular end-diastolic pressure (\( r=0.66, \ p<0.01 \)), suggesting that the depression in coronary reserve was related both to the elevated preload and the hypertrophic process itself. Thus, after an MI, the surviving myocardium exhibits a perfusion deficit involving the intramyocardial resistance vessels. This abnormality can render the heart more susceptible to develop ischemia even in the absence of large coronary artery disease. (Circulation 1990;81:238–246)
report to date on the consequences of reactive cardiac hypertrophy on the coronary circulation, Anversa et al.\textsuperscript{13} found that the capillary density of the spared myocardium was significantly reduced in rats after an MI. These findings raised the possibility that the noninfarcted myocardium was more vulnerable to additional ischemic insults. However, no measurements of coronary blood flow were performed in that study, and the functional significance of these anatomical changes in the capillary network remains unclear.

This study was, therefore, designed to test the hypothesis that, similar to other types of hypertrophy, coronary reserve is depressed in the noninfarcted myocardium. To address this issue, we investigated a well-established rat model of post–MI reactive cardiac hypertrophy\textsuperscript{26} and measured coronary reserve in conscious unrestrained animals 4 weeks after induction of the MI using the microsphere technique.

**Methods**

Male Sprague-Dawley rats (body weight, 125–150 g) (Hilltop Lab Animal, Scottsdale, Pennsylvania) were housed throughout these experiments. All rats were housed under identical conditions in a 12-hour light-dark cycle and given food and water ad libitum. All surgical procedures and handling of the rats were performed in accordance with our institutional guidelines on animal use in research.

**Induction of Myocardial Infarction**

MI was induced using a method previously described by Pfeffer et al.\textsuperscript{26} with slight modifications. The rats were anesthetized with pentobarbital (40 mg/kg i.p.) and intubated through the mouth. Artificial respiration was established with a small-animal respirator (Harvard model 680, Harvard Apparatus, South Natick, Massachusetts). Through a left thoracotomy, the heart was exposed and the pericardium incised. The left coronary artery was ligated between the pulmonary artery outflow tract and the left atrium using 6-0 prolene sutures. After closure of the chest, and after spontaneous respiration had resumed, the intratracheal tube was removed and the animal returned to its cage. Benzathine penicillin (100,000 units i.m.) (Bicillin) intramuscular was given to all animals to prevent sepsis. Sham-operated rats underwent exactly the same surgical procedure but without coronary ligation.

**Determination of Coronary Blood Flow**

Four weeks after MI induction, coronary blood flow and coronary reserve were determined in conscious unrestrained animals using LV injections of radioactive microspheres. Under ether anesthesia, LV and aortic catheters were positioned through the right carotid and femoral arteries, respectively. The aortic catheter was used for blood pressure recording and withdrawal of the reference sample. After catheter placement, the rats were allowed to recover for 3–4 hours in small cages where they sat quietly so that subsequent measurements were made in fully conscious unrestrained animals.

Microspheres 15 \( \mu \)m in diameter and labeled with either scandium 46, strontium 85, cerium 141, or iodine 125 (3M, St. Paul, Minnesota) were suspended in a 70% glucose solution with 0.05% Tween 80 as an antiaggregant. After thorough mechanical and ultrasonic agitation, approximately 200,000 microspheres were injected into the LV, which was then flushed with 0.30 ml saline over 15 seconds. In all instances, the proper location of the LV catheter was verified either by determining its position after killing the animal or by recording LV pressure before the microsphere injection. Blood was withdrawn by a Harvard pump (model 940, Harvard Apparatus) from the aortic catheter at a constant rate of 0.51 ml/min for 75 seconds. Two flow determinations, first under baseline conditions and then after maximal dilation with carbochrome, were performed in all animals using two differently radiolabeled microspheres. After the first determination, the blood withdrawn was replaced with an equal amount from a strain- and age-matched donor. Carbochrome was then infused through the LV catheter at a constant rate of 0.45 mg/kg/min up to a total dose of 12 mg/kg body wt to determine coronary reserve. We have previously shown that this dose causes maximal coronary dilation in rats.\textsuperscript{21} The second microsphere injection was performed 4 minutes after the end of the carbochrome infusion.

On completion of the experiment, the animals were anesthetized with 50 mg/kg pentobarbital administered by the LV catheter. A tracheotomy was performed and the animals ventilated with room air using a small-animal Harvard respirator (Harvard Apparatus). The heart then was fixed as detailed in the next section. The right ventricle (RV) was cut away leaving the LV and septum. Three parallel transversal slices, 1 mm in thickness, were taken from the basal, medial, and apical regions of the LV for histologic studies. The remaining myocardium was separated into two parts, the infarcted area and the noninfarcted area. Because flow to infarcted areas is small, scar tissue was carefully excluded from the noninfarcted tissue samples. Inclusion of scar tissue would have led to spurious reductions in flow and to an overestimation of coronary reserve decline in the remaining myocardium. A narrow band of nonischemic tissue surrounding the infarct zone was, therefore, cut away from the remaining myocardium along with the infarcted tissue. As a result and because in these experiments all MI affected at least 30% of the whole LV circumferential length, the amount of surviving tissue remaining in the free wall was small, and endocardial or epicardial samples could not be reliably obtained. All tissue samples were weighed and then counted in a gamma counter (Packard Minaxi Auto-Gamma 5000 Series, Packard Instruments, Downers Grove, Illinois). From the radioactivity in each sample and in the arterial blood withdrawn (reference sample), blood flow was computed...
according to standard formulae. Coronary vascular resistance was calculated by dividing mean arterial pressure recorded just before each microsphere injection by the corresponding coronary blood flow. Because perfusion of the infarct region was small or negligible, only flows to the surviving myocardium are reported in the MI group.

**Analysis of Infarct Size and Hypertrophy**

The heart was perfused through an aortic cannula with approximately 150 ml phosphate buffered-saline solution adjusted to pH 7.3–7.4. Procaine (30 ml 2% Procaine HCl) was added to the solution to produce maximal coronary dilation and induce cardiac arrest in diastole. The heart was then perfused at a pressure of 100 mm Hg with 150 ml 1.5% glutaraldehyde buffered to pH 7.3–7.4. After complete fixation, the heart was removed from the chest and dissected as previously described. The 1-mm-thick slices taken from the basal, midventricular, and apical regions were postfixixed overnight in 1.5% glutaraldehyde and embedded in Epon resin. Four to five 1.0-μm sections were obtained from each slice and stained with toluidine blue. All morphometric measurements were performed with the Bioquant IV image analyzer system (R & M Biometrics, Nashville, Tennessee). Sections were projected on to a video monitor using an Olympus BH-2 light microscope (Olympus, Lake Success, New York) connected to the monitor by a video camera at a final magnification of ×60. The perimeters of the structures of interests, that is, the infarcted and noninfarcted zones or the myocytes, were then traced on a digitizing pad interfaced with an Everex 3000 (Everex, Fremont, California) microcomputer. The corresponding areas or lengths were subsequently calculated using the Bioquant software (R & M Biometrics).

**Estimation of infarct size.** Infarct size was expressed as the ratio of scar length to total circumference of each cross section. Total circumference was computed as the mean of the sum of epicardial and endocardial circumferential and scar length measurements. Several studies have reported that the summation of these length measurements approximates the surface area of the infarcted zone.

**Estimation of ventricular hypertrophy.** Two methods were used to assess the degree of reactive hypertrophy. Left ventricle weight provides only an approximation of the degree of hypertrophy because edema or wall thinning will lead to an over or underestimation of reactive hypertrophy, respectively. Myocyte cross-sectional area was determined in a blind fashion on fibers arranged in transversal sections across the ventricular septum and the adjacent noninfarcted LV free wall. Only those sections with circular capillary profiles and fiber shapes, indicative of a true cross section, were analyzed. Myocyte cross-sectional area was morphometrically determined in fibers that showed a nucleus. When there was no visible nucleus within a myocyte, these fibers were included only if their size was comparable with that of the adjacent fibers that contained nuclei. Two to three sections were taken from the basal, midventricular, and apical myocardial regions, and from each section, approximately 20–40 fibers were analyzed. Thus 200–300 fibers per heart were sampled.

**Experimental Protocols**

MI was induced in 1.5-month-old rats using the procedure just described. Age-matched sham-operated animals served as controls. Coronary reserve, infarct size, and reactive hypertrophy were determined 4 weeks after induction of MI or the sham procedure. Nonoperated normal rats were not included in this study because their structural and coronary characteristics were similar to sham-operated animals. Previous studies have indicated that there are no detectable differences in cardiac mass and myocyte size between sham-operated and nonoperated rats. Furthermore, in this study, coronary blood flow and reserve measurements in the sham-operated animals were not different from those obtained in normal age-matched Sprague-Dawley rats in our laboratory.

**Statistical Analysis**

Comparisons between experimental groups were performed using an unpaired or paired t test as appropriate. Correlation coefficients were computed using a least-squares linear regression analysis. All computations were performed using a specifically designed software for flow calculations and the Statistical Analysis System statistical package.

**Results**

**Mortality and Mortality After Induction of Myocardial Infarction**

The immediate (24 hours) mortality rate was 35%, whereas late (1–30 days) mortality rate was 5%. Of the 60% surviving animals, all but 5% developed an acute MI. The early mortality rate after sham operation was 13%; no animals died after the first 24 hours.

**Systemic and Cardiac Hemodynamic Parameters**

Both baseline mean arterial pressure and cardiac function indexes were depressed (p<0.01) in the animals with MI, as shown by a decreased cardiac index and an elevated LV end-diastolic pressure. Carboxyhemoglobin induced a moderate but significant fall in total peripheral resistance associated with a compensatory rise in cardiac index in both groups. Despite similar peripheral vasodilation, however, cardiac index increased less in the MI group, a finding that confirms the impairment in cardiac function in these animals. Postcarboxyhemoglobin LV end-diastolic pressure was not measured in all instances but was found similar to baseline values in a subset of sham-operated and infarcted animals (Table 1).
Infarct Size and Reactive Hypertrophy

All animals developed large MIs in the size range of 30–51% (mean, 41%) of the LV area. Although the infarcted area was not included in LV mass measurements in the animals with MI, LV weight normalized for body weight was only slightly diminished in this group as compared with the sham-operated animals. Myocyte cross-sectional area in the remaining LV was 30% higher in the animals with MI than in the control rats (p<0.001). There were no significant differences in myocyte cross-sectional area within each group between the basal, medial, or apical sections of the left ventricle (data not shown). The RV weight of rats with MI was markedly augmented both when expressed in absolute terms or after normalization by the body weight (p<0.001). This RV hypertrophy was associated with a significant (p<0.01) degree of myocyte hypertrophy as evidenced by an increase in RV myocyte cross-sectional area (p<0.01).

Coronary Hemodynamics

Left ventricle baseline measurements. Baseline coronary blood flow to the surviving myocardium was mildly but significantly (p<0.05) elevated in the infarcted group. Because mean arterial pressure was decreased in this group, coronary resistance was also significantly (p<0.01) lower in the animals with infarction.

Left ventricle postcarbochrome measurements. After maximal coronary dilation with carbochrome, LV coronary blood flow increased fourfold (p<0.001) in the sham-operated animals. In contrast, there was only a twofold increment in coronary blood flow to the surviving myocardium in the infarcted animals. Similarly, LV coronary resistance decreased threefold in the control group but only twofold in the animals with MI. Thus, in the MI group, maximal coronary blood flow to the spared myocardium was significantly lower, whereas minimal coronary resistance was significantly elevated (p<0.001, for both) as compared with the sham-operated animals.

There were no significant differences in myocardial flow rate or coronary resistance in each group among basal, medial, or apical sections of the LV. There was a significant correlation between minimal coronary resistance and LV myocyte cross-sectional area (r=0.65, p<0.01) or between minimal coronary resistance and LV end-diastolic pressure (r=0.66, p<0.01). Similarly, a significant correlation was found between MI size and maximal LV coronary blood flow (r=−0.62, p<0.05).

Right ventricle. Changes in RV coronary blood flow were comparable with those measured in the LV both under baseline conditions and after maximal coronary dilation. Both coronary flow and vasodilator reserve were reduced in the infarcted

<table>
<thead>
<tr>
<th>TABLE 1. Systemic and Cardiac Hemodynamic Parameters</th>
<th>Sham-operated</th>
<th>MI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animals (n)</td>
<td>12</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>120±13</td>
<td>99±8</td>
<td>&lt;0.001</td>
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<tr>
<td>Postcarbochrome</td>
<td>112±10*</td>
<td>94±6*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>384±19</td>
<td>394±41</td>
<td>0.45</td>
</tr>
<tr>
<td>Postcarbochrome</td>
<td>398±25*</td>
<td>405±29</td>
<td>0.50</td>
</tr>
<tr>
<td>Cardiac index (ml/min/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>322±74</td>
<td>272±55</td>
<td>0.08</td>
</tr>
<tr>
<td>Postcarbochrome</td>
<td>421±71*</td>
<td>318±106</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total peripheral resistance (mm Hg/ml/min/kg)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.39±0.10</td>
<td>0.38±0.07</td>
<td>0.66</td>
</tr>
<tr>
<td>Postcarbochrome</td>
<td>0.27±0.06*</td>
<td>0.29±0.06*</td>
<td>0.27</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.0±2.5</td>
<td>30.0±6.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Postcarbochrome</td>
<td>9.3±3.7†</td>
<td>32.2±8.7‡</td>
<td>...</td>
</tr>
</tbody>
</table>

Data are mean±SD. *p<0.01, versus baseline (paired t test); †n=6; ‡n=4.

<table>
<thead>
<tr>
<th>TABLE 2. Cardiac Mass and Infarct Size</th>
<th>Sham-operated</th>
<th>MI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>305±29</td>
<td>285±23</td>
<td>0.08</td>
</tr>
<tr>
<td>Left ventricle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (mg)</td>
<td>912±128</td>
<td>791±69</td>
<td>0.05</td>
</tr>
<tr>
<td>Weight (mg/g body wt)</td>
<td>3.12±0.55</td>
<td>2.75±0.12</td>
<td>0.08</td>
</tr>
<tr>
<td>Myocyte CSA (μ²)</td>
<td>255±24</td>
<td>332±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right ventricle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (mg)</td>
<td>240±30</td>
<td>400±100</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (mg/g body wt)</td>
<td>0.80±0.09</td>
<td>1.40±0.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocyte CSA (μ²)</td>
<td>199±15</td>
<td>273±39</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are mean±SD. CSA, cross-sectional area.
animals. The 31% increase in minimal coronary resistance in the MI group, however, did not reach statistical significance ($p=0.07$).

**Discussion**

Our results confirm those of others\textsuperscript{7,8,13,16} that large MIs induce a 30% hypertrophic response of the surviving LV myocardium as early as 4 weeks after an MI. The new finding from this study is that this adaptive process is associated with functional alterations of the coronary circulation characterized by a 54% reduction in coronary vasodilator reserve.

Over the past decade, an increasing number of investigators have evaluated MI and its consequences on cardiac structure or function in a rat model.\textsuperscript{3,4,7,8,12,16,26,28--30,33,34} In rats, cardiac response to MI is closer in many respects to that of humans than is the response in dogs. After an occlusion of the left anterior descending coronary artery, rats develop large and transmural MIs that, like most human transmural infarcts, undergo expansion associated with an expansion of the remaining myocardium.\textsuperscript{2--5}

In the present study, all myocardial infarcts were transmural. In addition, the average infarct size as well as the magnitude of the hypertrophic response in the spared myocardium were within the range of values reported by previous investigators working with a similar model.\textsuperscript{3,4,13--16,26,28--30,33}

We chose to express coronary flow and vasodilator reserve as maximal flow and minimal resistance per unit mass\textsuperscript{30,23} rather than as a ratio between maximal and baseline values.\textsuperscript{34} The major usefulness of the concept of coronary reserve lies in that this measurement provides a quantitative index of the ability of the coronary vasculature to maintain an adequate metabolic supply when either perfusion pressure is reduced or when metabolic requirements are augmented. Calculation of coronary reserve in relative terms, that is, as a ratio between peak and baseline determinations and the subsequent comparison of these values between experimental groups, can be of little physiologic relevance if baseline measurements differ from the normal range or across groups. Under these circumstances, any observed difference can reflect changes in the denominator in the flow reserve calculation rather than a true alteration in the vasodilatory capacities of the coronary resistance vessels. In this study, baseline coronary blood flow was significantly elevated in the animals with MI, presumably as a result of increased myocardial oxygen needs, secondary to ventricular dilation and increased wall stress.\textsuperscript{35} Consequently, calculation of coronary reserve in relative terms would have markedly and erroneously overestimated the actual deficit in coronary reserve.

Our findings of coronary reserve abnormalities in the hypertrophied surviving myocardium are consistent with a previous report by Anversa et al\textsuperscript{13} in rats. The authors investigated the capillary adaption to an MI 40 days after the coronary ligation. Their results indicate that the reactive hypertrophy after large MIs is associated with a significant reduction in the capillary structural parameters relevant to tissue oxygenation. The capillary surface was diminished by 18%, whereas diffusion distance was increased by 16%. Smaller infarcts were characterized by similar changes but of a lower magnitude. Taken together, these observations and the results from the present study indicate that, after MI, reactive hypertrophy is associated with a generalized deficit of the coronary vasculature involving both the capillary network and the resistance vessels.

Minimal coronary resistance per unit mass has consistently been shown to be elevated in various experimental models of cardiac hypertrophy induced either by hypertension\textsuperscript{21,36--38} or other forms of pressure overload.\textsuperscript{18,39} In the present investigation, minimal coronary resistance per unit mass in the reactive hypertrophied myocardium was increased by 54%. This value is similar or higher than those reported in

### Table 3. Coronary Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Sham-operated</th>
<th>MI</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left ventricular</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary blood flow (ml/min/100 g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>348±90</td>
<td>450±142</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Carbochrome</td>
<td>1,479±361*</td>
<td>839±223*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary resistance (mm Hg/ml/min/100 kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.365±0.094</td>
<td>0.244±0.088</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Carbochrome</td>
<td>0.078±0.016*</td>
<td>0.120±0.036*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Right ventricular</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary blood flow (ml/min/100 g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>263±62</td>
<td>458±146</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carbochrome</td>
<td>1,760±498*</td>
<td>1,176±405*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Coronary resistance (mm Hg/ml/min/100 kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.477±0.117</td>
<td>0.240±0.086</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carbochrome</td>
<td>0.067±0.018*</td>
<td>0.088±0.030*</td>
<td>0.065</td>
</tr>
</tbody>
</table>

In the MI group, LV coronary blood flow refers to measurements obtained in the surviving myocardium.

*p<0.001, versus baseline (paired t test).
In the aforementioned studies,17-19 in addition, both post-MI reactive hypertrophy13 and pressure-overload hypertrophy40 induce similar deficits in myocardial capillarization. These results suggest that there are no fundamental differences in the response of the coronary circulation to cardiac hypertrophy, irrespective of the inciting stimulus, and that post–MI reactive hypertrophy can be considered, at least in that respect, as a form of pathologic hypertrophy rather than a successful adaptive process.44,45 In support of this conclusion is the finding of a shift in the myosin isoform distribution from V1 to V3 in animals after MI.29,43 This pattern in distribution is characteristic of pressure-overload–induced hypertrophy, although its functional significance is controversial.42

There are three potential mechanisms that can account for the decrement in the vasodilatory capacities of the coronary vasculature in the surviving myocardium. First, extensive histometric investigations by our group, in animals with acquired or genetic hypertension and cardiac hypertrophy, have revealed structural alterations in the coronary arteriolar network, including an increase in wall thickness and a reduction in arteriolar density.44,45 The former mechanism, which causes a limitation in the ability of each coronary resistance vessel to dilate,46 is probably related to the chronically increased perfusion pressure and is unlikely to be operative in reactive hypertrophy because blood pressure is normal or even decreased. In contrast, a reduction in arteriolar density can be brought about by fiber enlargement that spreads apart the vascular channels. Because myocyte hypertrophy is a common feature of both reactive and hypertensive cardiac hypertrophy, it can be postulated that this mechanism is also responsible for the depression of coronary reserve seen in reactive hypertrophy. Our finding of a significant correlation between coronary reserve and myocyte cross-sectional area supports this view. Second, an increase in the extravascular component of coronary resistance as a result of the elevated LV end-diastolic pressure can have participated in the reduction in coronary reserve. Moderate-to-marked elevations of LV end-diastolic pressure have been shown to reduce coronary blood flow in maximally dilated coronary beds perfused at a constant or near-constant pressure.47-49 Domenech47 reported a 22% decrease in total LV coronary blood flow after an increase in LV end-diastolic pressure from 3 mm Hg to 37 mm Hg. In another study, Archie48 concluded that there was a 20–40% reduction in coronary blood flow when LV diastolic pressure was raised to 30 mm Hg. In contrast, Ellis and Klocke49 have described a rather small (8%) and nonsignificant decrement in overall LV coronary blood flow after an increase in preload from 6 mm Hg to 20 mm Hg. In addition, in several of the above studies,47-49 coronary perfusion was maintained at a relatively low level (i.e., less than 65 mm Hg). Investigations by Archie and Brown50 suggest that total or transmural LV coronary blood flow is not significantly affected by preload when coronary perfusion pressure is more than 70 mm Hg. In our study, mean aortic pressure and presumably coronary perfusion pressure were much higher than this value in animals with MI. Thus, although an increase in extravascular compressive forces is likely to have participated in the development of the coronary reserve abnormalities in the MI group, as suggested by the significant correlation between minimal coronary resistance and LV end-diastolic pressure, it is doubtful that this sole mechanism fully accounts for our findings. A third potential mechanism involves the various neurohumoral systems that modulate coronary vasomotor tone.51 Plasma renin activity tends to be increased in rats with MI,29,52 although nonsignificantly because of a considerable interanimal variability.29,52 Studies in dogs have demonstrated that converting enzyme or angiotensin inhibitors decrease coronary resistance after stimulation of the renin-angiotensin system by sodium depletion.53 In addition, there is experimental evidence that the renin-angiotensin system can be activated during or after myocardial ischemia,54 and that blockade of the effects of this system exerts beneficial consequences on infarct size,29,54,55 or various indexes of cardiac function and metabolism.55 It has also been suggested that the sympathetic nervous system was activated in animals with combined MI and cardiac dysfunction.55 These two systems could have acted in concert to limit coronary reserve. On the other hand, however, plasma circulating levels of atrial natriuretic factor have been found to be higher in animals with MI.29,52 Because atrial natriuretic factor is a coronary vasodilator,56 these elevated levels could have antagonized angiotensin- and catecholamine-induced coronary vasoconstriction. Because our study was not designed to address the respective impact of these neurohumoral factors on the depression of coronary reserve, we cannot favor one interpretation over the other. Studies using various antagonists will help resolve these issues.

LV failure is one of the major complications of MI.57 Quantitative studies have shown that the occurrence of cardiac dysfunction is directly related to infarct size and the amount of contractile tissue loss. Rats with small LV infarcts (less than 30%) do not exhibit any significant alterations in either baseline hemodynamic indexes or peak pumping ability.26 In animals with moderate infarcts (30–45%), baseline LV function is normal; the ability of the ventricle, however, to maintain a normal output in response to increases in preload and afterload is diminished. In contrast, infarcts larger than 45% are associated with overt heart failure.26 Similar findings have been reported in humans.58 Using sophisticated histometric studies, Anversa et al.13 have demonstrated that reactive hypertrophy results in a complete restoration of myocardial mass in rats with small and moderate infarcts. When infarct size was large, however, the hypertrophic growth of the spared myocardium was insufficient to replace the tissue loss. Although these observations demonstrate that the
Infarct size and the degree of reactive hypertrophy are critical determinants of ventricular performance after an MI, the contractile properties and the integrity of the coronary circulation in the surviving myocardium can have an important role in this process as well. In that regard, the depression in coronary reserve found in the present investigation and the previously reported deficit in capillary growth can account, at least in part, for the impaired performance of infarcted hearts during preload and afterload stress. These maneuvers are likely to be associated with an increase in myocardial oxygen consumption and can, therefore, unmask a perfusion deficit that was of no or little consequence under baseline conditions when cardiac metabolic needs are lower.

Our results are in agreement with numerous studies in the rat model indicating that the RV also participates in the hypertrophic process that takes place after LVMI. Studies by Anversa et al have shown that, after an MI involving 40% of the LV, there was a significant degree of RV hypertrophy. The latter was characterized by a 30% increase in heart weight and a 13% increase in myocyte cross-sectional area with no change in myocyte length, indicating that the hypertrophy was concentric. Pfeffer, Fletcher and their colleagues reported even larger increases in RV mass in rats with MI, greater than 40% as determined by planimetry. This RV hypertrophy has been generally related to pulmonary hypertension because it occurs only in large infarcts associated with marked elevations in LV end-diastolic and RV systolic pressures. Although the difference in RV minimal coronary resistance between the sham-operated group and the animals with MI was of borderline significance in our study, a trend toward a depression in RV coronary reserve was obvious. It is noteworthy that, after an MI and similar to the LV, there is also an inadequate growth of the RV myocardial capillary network that can impair oxygen delivery. It is conceivable that this combination of vascular deficits will limit the ability of the RV to adapt to the increased pulmonary pressures and, thus, accelerate the development of global congestive heart failure.

Methodologic Considerations

There are three methodologic points that merit further consideration. First, right atrial pressure was not measured in this study and was not accounted for in the calculation of coronary resistance. Because right atrial pressure is higher in rats with MI, coronary resistance values tended to be slightly overestimated in these animals. Pfeffer et al, however, reported that right atrial pressure remains relatively small (4.4 ± 0.6 mm Hg) in rats with MIs larger than those observed in this study (47–59% versus 30–51%). Because mean aortic pressure was close to 100 mm Hg in the MI group, the inclusion of right atrial pressure in our calculations would have had a negligible impact on the values of coronary resistance.

Second, most studies have estimated infarct size by computing the ratio of endocardial and epicardial circumferential lengths of the necrotic area over those of the whole LV. More accurate estimates of the amount of necrotic tissue based on myocyte nuclei loss suggest that the circumferential length technique results in a 25% underestimation of infarct size. The former methodology is complex, however, and involves the computation of various intermediate parameters. These additional steps result in increased data variability and, possibly, a loss of precision. Furthermore, the principal objective of our study was to assess myocardial perfusion in the reactive hypertrophied myocardium. Consequently, an accurate method for measuring infarct size was not a critical component of our study, and we elected to use the less accurate but less intricate circumferential method.

Finally, one limitation of the use of myocyte cross-sectional area is that this parameter underestimates hypertrophic growth in the surviving myocardium if changes in fiber diameter are accompanied by modifications of myocyte length. Indeed, myocyte lengthening has been shown to occur in the nonnecrotic myocardium 40 days or even as early as 3 days after induction of an MI in rats. In contrast to myocyte cross-sectional area, however, reliable measurements of myocyte length cannot be obtained at the present time. Myocyte lateral expansion occurs proportionally to myocyte lengthening so that cross-sectional area measurements still provide correct estimates of the hypertrophic response in the surviving myocardium.

Functional Consequences and Clinical Implications

In addition to the amount of myocardium lost, the hypertrophic growth of the nonnecrotic myocardium appears to be an important determinant of cardiac performance and, possibly, long-term survival by restoring contractile tissue. This conclusion, however, remains to be directly established both in humans and animals by studies correlating cardiac function with reactive hypertrophy. Within a few weeks after MI, a subset of patients undergoes cardiac remodeling characterized by an expansion of the infarcted area and an elongation of the surviving myocardium. This early ventricular dilation is associated with a hemodynamic improvement, including a decrease in LV and pulmonary capillary wedge pressure and an increase in cardiac output. Tissue loss and infarct expansion augment the workload on the remaining myocardium, and it has, thus, been suggested that the surviving myocardium undergoes hypertrophy to normalize wall stress. This response is similar to that seen in other forms of cardiac hypertrophy and can prove essential to the maintenance of normal cardiac performance. In that respect, post–MI reactive hypertrophy can be viewed as a beneficial adaptive process. The long-term consequences of ventricular remodeling and reactive
hypertrophy, however, can prove detrimental if the hypertrophic process is associated with alterations in the contractile machinery or in myocardial perfusion, as in our study. Gay et al\(^6\) proposed that the noninfarcted myocardium initially shows a pattern of physiologic hypertrophy followed by pathologic hypertrophy. Our results are consistent with the proposal that reactive hypertrophy, even a few weeks after the ischemic insult, already shows some features suggesting pathologic hypertrophy, such as a decrement in coronary reserve. These perfusion abnormalities can play a role in the late development of heart failure in patients with MI. This sequence of events would be even more likely to unfold in the many patients with infarction and diffuse coronary artery disease\(^2\,\!\!^4\,\!\!^5\) because the perfusion deficit would involve both the large extramural and the small intramyocardial coronary arteries. Whether these combined alterations will have additive effects and render the heart more prone to develop ischemia, even in the presence of a small increase in oxygen requirements or fall in perfusion pressure, is still to be determined but is certainly an issue worthy of consideration.

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