Effects of Inhibition of Nitric Oxide Formation on Regional Blood Flow in Experimental Myocardial Infarction

Helmut Drexler, MD; Evi Hablawetz, BS; Wenyan Lu, MD; Urs Riede, MD; and Anke Christes, BS

Background. Large myocardial infarction is associated with reactive hypertrophy and dilation of the left ventricle, depressed coronary flow reserve, and the development of heart failure including systemic vasoconstriction. We hypothesized that changes in endothelial function, e.g., in the synthesis or action of nitric oxide in the coronary and peripheral vasculatures, might be involved in the depressed coronary flow reserve and increased systemic vascular resistance observed in postinfarction myocardial hypertrophy and failure.

Methods and Results. The regional blood flow changes that occur as a result of inhibiting the basal release of nitric oxide with $N^O$-monomethyl-L-arginine (L-NMMA) and how this regional pattern may be altered in large MI (infarct size, 30–51% of left ventricle) were examined. Measurements were made 24 hours and 8 hours after myocardial infarction or sham operation in conscious rats. The left ventricular end-diastolic pressure and effects of L-NMMA on left ventricular end-diastolic pressure was similar 24 hours and 8 hours after myocardial infarction. The effects of L-NMMA (30 mg/kg i.v.) on heart rate and blood pressure were similar in infarcted and sham animals. L-NMMA exerted a marked vasoconstriction in the renal, splanchnic, cutaneous, and cerebral circulations of similar magnitude in sham-operated rats and animals with myocardial infarction. The coronary vasoconstrictor effect of L-NMMA was attenuated significantly in the hypertrophied right and noninfarcted left ventricle of 8-week-old infarcted rats ($p<0.01$ versus sham-operated animals) but not 24 hours after induction of myocardial infarction when cardiac hypertrophy has not yet developed. The increase in left ventricular coronary resistance in 8-week-old infarcted animals was inversely related to infarct size ($r=-0.787$, $p=0.012$, $n=9$). Nitroglycerin exerted similar increases in coronary blood flow in rats with chronic myocardial infarction and sham-operated animals, arguing against a reduced vascular responsiveness to nitric oxide. Transmission electron microscopy of coronary resistance vessels in 8-week-old infarcted animals did not reveal endothelial abnormalities.

Conclusions. These data suggest that the basal release of nitric oxide in the renal, intestinal, and cutaneous circulations is not affected adversely in this model of myocardial infarction and failure. However, the blunted coronary vasoconstrictor effect of L-NMMA late after large myocardial infarction supports the view that the basal release of nitric oxide is impaired in postinfarction reactive cardiac hypertrophy. (Circulation 1992;86:255–262)

Key Words • myocardial infarction • nitric oxide • $N^O$-monomethyl-L-arginine • heart failure • microcirculation • endothelium

Recent studies have demonstrated that endothelial cells synthesize nitric oxide from L-arginine,1 which can be stereospecifically inhibited by the arginine analogue $N^O$-monomethyl-L-arginine (L-NMMA).2 L-NMMA has been shown to increase arterial blood pressure in laboratory animals.3 This indicates that continuous formation of nitric oxide from L-arginine contributes to the regulation of blood pressure by basal release of nitric oxide in resistance vessels. This basal release of nitric oxide (believed to represent endothelium-derived relaxing factor [EDRF])4 by the endothelium is involved in the regulation of regional vascular resting tone of different vascular beds,5 including the proximal and resistance coronary vessels.6,7

Large myocardial infarction is associated with reactive hypertrophy and dilation of the left ventricle,8,9 depressed coronary flow reserve,10 and development of heart failure including systemic vasoconstriction.11 We hypothesized that changes in endothelial function, e.g., in the synthesis or action of nitric oxide in the coronary and peripheral vasculatures, might be involved in the depressed coronary flow reserve and increased systemic vascular resistance observed in postinfarction myocardial hypertrophy and failure.10,11 Accordingly, we have investigated the role of endothelium-derived formation of nitric oxide in the control of regional vascular tone of

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rats with acute and chronic heart failure caused by large myocardial infarction and of sham-operated animals. To this end, we assessed the regional hemodynamic consequences of inhibiting the vascular endothelial production of nitric oxide by L-NMMA compared with nitroglycerin, which has a vascular dilator effect that is not adversely affected by endothelial dysfunction.

Methods

Experimental Preparations

Infarction was produced in male Sprague-Dawley rats by left coronary arterial ligation as described previously using a modification of the technique of MacLean et al. Subsequent experimental procedures were started either 24 hours or 8 weeks after surgery. Sham-operated animals served as controls. The selection of infarcted animals was based on a left ventricular end-diastolic pressure (LVEDP) of more than 16 mm Hg. Animals that did not meet this criteria were not included into the study (approximately 40% of the animals).

Instrumentation

Animals were anesthetized with halothane (1% in oxygen), and catheters (PE 50) were inserted into the left ventricle via the right carotid artery, tail artery, and right jugular vein as described in detail recently. After closure, animals were allowed to recover for a minimum of 3 hours before experimental procedures were initiated. This recovery period has been found to be of sufficient duration to ensure a return to steady-state conditions in the rat.

Regional Blood Flow Measurements

Radioactive microspheres (New England Nuclear, Dreieich, FRG) 15±5 μm in diameter were used to measure regional blood flow and cardiac output according to the reference sample technique as adapted for use in the rat and described recently. Regional blood flow (injection of microspheres) was measured twice—before and after drug intervention by injection of two different radioactive microspheres (141Ce and 103Ru).

At the end of the study, animals were killed by phenobarbital injection in the ventricle, and organs as well as tissue samples were removed. All samples were immediately blotted, weighed, and transferred to a two-channel y-scintillation counter for determination of radioactivity levels. Blood flow data concerning the left ventricle were obtained from noninfarcted myocardium. In sham-operated animals, coronary blood flow was measured in analogous portions of the left ventricle.

Hemodynamics

Tracings from the left ventricular and tail catheter were recorded and used to obtain heart rate, left ventricular peak systolic pressure, LVEDP, and mean arterial pressure (MAP). Total vascular resistance was determined from cardiac output and MAP data. Coronary vascular resistance was calculated by dividing MAP recorded just before each microsphere injection by the corresponding coronary blood flow. With the exception of cardiac output, hemodynamic data were collected immediately before the microsphere injection.

Determination of Infarct Size

The left ventricle and septum were separated from the right ventricle (free wall), weighed, and fixed in 10% formalin. Twenty-four hours later, the left ventricle was cut into three transverse pieces from apex to base. Three thin transversal slices of each piece were separated and used for histological examination. Thereafter, the remaining noninfarcted myocardium of the three pieces of the left ventricle was cut and prepared free of scar tissue and border zone. These three noninfarcted pieces of the left ventricle were pooled and counted for radioactivity, similar to the method of Karam et al. The three thin transverse slices were stained with van Gieson stain and mounted. With a planimeter digital image analyzer (Leica), the endocardial and epicardial circumferences of the infarcted and noninfarcted portions of the left ventricle were determined. The infarcted mean circumference (mean of epicardial and endocardial circumferences) of the three slices was summed and then expressed as a ratio of the summed mean circumference of the left ventricle, similar to the method of Pfeffer et al.

Experimental Protocol 1

Regional blood flow and hemodynamics were obtained in infarcted rats and sham-operated animals 8 weeks after surgery. Twenty-five minutes after obtaining baseline hemodynamics and the first microsphere injection, 30 mg/kg L-NMMA (CALBIOCHEM, Frankfurt, FRG) was injected intravenously. After the injection, the increase in MAP consistently arrives at a plateau within 1–2 minutes and lasts for at least 10 minutes. Therefore, the second injection of microspheres was performed 5 minutes after administration of L-NMMA. The dose of L-NMMA was based on a preliminary dose-finding study using cumulative doses (3, 10, 30, and 100 mg/kg) yielding a maximal effect on systemic and regional vascular resistance in the conscious rat with 30 mg/kg. The effect of L-NMMA on coronary output, coronary blood flow, and resistance was completely reversible after administration of excess L-arginine (300 mg/kg, n=6), indicating that the effect of L-NMMA was endothelium specific and not due to a nonspecific myocardial depressant effect.

Experimental Protocol 2

The effect of nitroglycerin on hemodynamics and regional blood flow was studied in a separate group of animals 8 weeks after surgery (different batch of rats with greater body weights). Twenty minutes after the first microsphere injection, nitroglycerin was infused via the jugular vein at an infusion rate of 100 μg/min ⋅ kg⁻¹ over 10 minutes. The second microsphere injection was performed during the last minute of nitroglycerin infusion. The dosage of nitroglycerin was based on pilot studies using cumulative doses to obtain a decrease of MAP of approximately 10 mm Hg and a maximal increase in coronary blood flow.

Experimental Protocol 3

In a separate group of animals (8 weeks after surgery), blood flow and hemodynamics were obtained before and after dipryridamole administration (2 mg/ min ⋅ kg⁻¹ over 10 minutes) as described previously by
Wangler et al. Coronary resistance was calculated as resistance as a ratio of arterial pressure to coronary blood flow (determined in the noninfarcted, hypertrophic myocardium). Minimal coronary vascular resistance refers to the coronary vascular resistance during the last minute of dipyridamole infusion. Coronary flow reserve was calculated as the ratio of coronary blood flow during dipyridamole to coronary flow at baseline.

Experimental Protocol 4
In a separate group of animals, regional blood flow and hemodynamics were obtained before and after injection of L-NMMA in infarcted rats and sham-operated animals 24 hours after surgery using a protocol identical to that performed in animals 8 weeks after surgery (see experimental protocol 1).

Electron Microscopy
To examine the ultrastructure of coronary arteriolar endothelium, the heart was fixed in situ in four sham-operated and infarcted animals as described by Anversa et al. In brief, during sodium pentobarbital anesthesia, the abdominal aorta was isolated, and a polyethylene cannula was inserted into the aorta. The heart was arrested by injection of 1 ml 1M KCl through the jugular vein, and the retrograde perfusion was started with pH 7.2 phosphate buffer at 85 mm Hg followed by a solution of 2% paraformaldehyde and 2.5% glutaraldehyde. The left ventricle then was sliced serially into 2-mm-thick rings perpendicular to the axis of the heart. One-millimeter pieces of noninfarcted myocardium from the middle slices were postfix in osmium tetroxide and embedded in eponaraldit. The specimens were examined with a transmission electron microscope (Phillips EM 200).

Statistical Analysis
Data are given as mean±SEM. Differences between the baseline values of both groups were evaluated by unpaired t test. The effects of L-NMMA and nitroglycerin, respectively, in each group were assessed by paired t test. The comparative effects of L-NMMA in sham-operated and infarcted animals (difference in treatment effects) were calculated by comparing the Δ (value obtained after L-NMMA subtracted by baseline value) and Fisher's exact test. Regression lines were fitted by the method of least squares and calculated by the RS/1 program (Bolt, Beramek, Mass.).

Results
The characteristics of sham-operated and infarcted animals are given in Tables 1 and 2. Animals with infarction were selected on the basis of increased LVEDP. This selection procedure resulted in large infarcts, increased right and left ventricular weights, and reduced MAP, which are indicative of chronic heart failure.

Effect of L-NMMA in 8-Week Infarcted and Sham-Operated Rats
L-NMMA increased MAP in both groups and systemic vascular resistance to similar extents in sham-operated and infarcted animals 8 weeks after surgery (see Tables 1 and 3). L-NMMA reduced cardiac output and heart rate. The double product (heart rate multiplied by left ventricular systolic pressure) remained unchanged in 8-week infarcted and sham-operated rats.

Regional blood flow was decreased to similar extents in both groups by L-NMMA in all tissues investigated except for the coronary circulation (Table 3). In sham-operated rats, L-NMMA decreased blood flow of the right and left ventricles by 45% and 30%, respectively. However, blood flow in right and noninfarcted left ventricles of 8-week infarcted rats was reduced only 7% and 10%, respectively, by L-NMMA (p<0.05 for treatment effects in sham-operated versus infarcted rats). The different vascular responses to L-NMMA in sham-operated and 8-week infarcted rats were even more evident when the changes in coronary vascular resistances were compared (Figure 1): i.e., the effect of L-NMMA on vascular resistance was markedly attenuated in the right and noninfarcted left ventricles of 8-week infarcted rats. There was a close inverse relation between infarct size and L-NMMA–induced change in left and right ventricular resistances (left ventricle:...
Effect of Nitroglycerin and Sham-Operated

The decreases in coronary vascular resistance with nitroglycerin were comparable in sham-operated and infarcted animals.

Effect of L-NMMA 24 Hours After Infarction or Sham Operation

To investigate the effects of L-NMMA in acute heart failure after infarction, L-NMMA-induced changes were studied 24 hours after infarction or sham operation. Due to our selection criterium, LVEDP was increased substantially in the infarct group, and this was associated with decreased MAP and cardiac output. Regional blood flow and vascular resistances were affected similarly by L-NMMA in sham-operated and 24-hour infarcted rats. In particular, the L-NMMA-induced changes in coronary blood flow and vascular resistances in right and left ventricle (see Figure 3) were not impaired in the infarct group. At 24 hours after infarction, it can be assumed that hypertrophy of the noninfarcted left ventricle has not yet developed. The right ventricular weights were similar for the two groups at this point.

Table 3. Effect of L-NMMA on Regional Blood Flow and Resistance

<table>
<thead>
<tr>
<th></th>
<th>Sham-operated (n=9)</th>
<th>Infarced (n=9)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>L-NMMA</td>
</tr>
<tr>
<td>BF LV</td>
<td>3.93±0.30</td>
<td>2.74±0.14*</td>
</tr>
<tr>
<td>BF RV</td>
<td>3.05±0.54</td>
<td>1.69±0.16†</td>
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<tr>
<td>BF kidney</td>
<td>5.06±0.50</td>
<td>2.82±0.25*</td>
</tr>
<tr>
<td>BF intestines</td>
<td>3.63±0.33</td>
<td>1.88±0.25*</td>
</tr>
<tr>
<td>BF skin</td>
<td>0.10±0.01</td>
<td>0.06±0.01†</td>
</tr>
<tr>
<td>BF brain</td>
<td>0.88±0.06</td>
<td>0.69±0.04*</td>
</tr>
<tr>
<td>R kidney</td>
<td>24±3.4</td>
<td>49±6.5*</td>
</tr>
<tr>
<td>R intestines</td>
<td>32±2.7</td>
<td>73±9.0*</td>
</tr>
<tr>
<td>R skin</td>
<td>1,272±226</td>
<td>2,534±630†</td>
</tr>
<tr>
<td>R brain</td>
<td>124±7.7</td>
<td>189±14.9*</td>
</tr>
</tbody>
</table>

L-NMMA, N^\text{\textsuperscript{O}}-monomethyl-L-arginine; BF, blood flow (ml/min·g); LV, noninfarcted left ventricle; RV, right ventricle; R, vascular resistance (mm Hg·min⁻¹·g⁻¹·ml⁻¹). Data are given as mean±SEM.

*p<0.01 and †p<0.05 versus baseline.
‡p<0.05 versus sham baseline.
§p<0.05 for treatment effects of L-NMMA in sham versus infarct.
Coronary Flow Reserve and Minimal Coronary Vascular Resistance

The coronary flow reserve as determined by intravenous dipyridamole infusion (protocol 3) averaged 1.96±0.23 in the hypertrophic, noninfarcted left ventricle in infarcted rats (n=5; infarct size, 38±3%) and was significantly different from sham-operated animals (n=4; 2.83±0.17; p<0.05). The minimal coronary vascular resistance after dipyridamole administration was 0.134±0.009 in the left ventricle of infarcted animals and 0.094±0.008 mm Hg/ml·min⁻¹·g⁻¹ (p<0.02).

Discussion

Evidence has been presented recently that L-NMMA inhibits the endothelial formation and release of nitric oxide.²,³ Previous studies with L-NMMA have shown and been confirmed by our observations that nitric oxide synthetized from L-arginine regulates vascular tone in the coronary circulation.⁶,⁷,¹⁹

The salient finding of the present study was that the effects of L-NMMA on coronary blood flow and resistance are attenuated substantially in postinfarction reactive cardiac hypertrophy, whereas no significant alterations were noted in the peripheral circulatory beds. Notably, 30 mg/kg L-NMMA caused maximal coronary vasoconstriction in preliminary studies; therefore, the attenuated effect of L-NMMA in the coronary circulation of hypertrophic myocardium represents a diminished maximal response to L-NMMA. Importantly, the coronary resistance vessels of hypertrophic myocardium demonstrated a normal response to nitroglycerin without ultrastructural evidence of endothelial damage. Therefore, the present data support the view that the basal release of nitric oxide from coronary vascular resistance vessels is impaired in postinfarction hypertrophy.

In attributing the attenuated response to L-NMMA in the coronary circulation of infarcted animals to a depressed basal release of nitric oxide, other potential mechanisms must be considered. It is unlikely that decreased sensitivity of guanylate cyclase or an abnormality of vascular smooth muscle account for the present findings because the coronary blood flow response to nitroglycerin was not altered in reactive hypertrophy. However, left ventricular hypertrophy, elevated LVEDP, and lower perfusion pressure in infarcted animals may affect basal coronary blood flow. If the coronary microcirculation in cardiac hypertrophy was already constricted by these factors relative to the norm, then further vasoconstriction might not be as apparent when tonic levels of nitric oxide are removed by L-NMMA. It should be noted, however, that basal coronary blood flow of analogous portions of the left and right ventricles was similar in sham-operated and

### Figure 1

**Effect of N°-monomethyl-L-arginine (L-NMMA) on coronary vascular resistance in the left (top panel) and right (bottom panel) ventricle in sham-operated and infarcted animals (n=9 for both groups).** Probability values denote the statistical significance for L-NMMA versus control. *p<0.01 for treatment effects of L-NMMA in sham-operated versus infarcted animals. Data are given as mean±SEM. ○, Control; □, L-NMMA.

### Figure 2

**Scatterplot of correlation of infarct size in percentage of the left ventricle and the change in left ventricular vascular resistance (Rlv).** Two animals had the same coronary resistance and infarct size.
infarcted animals, and arterial blood pressure was impaired to a similar extent in infarcted animals 24 hours and 8 weeks after coronary ligation. Importantly, the vasoconstrictor effect of L-NMMA 24 hours after coronary ligation was comparable to that of sham-operated animals studied 24 hours and 8 weeks after surgery; i.e., the effect of L-NMMA was not attenuated in acute heart failure when cardiac hypertrophy had not yet developed. Because LVEDP and arterial blood pressure were affected similarly 24 hours and 8 weeks after infarction, the increased extravascular component of coronary resistance or an altered perfusion pressure cannot account for the blunted response to L-NMMA in 8-week infarcted animals. The effects of L-NMMA on heart rate, blood pressure, and the double product (heart rate multiplied by left ventricular systolic pressure) as a crude measure of myocardial oxygen requirements were similar in sham-operated and infarcted animals. Therefore, it appears unlikely that the systemic effects of L-NMMA have altered left ventricular myocardial oxygen demand differently in the groups. Furthermore, the effects of L-NMMA were similar in the right and left ventricles, although effects caused by changes in myocardial metabolic demand (secondary to changes in systemic hemodynamics) may have a less-pronounced role in the right ventricle. Finally, the hemodynamic changes elicited by the systemic administration of L-NMMA might result in a different reflex response of the coronary circulation in heart failure. However, in previous studies from this laboratory, the coronary vasoconstrictor responses to intravenous norepinephrine were similar in infarcted and sham-operated animals, arguing against a different reflex-mediated coronary effect or an increased sensitivity to vasoconstricting substances.

The present study did not address potential mechanisms responsible for this blunted effect of L-NMMA on coronary resistance vessels in cardiac hypertrophy. Previous studies performed in this infarction model have focused on capillary adaptation and coronary reserve, indicating that after myocardial infarction, reactive hypertrophy is associated with a generalized deficit of the coronary vasculature involving both the capillary network and resistance vessels. Similarly, coronary flow reserve of the left ventricular myocardium, as determined by dipyridamole, was depressed significantly in the infarction group, confirming previous observations of Karam et al. These investigators suggested that the depressed coronary flow reserve in this model is related to both the elevated preload and the hypertrophic process itself because minimal coronary resistance was correlated to left ventricular myocyte cross-sectional area. In contrast to hypertensive animals developing structural alterations of coronary resistance vessels in response to chronically elevated perfusion pressure, structural abnormalities of coronary resistance vessels are not present in this model of myocardial

**TABLE 4. Effect of Nitroglycerin on Regional Blood Flow and Resistance**

<table>
<thead>
<tr>
<th></th>
<th>Sham-operated (n=6)</th>
<th>Infarcted (n=7)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Nitroglycerin</td>
</tr>
<tr>
<td>BF LV</td>
<td>4.72±0.30</td>
<td>6.14±0.55*</td>
</tr>
<tr>
<td>BF RV</td>
<td>3.54±0.32</td>
<td>4.87±0.65*</td>
</tr>
<tr>
<td>BF kidney</td>
<td>5.82±0.43</td>
<td>6.76±0.82</td>
</tr>
<tr>
<td>BF intestines</td>
<td>3.68±0.34</td>
<td>5.59±0.65*</td>
</tr>
<tr>
<td>BF skin</td>
<td>0.13±0.025</td>
<td>0.097±0.011</td>
</tr>
<tr>
<td>BF brain</td>
<td>1.04±0.05</td>
<td>1.13±0.11</td>
</tr>
<tr>
<td>R LV</td>
<td>23.4±1.7</td>
<td>17.3±1.8*</td>
</tr>
<tr>
<td>R RV</td>
<td>31.3±2.8</td>
<td>22.9±3.3*</td>
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<tr>
<td>R kidney</td>
<td>20.4±1.9</td>
<td>16.3±1.6</td>
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<tr>
<td>R intestines</td>
<td>30.9±1.3</td>
<td>20.8±2.3*</td>
</tr>
<tr>
<td>R skin</td>
<td>973±157</td>
<td>1,175±205</td>
</tr>
<tr>
<td>R brain</td>
<td>98.2±5.4</td>
<td>82±7.6</td>
</tr>
</tbody>
</table>

BF: blood flow (ml/min·g⁻¹); LV, noninfarcted left ventricle; RV, right ventricle; R, vascular resistance (mm Hg/min·g⁻¹·ml⁻¹). Data are given as mean±SEM.

* p<0.05, †p<0.01 versus corresponding baseline value, and ‡p<0.05 versus sham baseline value.

**FIGURE 3. Bar graph of change (mean percent data) in left ventricular vascular resistance induced by N⁵-monomethyl-L-arginine (L-NMMA) 24 hours and 8 weeks after myocardial infarction (MI) or sham operation (SH). *p<0.05 versus all other groups by ANOVA and Student-Newman-Keuls test. SH 24 hr, MI 24 hr, SH and MI rats 24 hours after surgery; SH 8 W, MI 8 W, SH and MI rats 8 weeks after surgery.**
infarction with reactive hypertrophy and normal or even decreased blood pressure. Furthermore, examinations by transmission electron microscopy did not identify endothelial damage of coronary resistance vessels in postinfarction cardiac hypertrophy. Endothelial regulation of relaxation is impaired in collateral-dependent myocardium, possibly because of failure of the collateral vasculature to develop at a rate sufficient to prevent periods of ischemia. In cardiac hypertrophy, subendocardial ischemia may emerge because of inadequate development of the coronary network and elevated LVEDP. Because myocardial ischemia can induce significant endothelial dysfunction, dysfunctional endothelium in the coronary microcirculation of reactive hypertrophy (including a depressed basal release of nitric oxide) may be attributed to myocardial ischemia.

A second possibility may be related to the vascular growth emerging in cardiac hypertrophy that results in functionally less-active endothelium in analogy to chronically impaired endothelium-dependent vascular relaxation after endothelial injury; i.e., proliferating endothelial cells may lose their ability to synthesize and release nitric oxide. Substantial hypertrophy of the right and noninfarcted left ventricular myocardia emerged in the infarct group (Table 1) in keeping with previous studies using this animal model and similar infarct sizes.

What would be the implications of impaired basal release of nitric oxide from coronary resistance vessels? Notably, basal coronary blood flow in postinfarction reactive hypertrophy was normal at rest, suggesting that coronary autoregulation was maintained despite decreased basal release of nitric oxide, e.g., by the concerted interaction of several mediators or mechanisms. However, inhibition of nitric oxide formation has been shown to result in reduced peak reactive hyperemic flow, enhanced reactive vasoconstriction after rapid increase in perfusion pressure (unopposed myogenic vasoconstriction), and abolished flow-mediated arterial dilation. These studies strongly suggest that endothelium-dependent dilation in the coronary microcirculation opposing myogenic vasoconstriction is due to the release of nitric oxide. As discussed by Kuo et al., the interaction of pressure and flow-induced response in coronary resistance vessels may represent an important mechanism for maintaining adequate tissue perfusion when pressure and shear stress increase simultaneously, i.e., during exercise and/or intense sympathoadrenal excitation. If this is true, then any functional impairment of the endothelium, i.e., impaired basal release of nitric oxide, would attenuate the effect of flow on vascular resistance in the coronary microcirculation and may result in inadequate tissue perfusion during intense metabolic demand such as exercise or rapid increase in blood pressure.

Inhibition of basal release of nitric oxide by L-NMMA resulted in a marked peripheral vasoconstriction and increased systemic vascular resistance impeding left ventricular ejection because of enhanced afterload. This mechanism most likely accounted for the substantial decrease in cardiac output observed in these animals. However, the reduction in coronary blood flow, particularly in sham-operated animals, may have contributed to this diminished cardiac output after L-NMMA.


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