Hemodynamic and Metabolic Effects of Sodium Nitroprusside on the Performance and Metabolism of Regional Ischemic Myocardium

By Protasio L. da Luz, M.D., James S. Forrester, M.D., H. L. Wyatt, Ph.D., John V. Tyberg, M.D., Ph.D., Robert Chagarasulis, B.S. William W. Parmley, M.D., and H. J. C. Swan, M.D., Ph.D., F.R.C.P.

SUMMARY
To assess the effects of sodium nitroprusside (5-10 μg/min) on total and regional cardiac performance, energetics, and lactate metabolism during acute ischemia, studies were performed in 21 open-chest dogs. For studies of regional function and metabolism, length gauges were sutured to the epicardial surface and an epicardial vein adjacent to the artery to be occluded was cannulated. Following occlusion of the left anterior descending coronary artery, cardiac output, mean arterial pressure, epicardial vein blood flow, and systolic shortening of the ischemic segment decreased significantly. In the blood samples from the ischemic zone, but not in those from the coronary sinus, lactate extraction shifted to production. In seven control dogs these alterations persisted throughout the experiment. In 14 animals treated with nitroprusside, cardiac output increased while peripheral resistance and mean arterial pressure decreased. Systolic shortening in the ischemic segment increased from 1.10 ± 0.24 (SEM) to 1.77 ± 0.30 mm (P < 0.005). In eight dogs, regional venous outflow increased from 1.9 ± 0.1 to 3.0 ± 0.4 ml/min despite a slight reduction in mean arterial pressure. Concomitantly, regional negative lactate balance was reduced from −61.0 ± 20.0 to −23.2 ± 5.7% (P < 0.05).

These results indicate that nitroprusside significantly improves both total cardiac performance and the mechanical performance of regional ischemic myocardium. Moreover, this improvement in mechanical function occurred concomitantly with apparent increase in regional perfusion and reduction in lactate production, suggesting that nitroprusside simultaneously alleviates ischemia.

PHENTOLAMINE and sodium nitroprusside have been found to dramatically improve both clinical state and effective cardiac performance in patients with left ventricular failure following acute myocardial infarction,3-4 by increasing cardiac output and decreasing left ventricular filling pressure. Since vasodilators reduce afterload and preload, two of the major determinants of myocardial oxygen demand, it has been postulated that such therapy might also alleviate the regional imbalance between oxygen supply and demand in the ischemic myocardium.5

However, peripheral vasodilators frequently reduce coronary perfusion pressure; it is, therefore, possible that the regional imbalance between oxygen supply and demand is actually aggravated by a reduction in myocardial oxygen supply that exceeds the reduction in oxygen demand.6-8 Furthermore, the effects of nitroprusside on the mechanical function of the regional ischemic myocardium are unknown. This lack of information is primarily due to the difficulty of obtaining simultaneous measurements of regional function and metabolism of the heart in man. Accordingly, in this study an experimental model was used in which, in addition to evaluation of total cardiac function, the systolic shortening, venous blood flow, oxygen extraction, and lactate balance of the regional ischemic myocardium could be studied during the administration of the vasodilator sodium nitroprusside.

Methods
Studies were carried out in 21 healthy mongrel dogs weighing from 22 to 28 kg. The animals received 2.2 mg/kg of morphine sulfate, intramuscularly, 20 minutes prior to anesthesia with chloralose (100 mg/kg, intravenously). After endotracheal intubation, respiration was maintained with a Harvard ventilator. A left thoracotomy was performed via the fifth interspace, and the heart was suspended in a pericardial cradle. The distal portion of the left anterior descending coronary artery (LAD) or one of its diagonal branches was isolated for subsequent occlusion. The sinus node was externally crushed and the heart rate maintained constant by atrial pacing, at an average of 110 beats/min. Systemic arterial pressure was continuously monitored with
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a P23Db pressure transducer (Statham Instruments, Hato Rey, Puerto Rico) by a transfemoral catheter advanced to the thoracic aorta. Left ventricular pressure was recorded by a transducer (Model BT-70, Bio-Tech, Pasadena, California), connected to a 10F catheter inserted in the ventricle through the apex. Left ventricular end-diastolic pressure (LVEDP) was controlled by the use of a large atrial catheter connected to a variable height reservoir. Fresh blood from a donor dog was used for infusion.

Cardiac output (CO) was determined by an ascending aortic electromagnetic flowmeter (Model RC1000, Micron Instruments, Los Angeles, California). Total peripheral resistance (TPR) and left ventricular stroke work (SW) were calculated by the formulae:

\[
TPR = \frac{\Delta P}{CO}
\]

\[
SW = SV \times (\Delta P - LVEDP) \times 0.0136
\]

where SV = stroke volume and \(\Delta P\) = mean arterial pressure.

For assessment of the regional function, a 1 cm mercury-in-silastic length gauge (0.31 mm, inner diameter; 0.62 mm, outer diameter) (Parks Electronics, Beaverton, Oregon) was sutured to the epicardial surface of the left ventricle parallel to the fibers perfused by the coronary artery to be occluded.11 Previously the stiffness of the gauge had been determined and found to be 1 gram force/5% elongation.11 The length gauge was prestressed for 30 minutes before each experiment; calibration was performed by attaching the ends of the gauge to the jaws of a vernier caliper and extending the gauge by fixed increments. Resting length of the gauge was 10 mm; when in use this length varied from 10 to 20 mm. Previous studies from this laboratory have demonstrated that within such a range, the calibration of the gauge is linear (±5% for up to eight hours).12 The output of the gauge was recorded on paper (Visicorder Model 1505, Honeywell, Inc., Denver, Colorado) and the systolic shortening during the ejection period of the left ventricle was measured.

For studies of oxygen extraction and lactate balance, blood samples were obtained simultaneously from the femoral artery, coronary sinus, and the vein accompanying the artery chosen for occlusion. The epicardial vein was cannulated using a 2 inch, 20 gauge, thin-walled teflon catheter (Beckton-Dickinson and Company, Rutherford, New Jersey). At each data collection period, outflow from this vein was determined by free drainage into a graduate cylinder. To avoid aspiration of blood from nonischemic zones, the blood from the ischemic zone was withdrawn through a Y system which allowed the operator to continuously visualize the aspirating pressure, which was not allowed to exceed 1 cm water. After blood withdrawal, samples for lactate measurement were prepared immediately. Samples for blood gas analysis were immediately immersed in ice water and all the analyses were performed within three hours. Hemoglobin concentration and oxygen saturation were measured in duplicate with a spectrophotometer (IL Co- oximeter, Model 182); pH and pO2 were measured in an IL electrode system (Model 113, Instrumentation Laboratory, Lexington, Massachusetts). Arteriovenous oxygen difference was calculated for the total heart and the ischemic region based on oxygen concentrations of coronary sinus blood and regional vein, respectively.

Blood lactate concentration was measured by the enzymatic, semiautomated method described by Marbach and Well.11 Lactate balance for both total heart and regional ischemic myocardium was calculated by the formula \([A - V]/A \times 100\), in which \(A\) = arterial lactate concentration and \(V\) = venous lactate concentration (either coronary sinus or regional vein).

Protocol

The experimental protocol was designed to allow study of the effects of altered afterload alone, and then the effects of simultaneous alteration in preload and afterload. To achieve this end, the following procedure was followed:

1. The LVEDP was raised to approximately 12 mm Hg in the preocclusion period by adjusting the height of the reservoir connected to the left atrial catheter and 20 minutes were allowed for stabilization of the preparation.
2. The coronary artery was occluded. After 20 minutes nitroprusside was administered for 30 minutes with the LVEDP maintained constant at approximately 12 mm Hg.
3. In the remaining 30 minutes of nitroprusside administration, the LVEDP was allowed to fall to levels of 6-7 mm Hg.

The administration of sodium nitroprusside was titrated in order to produce a significant reduction in peripheral resistance while the mean arterial pressure was maintained within a physiological range; the dose varied from 5 to 10 \(\mu g/\min\). In seven control animals the same procedure was followed but nitroprusside was not administered. The animals were observed for a total of 80 minutes following LAD occlusion.

Statistical Analysis

The paired Student's t-test was used for statistical analysis. Results are presented as mean ± standard error of the mean.

Results

Cardiac Function and Systemic Hemodynamics

Following coronary occlusion, reduction in mean arterial pressure, cardiac output, stroke volume, and stroke work were observed in both the control animals and in the dogs which subsequently received nitroprusside (table 1). In the control dogs these changes persisted throughout the experiment. However, in the group of animals that received nitroprusside following LAD occlusion, cardiac output and stroke volume increased significantly, while the peripheral resistance was significantly reduced (fig. 1).

The effects of sodium nitroprusside on systemic blood flow and blood pressure were related to the level of LVEDP. When the LVEDP was maintained at approximately 12 mm Hg, the cardiac output increased by a mean of 44%, and no significant changes were observed in mean arterial pressure. As the LVEDP was allowed to drop to levels of 6-7 mm Hg, the cardiac output was reduced to 1.94 ± 0.18 L/min, an insignificant change. The mean arterial pressure, however, decreased slightly but significantly and averaged 88.0 ± 6.0 mm Hg (table 1).
Table 1

Hemodynamic Variables in LAD Occlusion and During Nitroprusside Administration

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (control)</th>
<th>Group 2 (treated)</th>
<th>Nitroprusside</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preocclusion</td>
<td>Postocclusion</td>
<td>Preocclusion</td>
</tr>
<tr>
<td></td>
<td>20 min</td>
<td>50 min</td>
<td>50 min</td>
</tr>
<tr>
<td>AP (mm Hg)</td>
<td>124 ± 13.0</td>
<td>12.0 ± 7.0</td>
<td>124 ± 7.0</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>11.0 ± 1.0</td>
<td>13.0 ± 0.4</td>
<td>12.0 ± 1.0</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>1.89 ± 0.21</td>
<td>1.70 ± 0.15</td>
<td>2.23 ± 0.15</td>
</tr>
<tr>
<td>SV (ml/beat)</td>
<td>18.1 ± 2.2</td>
<td>16.3 ± 2.5</td>
<td>21.9 ± 1.9</td>
</tr>
<tr>
<td>TPR (u)</td>
<td>74.0 ± 14.0</td>
<td>59.0 ± 6.0</td>
<td>61.0 ± 8.0</td>
</tr>
<tr>
<td>SW (g·m/beat)</td>
<td>26.8 ± 4.0</td>
<td>20.1 ± 4.3</td>
<td>32.7 ± 2.7</td>
</tr>
<tr>
<td>L1 (min)</td>
<td>2.29 ± 0.37</td>
<td>1.32 ± 0.36*</td>
<td>2.99 ± 0.28</td>
</tr>
<tr>
<td>RVF (ml/min)</td>
<td>4.0 ± 0.6</td>
<td>2.2 ± 0.6*</td>
<td>3.9 ± 0.3</td>
</tr>
</tbody>
</table>

Values are given as mean and standard error of the mean.

*P < 0.05, compared to preocclusion values.
†P < 0.05, compared to 20 min postocclusion values.

Abbreviations: AP = mean arterial pressure; LVEDP = left ventricular end-diastolic pressure; TPR = total peripheral resistance; L1 = systolic contraction on the ischemic segment; CO = cardiac output; SW = stroke work; RVF = regional venous flow.

Regional Ischemic Function

A significant reduction in the magnitude of systolic shortening recorded from the ischemic segment was observed in both groups after LAD occlusion (table 1). In the control group, contraction of the ischemic segment remained depressed and unchanged throughout the experiment, averaging 1.40 ± 0.57. In contrast, in the nitroprusside group, the mean ischemic contraction increased to 2.67 ± 0.75 after nitroprusside administration (table 1).

Effects of ischemia and subsequent treatment with nitroprusside on the systolic shortening of regional ischemic myocardium is demonstrated in figure 1. Administration of nitroprusside increased mean ischemic contraction from 1.40 ± 0.57 to 2.67 ± 0.75.

Regional Ischemic Resistance

Hemodynamic response to sodium nitroprusside infusion in 14 dogs. Abbreviations: CO = cardiac output; TPR = total peripheral resistance; LVEDP = left ventricular end-diastolic pressure. *P < 0.05 compared to postocclusion values.
mm 80 minutes after LAD occlusion. To the contrary, among the nitroprusside-treated animals (fig. 2), systolic shortening increased from 1.10 ± 0.24 to 1.77 ± 0.30 mm (P < 0.005). In figure 3 a typical experiment is shown. This increase in regional contraction was observed even when preload was allowed to decrease in the second phase of nitroprusside administration.

Blood Flow and Metabolism of the Regional Ischemic Myocardium

Venous blood flow from the ischemic zone was measured in 12 dogs. In the control state, venous flow was approximately 4.0 ml/min. Following LAD occlusion a sharp drop in this local outflow was observed in all the animals. In the four control dogs the regional flow remained decreased and averaged 2.4 ± 0.05 ml/min at the end of the experiment. Among the dogs that received nitroprusside, the regional flow increased from 1.9 ± 0.1 ml/min to 3.0 ± 0.4 ml/min (P < 0.05) during the drug administration, even though the mean aortic pressure was significantly lower than the postocclusion values (fig. 4).

Reduction in regional flow following LAD occlusion was associated with significant reduction in local pH, no statistically significant change in pO2, and a small but statistically significant increase in arteriovenous oxygen difference and oxygen extraction ratio (table 2). Following nitroprusside, arterial pO2 was essentially unchanged, while coronary sinus and regional venous pO2 increased; concomitantly, arteriovenous oxygen difference and oxygen extraction ratio decreased significantly in both the total heart and regional ischemic myocardium. Nitroprusside did not induce significant changes in the regional venous pH.

Changes in myocardial lactate metabolism paralleled those in perfusion. In the preocclusion period the lactate balance was within normal limits in all the animals, averaging 35 and 33% in the control and treated groups, respectively. Following coronary artery occlusion, regional lactate extraction shifted to production. In contrast, only a decrease in the lactate extraction was demonstrated in the coronary sinus blood. In the control group (fig. 5a) regional lactate balance remained negative throughout the experiment, becoming slightly more negative toward the end of the period of observation. In the nitroprusside

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**Figure 3**

Effects of nitroprusside on systolic shortening of ischemic myocardium (upper panel), left ventricular and aortic pressures (lower panel) are illustrated in an individual experiment. Arrows indicate shortening during the ejection period.

**Figure 4**

The relationship between mean arterial pressure (unfilled circles) and blood flow (filled circles) from a vein draining the ischemic zone is shown in 12 dogs. Values represent mean ± standard error of the mean.
### Table 2

**Metabolic Effects of Coronary Occlusion and Treatment with Nitroprusside**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (control)</th>
<th>Group 2 (treated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preocclusion</td>
<td>Postocclusion</td>
</tr>
<tr>
<td></td>
<td>(7)</td>
<td>(13)</td>
</tr>
<tr>
<td></td>
<td>20 min</td>
<td>50 min</td>
</tr>
<tr>
<td><strong>pO₂</strong> (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Art.</td>
<td>93.0 ± 19.0</td>
<td>90.0 ± 18.0</td>
</tr>
<tr>
<td>CS</td>
<td>21.0 ± 1.0</td>
<td>22.0 ± 2.0</td>
</tr>
<tr>
<td>RV</td>
<td>21.0 ± 2.0</td>
<td>21.0 ± 2.0</td>
</tr>
<tr>
<td><strong>C(a-V DO₂)</strong> (vol %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>9.6 ± 0.9</td>
<td>10.2 ± 1.3</td>
</tr>
<tr>
<td>RV</td>
<td>9.2 ± 1.2</td>
<td>10.7 ± 1.7*</td>
</tr>
<tr>
<td><strong>O₂ extraction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>64.0 ± 2.0</td>
<td>66.0 ± 3.0</td>
</tr>
<tr>
<td>ratio</td>
<td>62.0 ± 2.0</td>
<td>70.0 ± 2.0*</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Art.</td>
<td>7.36 ± 0.03</td>
<td>7.33 ± 0.02</td>
</tr>
<tr>
<td>(u)</td>
<td>7.32 ± 0.03</td>
<td>7.30 ± 0.02</td>
</tr>
<tr>
<td><strong>Lactate</strong> (mM/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Art.</td>
<td>1.48 ± 0.20</td>
<td>1.40 ± 0.20</td>
</tr>
<tr>
<td>(mM/L)</td>
<td>0.99 ± 0.17</td>
<td>1.08 ± 0.21</td>
</tr>
<tr>
<td>RV</td>
<td>1.01 ± 0.16</td>
<td>2.14 ± 0.42*</td>
</tr>
<tr>
<td><strong>Lactate balance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>34.0 ± 4.0</td>
<td>25.0 ± 5.0*</td>
</tr>
<tr>
<td>%</td>
<td>34.0 ± 4.0</td>
<td>-49.0 ± 11.0*</td>
</tr>
</tbody>
</table>

Values are given as mean and standard error of the mean.

* = P < 0.05, compared to preocclusion values.
† = P < 0.05, compared to 20 min postocclusion values.

Abbreviations: Art. = arterial; CS = coronary sinus; RV = regional vein; C(a-V DO₂) = arteriovenous oxygen difference.
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Discussion

In this study infusion of sodium nitroprusside increased cardiac output substantially and decreased arterial pressure slightly as total peripheral resistance was reduced. Since heart rate was held constant, the increase in cardiac output was due solely to an augmentation in stroke volume. Papillary muscle studies have indicated that sodium nitroprusside does not have a positive inotropic effect; therefore, enhancement of myocardial contractility is unlikely to explain the increase in stroke volume. Preload also was maintained constant, although at different levels in the two phases of the experiment. Therefore, the reduction in resistance to left ventricular ejection remains as the most likely cause for the increase in stroke volume and cardiac output.

Ross and Braunwald demonstrated that increasing afterload by angiotensin infusion produced a further reduction in cardiac performance in clinical heart failure. Our results are consistent with this study and may be interpreted as its counterpart since it shows an increase in cardiac performance when the afterload is decreased. Our results are also consistent with previous studies in man by Chatterjee et al. and Franciosa et al., in which nitroprusside administration induced increases in cardiac output with minimal changes in heart rate.

The magnitude of the increase in cardiac output induced by nitroprusside was dependent on the level of left ventricular filling pressure. Changes in cardiac output were larger when the LVEDP was maintained at 12 mm Hg than when it was allowed to fall to 6-7 mm Hg. These data indicate that the level of preload remained an important controlling factor in the level of cardiac output at a given afterload reduction. The data parallel our own previous observation and those of others, in which both phentolamine and sodium nitroprusside failed to increase cardiac output when given to patients without elevated filling pressures.

That arterial pressure (P) remained within physiological range was an important feature of our results. When the dose of nitroprusside is properly regulated, a proportional increase in cardiac output (F) can result from a reduction in peripheral resistance (R) with little change in arterial pressure (P = F x R). The importance of maintenance of arterial pressure has been emphasized by the studies of both Maroko et al. and Smith et al., in which evidence of increased myocardial ischemia was found as perfusion pressure was reduced. When arterial pressure is abnormally elevated, however, reduction of arterial pressure might be warranted. Watanabe and coworkers demonstrated that in the depressed canine heart hypertension results in an increase in infarct size. In the clinical setting, nitroprusside would be particularly useful since improved cardiac function could be obtained while arterial pressure is manipulated into the desired range.

Regional Ischemic Function and Metabolism

During administration of sodium nitroprusside, mechanical function of the ischemic segment improved significantly. It is hypothesized that this improved mechanical function contributed to the overall increase in cardiac output by two mechanisms. The first is the direct contribution of a segment to the per-
formance of the sum of the segments. In addition, a significant amount of volume displacement is dissipated in expanding the noncontractile muscle. Although the restoration of contraction in the ischemic segment was partial, the energy loss incurred by systolic expansion was probably reduced.

Improvement in the function of the ischemic myocardial segment was associated with a decrease in both lactate production and arteriovenous oxygen difference, suggesting that the improved effective mechanical performance was not accompanied by an aggravation of the imbalance between oxygen supply and demand. This is in contrast to the effect of isoproterenol, which increases transiently the contractility of the ischemic segment, but also increases the magnitude of myocardial ischemia. The effects of nitroprusside also contrast to those of propranolol, which decreases oxygen consumption and improves lactate metabolism in the ischemic area but reduces developed force. Our results also are consistent with, but less dramatic than those of Müller et al., who found complete reversal of regional negative lactate balance following administration of nitroprusside to dogs with LAD occlusion.

Since nitroprusside administration reduced both afterload and preload in the second phase of these experiments, the trend toward diminished regional lactate production might be explained solely on the basis of a decrease in myocardial oxygen demand. In addition, however, nitroprusside administration resulted in a consistent increase in the venous outflow from the ischemic area despite the fact that coronary perfusion pressure had been decreased. These data strongly suggest that collateral blood flow to the ischemic area was increased. The hypothesis is consistent with the known effects of an analogous group of vasodilator drugs, including nitroglycerin and with the recent demonstration that total coronary blood flow in dogs increased by 53% during nitroprusside infusion. This increase in local flow in the presence of a reduction in perfusion pressure presumably reflects a direct vasodilatory effect upon regional collateral vessels, since hypotension induced by hemorrhage led to a reduction in regional coronary perfusion.

The significant reductions in regional arteriovenous oxygen difference and oxygen extraction ratio after nitroprusside infusion were somewhat unexpected. Complete relief of the imbalance between oxygen supply and demand might be expected to result in narrowing of the regional arteriovenous oxygen difference; however, the response of both regional function and lactate metabolism indicates that improvement was not complete. Therefore, it should be noted that apparent reduction in both oxygen extraction and lactate production could be due in part to a pharmacologically induced arteriovenous shunt. In addition, the decrease in lactate production could be partially due to a dilutional effect accounted for by the increment in regional venous flow without a true reduction in lactate output from the ischemic zone. In such circumstances, however, regional function could be expected to deteriorate, and this was not the case.

Within the constraints of the experimental model, therefore, this study indicates that nitroprusside administration produced improved total cardiac performance in the presence of acute myocardial ischemia. Contributory to the improvement in over-all cardiac function is the increase in systolic contraction of the ischemic segment. Moreover, improved performance of the ischemic myocardium does not occur at the cost of aggravation in ischemia. Improved regional myocardial lactate balance, in turn, is apparently a result of both an increase in myocardial oxygen supply and a reduction in oxygen demand. Since this experimental model resembles the clinical condition in which nitroprusside is administered, these results tend to support the use of sodium nitroprusside in selected groups of patients with left ventricular failure following acute myocardial infarction.

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References

8. BRAUNWALD E, SARNOFF SJ, CASE RB, STAINBY WN, WELCH GH Jr: Hemodynamic determinants of coronary flow: effect of changes in aortic pressure and cardiac output on the

Circulation, Volume 52, September 1975
12. Ross Jr, Braunwald E: The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotensin. Circulation 29: 739, 1964
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