Effects of Nitroprusside on Myocardial Blood Flow and Oxygen Consumption in Conscious Lambs With an Aortopulmonary Left-to-Right Shunt

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We studied the effect of vasodilation on regional myocardial blood flow and oxygen consumption of the left ventricular free wall by infusing 10 μg/kg/min sodium nitroprusside into 7-week-old conscious lambs with and without aortopulmonary left-to-right shunts. Resting myocardial oxygen consumption in the 13 shunt lambs was significantly higher than in the nine control lambs (989±104 ±SEM) vs. 432±41 μmol/min/100 g left ventricle). This was achieved by a significantly higher left ventricular myocardial blood flow (294±33 vs. 143±16 ml/min/100 g left ventricle) because the arteriovenous oxygen concentration difference across the left ventricular free wall was similar in shunt and control lambs. Infusion of nitroprusside did not significantly change myocardial oxygen consumption and regional myocardial blood flows at 10 and 50 minutes after the onset of the infusion. This occurred despite a substantial drop in aortic and left atrial pressures and stroke volume, which decreases wall stress as well as external work of the left ventricle. Heart rate, however, increased significantly. We postulate that, during infusion of nitroprusside, the potential decrease in myocardial oxygen consumption due to a decrease in wall stress and external work of the left ventricle is neutralized by the consequences of the increased heart rate. In view of this and because of its hemodynamic effects, we do not consider sodium nitroprusside useful in the treatment of circulatory congestion in patients with left-to-right shunts, normal arterial pressures, and normal systemic blood flows. (Circulation 1990;81:319–324)

The use of vasodilators has in recent years become of interest in the treatment of children at risk of a circulatory congestion due to a left-to-right shunt. Three considerations support the use of vasodilators in these cases. Vasodilators have been shown to increase systemic blood flow and to decrease shunt flow through a ventricular septal defect in experimental animals and patients.1-3 Furthermore, by inducing venodilation, vasodilators could decrease preload and, thus, help to decrease left atrial pressure and left ventricular end-diastolic volume. Last, vasodilators might decrease cardiac work and, therefore, myocardial oxygen consumption through the decreased afterload accompanying dilation of the resistance vessels.

The lack of uniformity in experimental data concerning the importance of the above mechanisms and the beneficial effects of vasodilation has prompted us to investigate the hemodynamic changes caused by the infusion of sodium nitroprusside. We infused this commonly used vasodilator8,9 into chronically instrumented lambs with and without aortopulmonary left-to-right shunts.6 In these studies, it was shown that, in lambs with shunts, sodium nitroprusside decreased the flow through the shunt in the first few minutes after the onset of infusion. The decrease, however, was of a duration too short to consider beneficial. Systemic blood flow hardly changed, whereas heart rate increased substantially. We ascribed this lack of favorable hemodynamic effects to the abrupt pressure decrease induced and to the activation of countering mechanisms. On the other hand, we did show that preload decreased during nitroprusside...
infusion, as indicated by decreased left atrial pressures. This could favorably affect symptoms of pulmonary edema, often present in patients with large left-to-right shunts at the ventricular or ductal level. It could also decrease left ventricular end-diastolic volume and, thus, myocardial oxygen consumption.

The present study deals with the third mechanism, through which vasodilation could be beneficial to patients with this type of lesion, which is the capacity of vasodilation to decrease the elevated resting myocardial oxygen consumption toward normal values, thereby increasing the reserve for further energy demands. Earlier we have shown that the basal left ventricular free wall oxygen consumption per unit of mass in lambs with left-to-right shunts is almost twofold that in normal lambs. Apparently, an increased regional blood flow to the left ventricular free wall made this rise in oxygen consumption possible because the arteriovenous difference in oxygen content was the same. We hypothesized that the increase in resting heart rate in the lambs with shunts was one of the main factors responsible for this increase in oxygen consumption. Therefore, it seemed worthwhile to investigate whether a further increase in heart rate, such as results from nitroprusside infusion, would further increase myocardial oxygen consumption in lambs with a shunt or whether, on the contrary, nitroprusside would decrease myocardial oxygen consumption through a decrease in ventricular afterload as well as through a decrease in wall stress because of a decreased left ventricular end-diastolic volume.

**Methods**

We studied 22 lambs of mixed breed with documented dates of birth. They were divided into two groups, that is one group (13 lambs) with and another group (nine lambs) without aortopulmonary left-to-right shunts. On the day of the study, the lambs with shunts were 14–79 days old, and the control lambs were 29–70 days old. Some of the lambs had been used for other studies, but at least 1 day was allowed between the last experiment and the present study. Between surgery and the day of the study, lambs less than 60 days old remained with their mothers.

**Surgical Procedures**

Surgical preparation, catheter care, and antibiotic administration were carried out as previously described. Under halothane anesthesia (0.5–1% in O2), the lambs were ventilated by an Engström intermittent positive-pressure respiratory pump (Engström, Bromma, Sweden). Analgesia was maintained by 2 mg/kg pirritramide. A left thoracotomy was performed in the third or fourth intercostal space; polyvinyl catheters (1.0 mm i.d., 1.5 mm o.d.) were passed from the internal thoracic artery and vein into the aorta and superior vena cava, respectively. The pericardium was incised over the main pulmonary artery to within 2–3 mm of the vagus nerve. A Goretx conduit (6 or 8 mm i.d.) (W.L. Gore and Assoc, Flagstaff, Arizona) was sutured between the aorta and the main pulmonary artery. Through purse-string sutures, catheters were inserted into the right ventricle, pulmonary artery, and through the left atrial appendage into the body of the left atrium. We ligated the hemiazygos vein distally and inserted a catheter so that its tip was located where the coronary sinus is formed by the confluence of the great cardiac and hemiazygos veins. Precalibrated electromagnetic flow transducers (10–15 mm i.d.) (Skalar Medical, Delft, The Netherlands) were applied around the pulmonary artery proximal to the conduit and around the ascending aorta just above the coronary arteries. An 8F polyvinyl catheter was placed in the left pleural cavity for chest drainage. The control lambs were instrumented in the same way except for the conduit, the flow transducer around the aorta, and the right ventricular catheter. All vascular catheters were filled with heparin and led to the left flank of the lamb, together with the chest tube and the flow transducer cable(s), and protected by a Teflon cloth pouch that was sewn to the skin after the chest had been closed in layers. The measurements were started at least 4 days (4–18 days) after surgery to allow normal cardiovascular function to return.

**Experimental Protocol**

The lambs were allowed to feed until 2 hours before the measurements. At that time, they were weighed and placed in canvas slings, which supported them in the upright position. Ambient temperature was kept constant between 22° and 23°C. Data were collected only when the lambs were calm and resting. In the lambs with shunts, pulmonary and systemic blood flows were measured continuously with the electromagnetic flow transducers around the aorta and the pulmonary artery, respectively. Because the aortic flow transducer was applied around the aorta just above the coronary arteries, it measured pulmonary minus coronary blood flow. In the lambs without shunts, only pulmonary blood flow was measured with the flow transducer around the pulmonary artery. In both groups, we measured aortic, pulmonary arterial, left atrial, and central venous pressures every 5 minutes for 30 minutes. Then 0.8-ml blood samples were drawn simultaneously from the aorta and coronary sinus. In each sample, oxygen saturation, hemoglobin concentration, pH, and oxygen and carbon dioxide tensions were measured in duplicate. Immediately after the blood samples had been taken, 15-μm diameter microspheres labeled with either niobium 95, cesium 141, or ruthenium 103 were injected into the left atrium while a reference sample was withdrawn continuously from the ascending aorta through the internal thoracic arterial catheter. After taking measurements for 30 minutes, we infused 10 μg/kg/min nitroprusside for 1 hour and measured the same variables as during the control period. Blood samples were drawn at 5–10 minutes and 50–60 minutes after the onset of infusion, after which microspheres were injected in random order.
If possible, we obtained blood samples just before each microsphere injection in each lamb but, due to occasional technical problems in two of eight control lambs, the intended coronary sinus samples could not be obtained during the nitroprusside infusion. At the end of the study, each lamb was killed with an overdose of intravenously administered sodium pentobarbital.

**Measurements and Calculations**

Aortic, pulmonary arterial, left atrial, and central venous pressures were measured with Gould P23 pressure transducers (Spectramed, Oxnard, California) referenced to atmospheric pressure with zero obtained at the midchest position. The precalibrated electromagnetic flow transducers were connected to Skalar MDL 400 flowmeters. Heart rate was obtained from the flow transducer signal by a cardiometer. All variables were recorded on an Elema Minograf 800 ink-jet recorder (Siemens-Elmra AB, Solna, Sweden). Blood gas tensions and pH were measured with a Radiometer ABL 2 blood gas analyzer (Radiometer A/S, Copenhagen, Denmark); hemoglobin concentration and blood oxygen saturation were measured with a Radiometer OSM 2 special photometer. Blood oxygen content (µmol/l) was calculated by multiplying the product of oxygen saturation (%) and hemoglobin concentration (g/dl) by the factor 0.167; this factor includes, for the oxygen capacity, 1.36 ml oxygen per gram hemoglobin.16

During injection of microspheres into the left atrium, a reference sample was continuously drawn into preweighed syringes for 1.25 minutes at a rate of 7 ml/min. After the lambs had been killed, the hearts were removed and weighed, fixed in 8% formalin for 4–7 days, and then reweighed. Great vessels, chordae, and epicardial fat were removed. The atria, septum, and the right and left ventricular free walls were separated, and the latter divided into three transmural layers. Each tissue sample was corrected for the weight change caused by fixation. The radioactivity of the different parts of the heart was determined in a Beckman 9000 gamma counter (Beckman Instrs., Inc., Fullerton, California). Regional myocardial blood flow was calculated with a special software package17 on a PDP 11/15 (Digital Equip. Corp., Maynard, Massachusetts) minicomputer. Myocardial blood flow was expressed as flow per 100 g of fresh weight (ml/min/100 g). The transmural distribution of the left ventricular myocardial blood flow was determined by dividing blood flow to the subendocardial layer by flow to the subepicardial layer of the left ventricle, thus obtaining the endocardial-to-epicardial ratio for the left ventricular free wall. Adequate mixing of microspheres within the circulation in a given experiment was confirmed by ascertaining that the blood flows to the cerebral hemispheres per 100 g of tissue did not differ more than 10%.

Pulmonary blood flow in the shunt lambs was obtained by adding coronary blood flow measured with the microspheres to the flow measured with the electromagnetic flow transducer around the aorta.9 The left-to-right shunt was calculated by subtracting systemic blood flow from pulmonary blood flow, whereas the left-to-right shunt fraction was obtained by dividing shunt flow by pulmonary blood flow. The systemic and pulmonary vascular resistances were calculated according to standard equations. Coronary vascular resistance was estimated by dividing the mean aortic blood pressure by flow per 100 to the total heart tissue. Left ventricular myocardial oxygen consumption was determined by the product of the blood flow to and the arteriovenous difference of oxygen across the left ventricular free wall.

**Statistical Analysis**

Results are expressed as mean±SEM. ANOVA was used to test the differences between shunt and control lambs at corresponding times and the responses to the infusion of nitroprusside within each group.18 If the responses to the infusion were significantly different, the Newman-Keuls test was used. A p value of less than 0.05 was considered significant.

**Results**

The data obtained for weight, age, blood flows, pH, blood gases, hemoglobin concentration, and oxygen saturation in aorta and coronary sinus in both groups of lambs are summarized in Table 1. Weight and age were the same in the two groups. There were significant differences in resting cardiovascular function and arterial blood gases between the shunt and control lambs. Pulmonary and coronary blood flows were significantly higher in shunt than in control lambs, which was also true for heart rate, left atrial pressure, and left ventricular stroke volume (Table 2). The effective left ventricular stroke volume, which

<p>| TABLE 1. Preinfusion Data for Shunt and Control Lambs |
|-----------------------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Shunt</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Age (days)</td>
<td>49±5</td>
<td>52±4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>15.4±1.3</td>
<td>15.4±1.0</td>
</tr>
<tr>
<td>Blood flows (ml/min/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>110±7</td>
<td>131±8</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>256±13*</td>
<td>131±8</td>
</tr>
<tr>
<td>Coronary</td>
<td>14.1±1.5*</td>
<td>5.4±0.7</td>
</tr>
<tr>
<td>Left-to-right shunt (%)</td>
<td>56±3</td>
<td></td>
</tr>
<tr>
<td>Arterial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>9.4±0.3</td>
<td>9.7±0.3</td>
</tr>
<tr>
<td>pH</td>
<td>7.41±0.01*</td>
<td>7.46±0.01</td>
</tr>
<tr>
<td>PO₂ (mm Hg)</td>
<td>101±3</td>
<td>98±2</td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td>45±2*</td>
<td>40±1</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>89±1</td>
<td>92±1</td>
</tr>
<tr>
<td>Coronary sinus</td>
<td>26±3</td>
<td>37±4</td>
</tr>
</tbody>
</table>

Values are given as mean±SEM. ANOVA was used. *p<0.05, vs. control lambs.
is left ventricular stroke volume minus the left-to-right shunt volume per beat, was significantly lower in shunt than in control lambs. In the shunt lambs, arterial pH was lower, whereas CO₂ tension was higher, explaining the lower pH values.

Blood flow per 100 g to the left ventricular wall, atria, septum, and total heart were also higher in the shunt than in the control lambs (Table 2). Because arteriovenous differences in oxygen across the left ventricle of the shunt and control lambs were similar and blood flow per 100 g of left ventricular free wall was significantly higher in the shunt lambs, their myocardial oxygen consumption was also higher (Table 2).

**Nitroprusside Infusion**

Heart rate increased during nitroprusside infusion in both shunt and control lambs (Table 2). The increase was such that there was no longer a significant difference between the two groups during the infusion period. In contrast, left atrial pressure and left ventricular stroke volume were still significantly higher in the shunt than in the control lambs. Although the decrease in left atrial pressure in both groups was substantial, it was only significant in the control lambs at 10 minutes after the onset of the infusion (Table 2). Peak systolic aortic pressure and left ventricular stroke volume, on the other hand, both decreased significantly at 10 and 50 minutes after the onset of the infusion in both groups of lambs, except for left ventricular stroke volume in the shunt lambs at 50 minutes.

Nitroprusside infusion did not change regional myocardial blood flows significantly in lambs with and without shunts (Table 2). In the control lambs, there was a trend of an increase in all regional flows. The significant differences in total and regional blood flows between the shunt and control lambs disappeared during infusion, except for the total myocardium, left ventricular free wall, and septum at 10 minutes after the onset of infusion.

The oxygen concentration difference between arterial and coronary sinus venous blood did not significantly change throughout the infusion period. Moreover, there was no substantial difference in arteriovenous oxygen concentration between shunt and control lambs. This means that the changes noted in the blood flow to the left ventricular free wall will be reflected in the myocardial oxygen consumption (Table 2). The existing difference in myocardial oxygen consumption between shunt and control lambs disappeared during nitroprusside infusion.
neutralizes the influence on myocardial oxygen consumption of a decreased wall stress and external work of the left ventricle. This led us to calculate the consumption of oxygen by the left ventricular free wall per beat (Figure 1). This calculation shows that left ventricular free wall oxygen consumption tends to decrease in the shunt lambs (preinfusion, 6.7±0.7 vs. 4.8±0.7 μmol/100 g left ventricle/beat at 10 minutes) and in the control lambs (preinfusion, 3.8±0.4 vs. 2.8±0.2 μmol/100 g left ventricle/beat at 10 minutes). Although this decrease was not statistically significant, it might indicate that the increase in heart rate does not completely offset the myocardial oxygen consumption caused by the changes in external work and wall stress. Similarly, the myocardial oxygen consumption difference, between lambs with and without a shunt, persisting throughout the nitroprusside infusion despite the equal heart rates, can indicate differences in other determinants of myocardial oxygen consumption in the lambs with a shunt.

The arteriovenous difference in oxygen concentration of the coronary bed is usually large and relatively constant, even under different experimental conditions.21,22 This was also true in the present experiments (Table 2). Because the flow to the left ventricular free wall was unchanged at 10 and 50 minutes after the onset of the nitroprusside infusion when compared with the preinfusion values, the oxygen consumption by the left ventricular free wall did not change, either. Besides, total myocardial blood flow and the other regional myocardial blood flows did not change significantly, although arterial blood pressure was reduced substantially (Table 2). It might be that the decrease in myocardial blood flow due to the decreased arterial pressure is restored by autoregulatory mechanisms of the coronary vascular bed. Another compensatory factor might be the increase in heart rate during infusion because there is a direct relation between heart rate and myocardial blood flow.23 Also, in experimental chronic volume overload, it has been shown that myocardial regional blood flows increased when resting heart rates increased,24,25 whereas in those cases where heart rates were not significantly different from those of control animals, regional myocardial blood flows remained unchanged.26,27

In our earlier report on the hemodynamic effects of sodium nitroprusside in case of an aortopulmonary left-to-right shunt,6 we described the complex pattern of blood flow changes during nitroprusside infusion. Although we observed an initial hemodynamic improvement (shunt fraction decreasing from 51% to 40% of pulmonary blood flow), this lasted only a few minutes and, after that, systemic and pulmonary blood flows stabilized at almost unchanged levels, whereas heart rate was markedly elevated throughout the infusion period. The hemodynamic changes in the present study were identical to those previously reported. Thus, our present data, together with our earlier observations on the hemodynamic effects of sodium nitroprusside in case of an aortopulmonary

**Discussion**

The present study shows that, during infusion of sodium nitroprusside, the oxygen consumption by the left ventricular free wall does not change significantly in both shunt and control lambs, despite a substantial decrease in left atrial pressure, aortic pressure, and left ventricular stroke volume. The decrease in left atrial pressure is partly the result of a decreased venous return, which results in a smaller end-diastolic volume of the left ventricle. The smaller end-diastolic volume will not only cause a diminished force of contraction, but will also set a smaller radius of the left ventricle for the subsequent systole and will, therefore, decrease wall stress. Apart from this, wall stress will also decrease due to a decrease in peak ventricular pressure as a consequence of the decreased peak aortic pressure. This decreased aortic pressure will in its turn, together with the decreased stroke volume, decrease the external work done by the left ventricle.19 Because external work and wall stress are both major determinants of myocardial oxygen consumption,20 a decrease in left ventricular myocardial oxygen consumption during the infusion of nitroprusside can be expected. Heart rate, however, is another major determinant of myocardial oxygen consumption, and it is likely that the increase in heart rate during the infusion of nitroprusside

![Figure 1. Graph showing myocardial oxygen consumption of left ventricular free wall per heart beat in shunt (○) and control lambs (●) before and 10 and 50 minutes after onset of 10 μg/Kg/min sodium nitroprusside infusion. *Significantly different from control lambs at corresponding time. C, Preinfusion period. Data are mean±SEM.](http://circ.ahajournals.org/doi/abs/10.1161/01.CIR.0000136845.88888.AB)
left-to-right shunt,6 have implications for the use of sodium nitroprusside in the treatment of infants with a circulatory congestion. In view of the unchanged pulmonary and systemic blood flows, and the unchanged oxygen consumption of the left ventricle when a steady state has been reached during the infusion of nitroprusside, we consider the use of nitroprusside in infants with similar types of left-to-right shunts, and normal systemic blood flow and vascular resistance, of limited value.

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References


KEY WORDS: oxygen, ventricular function, volume overload, nitroprusside
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