Nitroprusside and Regional Vascular Capacitance in Patients With Severe Congestive Heart Failure

Cecilie Risøe, MD; Svein Simonsen, MD, PhD; Kjell Rootwelt, MD, PhD; Svein Sire, MD; and Otto A. Smiseth, MD, PhD

Background. This study investigates the effects of sodium nitroprusside on regional vascular capacitance in eight patients with severe congestive heart failure (New York Heart Association class IV) and pulmonary hypertension.

Methods and Results. Regional relative blood volumes in the splanchnic and pulmonary region were determined by equilibrium blood pool scintigraphy. Hepatic venous wedge pressure and the mean of pulmonary artery and pulmonary capillary wedge pressure were used to represent the distending pressures of the splanchnic and pulmonary capacitance vessels, respectively. The dose of sodium nitroprusside was increased stepwise until systolic pulmonary artery pressure decreased below 50 mm Hg. This caused reductions in mean aortic pressure from $89\pm5$ to $66\pm3$ mm Hg ($p<0.005$), in pulmonary capillary wedge pressure from $31\pm1$ to $16\pm2$ mm Hg ($p<0.001$), and in hepatic venous wedge pressure from $10.0\pm1.0$ to $5.9\pm0.6$ mm Hg ($p<0.005$). Intestinal blood volume increased by $26\pm7\%$ ($p<0.005$), whereas hepatic blood volume decreased by $9\pm3\%$ ($p<0.02$). Pulmonary blood volume was unchanged. Analysis of intestinal and pulmonary vascular pressure–volume relations showed larger or equal blood volumes contained at lower distending pressures, indicating that sodium nitroprusside reduced smooth muscle tone of the capacitance vessels in these regions. The reduction of hepatic blood volume was compatible with passive expulsion of blood subsequent to reduced venous pressure. There was no change in the count rate from the spleen.

Conclusions. Nitroprusside reduced venous pressure in patients with congestive heart failure by active relaxation of intestinal and pulmonary capacitance vessels. Hepatic vascular volume was probably reduced by a passive mechanism. (Circulation 1992;85:997–1002)

KEY WORDS • splanchnic blood volumes • pulmonary circulation • radionuclide method • venous capacitance

The capacitance circulation plays an important role in the regulation of cardiac filling pressure and is therefore a main target for therapeutic interventions in congestive heart failure patients. Our understanding of how the human capacitance circulation functions, however, is limited. Effects on arterial resistance can be assessed from the measurement of cardiac output and systemic perfusion pressure, but there has been no simple way of quantifying effects on venous capacitance. The most commonly used techniques for studying venous capacitance are various types of limb plethysmography. These techniques provide information about cutaneous veins in the limbs but cannot be used to assess capacitance in the large and probably more important blood reservoirs in the abdomen and the chest. Equilibrium blood pool scintigraphy, however, has proven to be a useful technique for studying vascular volumes of the chest and abdomen.1–7

Changes in blood volume of an organ may be caused not only by changes in the smooth muscle tone of the capacitance vessels (active changes) but also by changes in vascular distending pressure (passive changes). Active changes in vascular capacitance cannot be separated from passive responses if only vascular volumes are measured. By relating vascular volumes to pressures, however, vascular pressure–volume relations can be defined, and active and passive responses can be distinguished. A change in volume by an active mechanism (i.e., a change in smooth muscle tone) will result in a shift of the venous pressure–volume curve, whereas a passive response is characterized by a change in volume along a single pressure–volume curve.

The present study was designed to determine mechanisms of changes in vascular capacitance during infusion of sodium nitroprusside in patients with severe congestive heart failure. Regional relative blood volumes in the splanchnic region and the lung were assessed by equilibrium blood pool scintigraphy. To distinguish between blood volume changes caused by active and passive mechanisms, we studied regional pressure–volume relations.
Methods

Patients

Candidates for heart transplantation with pulmonary hypertension (systolic pressure above 50 mm Hg) are routinely tested in our department for reversibility of the elevated pressure by infusion of sodium nitroprusside. We studied eight patients (age, 39–54 years; median age, 45 years) with chronic heart failure (New York Heart Association class IV) caused by ischemic heart disease (five patients) or cardiomyopathy (three patients). Their usual morning medication was withheld the day of investigation; thus, none of the patients received vasodilating drugs during the 12 hours preceding the investigation. The study was approved by the ethical committee, and all patients gave informed consent.

Hemodynamics

After fasting overnight, a standard right heart catheterization was performed in the supine position without premedication. A Swan-Ganz 7F thermoludtion catheter (American Edwards Laboratories, Santa Ana, Calif.) was introduced into the femoral vein, and a 16-gauge catheter (Secalon T, Viggo Products, Swindon, UK) was inserted into the femoral artery for aortic pressure measurements. All pressures were measured with SenoNor 840 (Horton, Norway) transducers, using a Mingo- graph 7 (Siemens-Elema, Solna, Sweden) ink jet recorder with zero level at the midaxillary line. An Elecath 4000 computer was used for cardiac output measurements. The hemodynamic recordings included pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), aortic pressure (PAo), cardiac output (CO), and heart rate. Pulmonary distending pressure was calculated according to Milnor et al. as \( \frac{1}{2} \times (PAP + PCWP) \). Systemic vascular resistance was calculated as (PAo – RAP)/CO, and pulmonary vascular resistance as (PAP – PCWP)/CO.

Radionuclide Studies

Relative regional blood volumes were determined by equilibrium blood pool scintigraphy. Erythrocyte labeling was performed as follows: 20 minutes after intravenous injection of 3 mg stannous chloride and 15 mg sodium pyrophosphate, approximately 3.5 ml venous blood was drawn into a syringe containing 900 MBq \(^{99m}\)Tc pertechnetate (Institutt for energiteknikk, Kjeller, Norway) with a citrate-glucose solution added as anticoagulant. The content was reinjected intravenously after incubation for 5 minutes at room temperature. In our laboratory, this procedure has a 95.5% labeling efficiency with a 95% confidence interval from 92.6% to 98.4%. A mobile gamma camera (Starcam, General Electric, Milwaukee, Wisc.) with a diverging collimator was positioned 5–15 cm above the chest and abdominal wall of the patient for an anterior view that included the abdomen cranial to the urinary bladder and a large enough pulmonary region to be considered representative. Emitted radioactivity was recorded continuously and stored in frames of 30 seconds (matrix size, 64 x 64). Regions of interest were drawn within the liver, spleen, and right lung. An intestinal region was drawn caudal to the left kidney, excluding the great vessels and urinary bladder. Time activity curves from the different regions of interest were created automatically by the camera software and corrected for physical decay according to standard methods.

The count rate of each frame was corrected for physical decay according to standard methods. To correct for biological decay, venous blood samples were drawn approximately every 10 minutes during each study period. The counts per milliliter in these samples were measured at the end of the study, and a time activity curve was calculated by an exponential fit after correction for physical decay. The count rates of the activity curves for regions of interest were corrected for biological decay by division with the corresponding blood sample counts. Background activity was assumed constant throughout each study.

For each region of interest, the physical and biological decay-corrected count rate during the last frame before nitroprusside infusion was assigned a value of 100%. All other count rates during the study period were expressed in percent relative to the regional count rate of this frame. Because of the possibility of a variable and unknown hematocrit of the spleen, the relative counts within this region may not express volume changes.9 We therefore report changes in the splenic region as relative counts.

Study Protocol

After instrumentation, the patients rested for 15 minutes before the continuous radionuclide recording was started. Baseline regional blood volumes were recorded for 5–15 minutes, during which a set of hemodynamic measurements was made. Infusion of sodium nitroprusside (Nipride, Hoffmann-La Roche) in 5% glucose was started at a rate of 0.025–0.05 mg/min. PAP and PAo were recorded after 2 minutes at each infusion rate, and the rate was increased stepwise until the systolic PAP was below 50 mm Hg or until symptomatic arterial hypotension. A full set of hemodynamic recordings was taken during the maximal infusion rate of nitroprusside. The 7F thermoludtion catheter was positioned in the hepatic vein under fluoroscopy shortly before the baseline recordings. When the hepatic venous pressure measurements had been taken, the catheter was advanced to the pulmonary artery for continuous recordings. Hepatic venous pressure measurements were repeated on catheter withdrawal within 5 minutes after the last hemodynamic measurements with unchanged rate of nitroprusside infusion. Thus, one point was defined for the hepatic and intestinal pressure-volume relation curves during control and one point during intervention.

Statistical Analysis

Hemodynamic variables and blood volumes at baseline and during the maximal rate of nitroprusside infusion were compared by Student’s paired t test. Results are expressed as mean±SEM and were considered significant at p<0.05.

Results

The median infusion rate of nitroprusside necessary to lower systolic PAP to less than 50 mm Hg was 0.125 mg/min (range, 0.025–0.425 mg/min). This caused reductions in mean PAo from 89±5.0 to 66±3.1 mm Hg, in PCWP from 31±1.3 to 16±1.6 mm Hg, and in hepatic venous wedge pressure from 10.0±1.0 to 5.9±0.55.
Table 1. Hemodynamic Variables and Relative Regional Blood Volumes in Eight Patients Before and After Nitroprusside

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Nitroprusside</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>7.6±1.0</td>
<td>3.6±0.62*</td>
</tr>
<tr>
<td>Systolic pulmonary artery pressure (mm Hg)</td>
<td>67±3.8</td>
<td>43±3.4†</td>
</tr>
<tr>
<td>Diastolic pulmonary artery pressure (mm Hg)</td>
<td>31±1.3</td>
<td>17±1.6†</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mm Hg)</td>
<td>46±2.0</td>
<td>27±2.1†</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>31±1.3</td>
<td>16±1.6†</td>
</tr>
<tr>
<td>Pulmonary distending pressure (mm Hg)</td>
<td>39±1.6</td>
<td>21±1.7†</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (mm Hg Min/l)</td>
<td>3.7±0.38</td>
<td>2.0±0.22†</td>
</tr>
<tr>
<td>Hepatic venous wedge pressure (mm Hg)</td>
<td>10.0±1.0</td>
<td>5.9±0.55*</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>89±5.0</td>
<td>66±3.1†</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.4±0.13</td>
<td>3.2±0.28*</td>
</tr>
<tr>
<td>Systemic vascular resistance (mm Hg Min/l)</td>
<td>22±2.4</td>
<td>12±1.1*</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>86±4.0</td>
<td>79±5.2‡</td>
</tr>
</tbody>
</table>

Relative blood volumes

<table>
<thead>
<tr>
<th>Region</th>
<th>Baseline</th>
<th>Nitroprusside</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal region (%)</td>
<td>99.2±0.29</td>
<td>126.2±6.6*</td>
</tr>
<tr>
<td>Hepatic region (%)</td>
<td>100.2±0.15</td>
<td>91.1±2.3‡</td>
</tr>
<tr>
<td>Pulmonary region (%)</td>
<td>100.1±0.33</td>
<td>100.8±2.5</td>
</tr>
<tr>
<td>Splanic regional count rate (%)</td>
<td>100.0±0.32</td>
<td>101.5±2.6</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

*p<0.005, †p<0.001, ‡p<0.02 compared with baseline.

mm Hg. RAP (mean) decreased from 7.6±1.0 to 3.6±0.62 mm Hg (Table 1). Systemic and pulmonary vascular resistances decreased, and cardiac index increased from 2.4±0.13 to 3.2±0.28 l/min/m². Infusion of nitroprusside was associated with marked changes in blood volume distribution. Figure 1 shows one representative patient. Shortly after start of infusion, there was a substantial increase in intestinal blood volume and a decrease in hepatic blood volume. Individual data from all other patients are shown in Figure 2. Pulmonary relative blood volume did not change with nitroprusside, and there was no change in the relative count rate over the spleen. Mean values for each region are given in Table 1.

Figure 3 relates regional blood volumes to distending pressures. The increase in intestinal blood volume was associated with a decrease in hepatic venous wedge pressure, indicating a leftward and upward shift of the pressure–volume relation. In the liver region, there was a reduction in pressure as well as in volume, and therefore apparently no shift of the pressure–volume relation. In the lung, there was a dramatic reduction of vascular distending pressure with no accompanying reduction in volume, suggesting a leftward shift of the pressure–volume relation.

Regional blood volumes were stable during the baseline period. For each patient, the standard deviation of 10–30 baseline count rates was less than 2.7% within all regions. The biological decay during the period of investigation did not exceed 10% in any patient.

Discussion

In the present study, we assessed the effect of sodium nitroprusside on regional vascular capacitance in patients with congestive heart failure. Relative blood volumes were determined in the splanchnic region and in the lung by using equilibrium blood pool scintigraphy12; the main limitation of this method in assessing vascular capacity is that relative volumes are obtained rather than volume in absolute units. Accordingly, absolute blood volume changes in different regions cannot be compared quantitatively. Attenuation correction has been suggested10 but is difficult and may introduce new

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Graph shows effect of nitroprusside on regional blood volumes in one representative patient. Relative blood volume along y axis: for each region, 100%=blood volume immediately before nitroprusside infusion was started (arrow). The nitroprusside dose was gradually increased during the time of investigation (x axis). Note marked increase in intestinal blood volume with a concomitant reduction in hepatic blood volume. Pulmonary blood volume was unchanged.
sources of error. We have therefore chosen to present our findings as relative volumes. We have previously demonstrated in heart failure patients that regional blood volumes and pressures remain stable over a study period comparable with that of the present study. Therefore, in the present study, we used measurements during a 5–15-minute baseline period for comparison.

To determine the mechanism of the blood volume changes, we related vascular volumes to regional pressures. Intestinal blood volume was related to hepatic venous wedge pressure, which was used as an estimate of portal pressure. Because experimental data indicate that portal pressure approximates the pressure in the hepatic capacitance vessels, we also related hepatic vascular volume to hepatic venous wedge pressure. This may not be entirely correct, because a large fraction of the hepatic blood is in the hepatic veins. The RAP, however, decreased 4.0 mm Hg during nitroprusside infusion compared with the 4.1 mm Hg decrease in hepatic venous wedge pressure. The decrease in hepatic outflow pressure must therefore have been of similar magnitude. It is less obvious which pressure best reflects the effective distending pressure of the pulmonary capacitance vasculature. In accordance with Milnor et al, we used the mean of PAP and PCWP.

In this study, nitroprusside caused an increase in intestinal blood volume, a decrease in hepatic blood volume, and a concomitant decrease in hepatic venous wedge pressure. Thus, the pressure–volume relation of the intestinal region was shifted upward and to the left during nitroprusside infusion (Figure 3), which means that the intestinal vascular bed contained more blood at a lower intravascular pressure. Ideally, to distinguish between active and passive changes, a complete pressure–volume curve should be defined during control as well as during intervention. Although we have obtained only single
points in the present study, the direction and the magnitude of the shifts strongly suggest that nitroprusside increased intestinal and pulmonary vascular volumes through a reduction in smooth muscle tone of the capacitance vessels. We cannot exclude, however, that the observed blood volume changes may have been modified by passive translocation of blood from arteries to veins subsequent to reduced arterial pressure. Our results are essentially the same as those of Smiseth et al in splenectomized dogs without heart failure in which nitroprusside caused qualitatively similar shifts of the relation between portal pressure and intestinal blood volume.

Haase and Shoukas have recently shown in rats that intestinal venules actively constrict during bilateral carotid occlusion and that the changes in the venular properties are due to the increased sympathetic nerve activity. In the present study, the nitroprusside-induced reduction in arterial blood pressure would tend to activate the baroreceptor reflex, which would counteract the increase in intestinal blood volume. The fact that nitroprusside caused a marked increase in intestinal blood volume suggests that reduced arterial pressure did not play a major role, possibly because the baroreceptor reflex is attenuated in heart failure patients.

One potential objection to our interpretation of splanchnic pressure–volume changes is that we are relating venous pressure to a lumped blood volume that includes all vascular elements between the large arteries and the portal vein. Therefore, it might be argued that flow-induced pressure changes in vascular elements upstream from the portal vein may have changed the volume by a passive mechanism, and this would appear as a shift of the relation between the lumped vascular volume and venous pressure. In the present study, however, there were reductions in arterial pressure as well as in estimated portal pressure, and therefore probably in all vascular segments in between. If so, any potential passive effect in upstream vessels would tend to reduce volume. This passive response would tend to reduce the magnitude of the shift of the intestinal pressure–volume relation after nitroprusside and would influence our data interpretation in a quantitative manner only. These assumptions are supported by a recent study in dogs by Wang et al in which they showed that the nitroprusside-induced increase in intestinal blood volume was augmented when arterial pressure was adjusted to the control level before nitroprusside infusion.

The effect of nitroprusside on hepatic vascular volume was directionally opposite to the effect on the intestine. This reduction in hepatic blood volume is compatible with passive expulsion of blood subsequent to reduced distending pressure. This mechanism is consistent with the observations of Greenway and Greenway and Innes in a cat model in which nitroprusside had little or no effect on hepatic venous tone. In a previous study in splenectomized dogs without heart failure, nitroprusside did not change hepatic vascular volume, although central venous pressure and portal pressure decreased. This was interpreted as suggestive of venodilatation. We cannot explain this apparent discrepancy, because heart failure patients should be more vasoconstricted than these dogs and thus more susceptible to venodilating stimuli. The difference might reflect species differences.

In the pulmonary circulation, there was a dramatic reduction in vascular pressure with no change in blood volume. This is not compatible with changes along a single pressure–volume curve and must reflect a shift of the pulmonary vascular pressure–volume relation. These results suggest that nitroprusside increased pulmonary vascular capacitance and are consistent with an experimental study in which nitroprusside was shown to dilate pulmonary veins in dogs.

We found no change in the radionuclide count rate over the spleen. Estimated portal venous pressure and arterial pressure decreased markedly, however, and splenic distending pressure most probably decreased. One possible interpretation of these findings is that splenic vascular capacitance increased due to venodilation. A previous study in dogs concluded that the spleen
is the major site of changes in vascular volume caused by nitroprusside. These studies may not be comparable, however, as the canine spleen is generally believed to be of much larger importance hemodynamically than the human spleen. Further, their dogs did not have heart failure. An important objection to this interpretation of splenic vascular capacitance in the present study is that the splenic hematocrit may have varied during the intervention, so that changes in relative count rate may not adequately express blood volume changes.

The substantial reductions in vascular pressures and resistances in this study agree with previous reports on hemodynamic effects of this drug. Reduction in left ventricular filling pressure with nitroprusside in the present study may be attributed at least in part to an increase of intestinal, pulmonary, and possibly splenic vascular capacitance caused by a reduction in venous smooth muscle tone. The nitroprusside effect on the intestine is consistent with the study by Engler et al in chronically congested dogs, in which nitroprusside decreased resistance to splanchnic venous return.

Conclusions

In patients with severe congestive heart failure, nitroprusside reduced venous pressure by smooth muscle relaxation of the intestinal and pulmonary capacitance vessels. This was accompanied by a decrease in hepatic vascular volume that was attributed to passive expulsion of blood secondary to reduced distending pressure.

Acknowledgments

We are grateful to Aaslaug Eldjarn, CNMT, and Synnøve Dybevold, CNMT, for excellent help with the mobile gamma camera recordings.

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Nitroprusside and regional vascular capacitance in patients with severe congestive heart failure.
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Circulation. 1992;85:997-1002
doi: 10.1161/01.CIR.85.3.997

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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