Effect of Nitroprusside on Hydraulic Vascular Loads on the Right and Left Ventricle of Patients with Heart Failure

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SUMMARY We studied the effect of nitroprusside on the hydraulic vascular load of the right and left ventricle in seven patients with severe left ventricular failure. At doses of 0.25–0.75 μg/kg/min, stroke volume increased progressively from 40.1 to 48.6 ml and left ventricular end-diastolic pressure decreased from 24.5 to 11.2 mm Hg. Accompanying this improvement in left ventricular performance were dose-related decreases in mean ventricular pressures, pulmonic and systemic resistances and the lower-frequency components of input impedance moduli. Characteristic impedance and both total and oscillatory external power were decreased in the pulmonic, but not the aortic, vasculature. In this class of patients, right ventricular unloading is a striking and direct effect of nitroprusside and may account, in part, for improved left ventricular performance through ventricular interdependence.

VASODILATORS have become a mainstay in the treatment of acute and chronic left ventricular failure.1–9 In many patients, they improve forward output while decreasing left ventricular filling pressures. The improvement in ventricular function has been attributed primarily to lowering of the arterial load or impedance faced by the ejecting left ventricle.1,2 However, recent data suggest that the beneficial actions of vasodilators cannot be explained simply by an alteration in the arterial load to left ventricular ejection. In patients with heart failure treated with nitroprusside, improved left ventricular output and filling pressures persisted and aortic pressure, resistance and impedance were returned to baseline values when phenylephrine was added to nitroprusside.10 In a dog model of heart failure, increased cardiac output produced by nitroprusside was attributed to a shift of blood volume from central (pulmonary) to systemic vascular beds that accompanied an increase in systemic capacitance.11 Several studies have demonstrated that vasodilators produce a downward, parallel shift of the left ventricular diastolic pressure-volume curve.12–17 This shift in the left ventricular pressure-volume curve is not clearly attributable to the systemic vascular effects of vasodilators, since in isolated heart preparations, no such effect of changing impedance has been noted. Several studies suggest that events in the right heart have an important influence on the altered left ventricular pressure-volume relationship, especially with an intact pericardium.18–27 In man, Ludbrook et al.12 demonstrated a shift in the left ventricular pressure-volume curve with nitroglycerin but not with amyl nitrite. Both nitroglycerin and amyl nitrite had similar effects on aortic pressure, but only nitroglycerin decreased right ventricular pressure, suggesting that nitroglycerin may alter external restraints on the left ventricle, such as pericardial pressure or septal position, thereby producing a shift in the left ventricular pressure-volume relationship.

This additional mechanism of action of vasodilators on left ventricular performance may result from right ventricular unloading produced by decreases in right ventricular hydraulic load. Many studies, in fact, have shown that pulmonary resistance falls when left ventricular output is increased.18,21,25,27 Without more detailed measurements, however, it is unclear whether this is a primary effect on the pulmonary vasculature or is secondary to decreased left ventricular filling pressures.

We sought to determine the mechanism and magnitude of right ventricular unloading and the dose-response relationship of right relative to left ventricular hydraulic unloading with nitroprusside in patients with severe left ventricular failure. A primary concern was whether this agent, in doses just sufficient to produce a measurable alteration in systemic resistance and left ventricular performance, had a primary effect on right ventricular load through a direct effect on pulmonary vascular resistance and impedance.

Methods

Patients

We studied patients with severe, chronic left ventricular failure from various causes. Clinically overt left ventricular congestive heart failure was manifested by pulmonary vascular congestion on chest x-ray, ventricular gallop sounds and recent history of both dyspnea and shortness of breath at rest. Patients who were scheduled to undergo diagnostic cardiac catheterization were asked to participate in the study. Any patient with suspected valvular or congenital heart disease was excluded. From this population, 20 patients were entered into the study after they gave informed consent.
Seven of these 20 patients had technically suitable data and constitute the study population (Table 1).

**Table 1. Clinical Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Other disease</th>
<th>CAD</th>
<th>Angiographic EF</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>F</td>
<td>ICM</td>
<td>DM</td>
<td>3-V</td>
<td>49%</td>
<td>Dig, HCTZ</td>
</tr>
<tr>
<td>2</td>
<td>76</td>
<td>M</td>
<td>ICM</td>
<td>—</td>
<td>2-V</td>
<td>21%</td>
<td>Dig, Lasix</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>M</td>
<td>CM</td>
<td>—</td>
<td>None</td>
<td>20%</td>
<td>Dig, Lasix, Quinidine</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>M</td>
<td>ICM</td>
<td>—</td>
<td>2-V</td>
<td>30%</td>
<td>Dig, Lasix</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>F</td>
<td>ICM</td>
<td>DM, HPT</td>
<td>2-V</td>
<td>19%</td>
<td>Dig, Lasix, NP</td>
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<tr>
<td>6</td>
<td>50</td>
<td>F</td>
<td>CM</td>
<td>HPT</td>
<td>None</td>
<td>18%</td>
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</tr>
<tr>
<td>7</td>
<td>45</td>
<td>M</td>
<td>ICM</td>
<td>—</td>
<td>2-V</td>
<td>23%</td>
<td>Lasix</td>
</tr>
</tbody>
</table>

Abbreviations: CAD = coronary artery disease; ICM = ischemic cardiomyopathy; CM = idiopathic cardiomyopathy; DM = diabetes mellitus; 2-V and 3-V = two- and three-vessel; HTP = hypertension; Dig = digoxin; HCTZ = hydrochlorothiazide; NP = Nitrol paste.

**Catheterization**

All studies were performed in a fasting, postabsorptive state after premedication with benadryl, 50 mg orally, valium, 10 mg orally, and atropine, 0.5 mg subcutaneously. Routine right-heart catheterization was performed from either an antecubital vein cut-down or a femoral vein percutaneous approach. Left-heart catheterization was performed using the Seldinger technique from the femoral artery. After routine coronary angiography and left ventriculography, the standard catheters were replaced by specially designed high-fidelity transducer catheters (Millar Instruments). The right-heart catheter was a #8F catheter with a #6F leader that was advanced into either the right or left pulmonary artery. The leader helped to stabilize the catheter. Pressure and flow velocity sensors were located 10 cm proximal to the tip to allow measurement of main pulmonary artery pressure and flow velocity. A second pressure transducer was located 5 cm more proximally to allow simultaneous measurement of right ventricular pressure. The #7F arterial catheter had a pressure transducer located 1 cm from the tip. The catheter tip was advanced across the aortic valve to help stabilize the catheter and to keep the sensors in the center of the stream while also allowing measurement of left ventricular pressure. Aortic pressure just above the sinuses of Valsalva was measured with a pressure sensor located 6 cm proximal to the tip. Ascending aortic flow velocity was measured with a sensor located 3 cm distal to the pressure sensor. The pulmonary artery and aortic flow velocity sensors were connected to two identical Biotronex BL-610 flowmeters (Biotronex Laboratories) whose signals were amplified by two identical, specially constructed, non-inverting operational amplifiers. Each system had a phase lag of 1.3°/Hz, which was accounted for in subsequent calculations.

Before inserting each catheter, the sensors were prewarmed for at least 3 hours in dextrose or saline at 37°C. After they were withdrawn from the patient, the drift of the pressure transducers was checked by reimmersion in the bath. In only one case was there more than 2–3 mm Hg of drift in the baseline zero pressure reading. The pressure reading at the end of the completion of the study with the pressure sensor barely submerged in the fluid at atmospheric pressure was used as the zero pressure reference signal for the study. The flow velocity signals together with the four pressure signals and surface ECG were recorded on a Hewlett-Packard 3968A eight-channel analog tape recorder for subsequent analysis. The signals were also monitored during the study with both a six-channel recorder (Honeywell Meddars 200) and a four-channel Tektronix 5441 storage oscilloscope.

An estimation of ascending aortic cross-sectional area during each steady-state condition was obtained by measuring the ascending aortic diameter with an M-mode echocardiogram (Irex Instruments). In patients with suitable-quality echocardiograms, left ventricular end-diastolic diameter was measured from the posterior or wall endocardial surface to the left side of the septum in the region where the tip of the anterior mitral valve leaflet was visible.

**Protocol**

Each catheter was manipulated to obtain an optimal flow velocity signal characterized by a steady diastolic level with maximal systolic amplitude and minimal late systolic negative flow. Pressures, flows and echocardiograms were recorded with the patient resting quietly and breathing shallowly or at held midexpiration. This initial period, which followed the last injection of contrast material by at least 20 minutes, constituted the baseline condition. Stepwise infusions of sodium nitroprusside at doses of 0.25, 0.50 and 0.75 μg/kg/min were then begun with an infusion pump. After 3–5 minutes at each infusion level, when pulmonary artery and left ventricular pressures had reached a steady state, the recordings were repeated. If a patient’s systolic arterial pressure decreased by 15% or more of its preinfusion level, the next higher dose was not given. After attaining the maximum dose, the infusion was stopped and recordings were repeated 5–10 minutes later to verify that the pressures had returned or were very close to their baseline values.

**Calculations and Data Analysis**

The analog records were digitized at a rate of 250 Hz and analyzed on a Data General S/130 minicomputer.
The digitized flow velocity signals were displayed on the terminal screen and only beats that had no significant baseline drift and no significant negative dip or secondary rise in diastole were considered acceptable for analysis. Zero flow was assumed to be that in late diastole. The calibration of the flow velocity probes was performed in vivo as follows. At the completion of two studies, each catheter was placed in turn into the aorta with its tip advanced across the aortic valve. Under this baseline condition, flow velocity signals were recorded while an echocardiogram of the ascending aorta was performed. Duplicate indocyanine green dye-dilution cardiac outputs were then measured. The velocity signals for each probe were digitized and a time-averaged flow velocity was determined. This was converted to volume flow by multiplying by the aortic cross-sectional area. The appropriate calibration factor for each probe was then determined by matching the cardiac outputs calculated from the dye-dilution curves with those of the digitized signals.

From the calibrated flow velocity, the aortic volume flow at desired times in the study was calculated by multiplying by the echocardiographically measured aortic cross-sectional area. The main pulmonary artery diameter could not be reliably measured, so the mean pulmonary artery volume flow was assumed to be equal to the mean aortic volume flow. This assumption, together with the directly measured mean velocity, enabled calculation of the main pulmonary artery diameter, which was needed to calculate the kinetic components of external power. As previously described, the mean kinetic power term is of the form \( \frac{1}{2} \rho Q_0^2 \text{area}^2 \), where \( \rho \) = fluid density, \( Q_0 \) = mean volume flow and area = the cross-sectional area of the vessel, which is the derived term in the pulmonary vasculature.

The noise level of the flow signal was determined for each patient by performing Fourier analysis of the diastolic portion of the flow signal. Only flow harmonics whose moduli were greater than twice the maximum noise level were included in the subsequent calculations. For acceptable beats, the pressure and flow signals were resolved into their Fourier harmonics. The input impedance modulus and phase angle for each harmonic were calculated as the ratio of the pressure to flow moduli and the difference of the pressure and flow phase angles, respectively. The characteristic impedance was estimated by averaging the impedance moduli in the frequency range of 4–15 Hz. Total external power, consisting of both the pressure and kinetic terms for both ventricles, was calculated as previously reported. The oscillatory power and steady power terms and the ratio of oscillatory to total power, indicating the efficiency with which the pulsatile energy was converted into forward flow, were also calculated.

A portion of the reflection characteristics of each vascular bed was assessed by calculating the difference between the maximum and minimum impedance moduli for frequencies between 4 and 15 Hz (\( \Delta Z \)) and by estimating first zero crossing of the phase angle, which was obtained by linear interpolation.

All signals were differentiated with a five-point differentiation algorithm. The ventricular end-diastolic pressures were measured at the point of minimum \( \text{dP/dt} \) immediately after the P wave of the ECG. The resistance of each vasculature was calculated by subtracting the appropriate estimated mean atrial pressure from the mean arterial pressure and dividing by mean flow. Mean atrial pressures were estimated as follows: Atrioventricular valve opening was assumed to occur when the ventricular pressure fell to its end-diastolic value. The time average of ventricular pressure from this point until end-diastole was the estimated atrial pressure. Mean ventricular pressure has been proposed as one index of ventricular load. When the average is taken over the entire cardiac cycle, this measurement also is an indirect index of oxygen demand of the ventricle. For these reasons, we also calculated mean ventricular pressures for both ventricles.

Five to eight nonconsecutive beats during each of the baseline and nitroprusside infusion periods were analyzed as described above. The data for these beats were averaged and are those presented subsequently. Statistical analysis to ascertain effects across the dose range was performed on each variable by using analysis of variance with repeated measures and orthogonal contrasts during the baseline and each drug level. To compare the relative effects of the drug on the pulmonary artery and aorta, where the absolute values of some of the parameters may differ greatly, two-way analysis of variance using repeated measures was performed. When interactions between dose effects or location (pulmonary artery versus aorta) were present, the interacting effects were analyzed separately to delineate the influence of the individual underlying effects. An effect was considered to be significant at the \( p = 0.05 \) level. Data are presented as mean \( \pm \) SEM.

Results

Pertinent clinical information for each of the subjects is summarized in table 1. Five of the patients had ischemic cardiomyopathy and two had idiopathic cardiomyopathy. Two of these patients also had concurrent hypertension. Six patients were receiving digoxin at the time of catheterization and only one patient had received vasoactive medications within 12 hours of catheterization; patient 5 was receiving Nitrol paste, 3 inches every 6 hours, at the time of catheterization.

Representative tracings from patient 6 showing the pressures and flows during baseline and during the three steady-state levels of nitroprusside infusion are illustrated in figure 1. Even with the first dose, the aortic and pulmonary flow velocities increased and left and right ventricular diastolic pressures and pulmonary artery pressure decreased. These changes were progressive over the next two doses. Aortic pressure changed only slightly. The aortic and pulmonary arterial input impedance spectra (except for the zero frequency term) for each patient for baseline and the 0.25- and 0.75-\( \mu \)g/kg/min doses are illustrated in figure 2. In both vasculatures, the effect of the drug was more pronounced for the lower (< 5-Hz) frequency
terms. This decrease in the low-frequency moduli of the input impedance spectra is one manifestation of the decreased central effects of peripheral reflections produced by the vasodilation. Although not every patient demonstrated a decrease in the pulmonic characteristic impedance, statistical analyses across all of the doses demonstrated that these decreases in characteristic impedance in the pulmonary vasculature were significant. There were no significant changes in the characteristic impedance in the systemic vasculature. There was no clearly discernible effect of the drug on the impedance phase angles.

**Right and Left Ventricular Hemodynamics**

The averaged values of the ventricular hemodynamic parameters during baseline and the three doses of nitroprusside are summarized in table 2. Compared with baseline levels, the highest dose of the drug produced a mean flow increase of 28%; a left ventricular stroke volume increase of 21%; a left ventricular end-diastolic pressure decrease of 54%; a mean ventricular pressure decrease of 21%; and no changes in heart rate, peak dP/dt or peak negative dP/dt. Right ventricular end-diastolic pressure decreased by 76% and mean ventricular pressure by 47%. In measurements that were altered, large changes occurred even with the initial dose of the drug. Thus, left ventricular performance improved significantly, both in terms of an increase in forward output and a decrease in filling pressures. These functional improvements occurred without a significant change in echocardiographically measured left ventricular diastolic dimensions.

**Aortic and Pulmonary Arterial Hemodynamics**

The mean values of the impedance and power parameters during baseline and the three doses of nitroprusside are summarized in table 3. Compared with baseline levels, the highest dose of the drug produced a systemic resistance decrease of 26%; systolic and mean pressure decreases of borderline significance; an external power increase of 22%; and no changes in diastolic pressure, characteristic impedance, reflectance indexes, percent oscillatory power or flow acceleration. In contrast to the aorta, most of these measurements were altered in the pulmonary artery. Pulmonary resistance decreased by 36%; characteristic impedance decreased by 36%; systolic, mean and diastolic pressures all significantly decreased; peak flow acceleration increased and oscillatory power decreased; and total external power and the reflectance index ΔZ decreased, but the changes were of borderline significance. The first zero crossing of phase angle and the percentage of oscillatory power did not change.

Thus, over this dose range, left ventricular performance improves concomitantly with a reduction in both systemic and pulmonic hydraulic load. The decrease in left ventricular load was manifested by a fall in resistance and mean ventricular pressure, whereas significant unloading of the right ventricle was manifested by decreases not only in mean ventricular pressure and resistance, but also by decreases in pulmonary artery pressure and characteristic impedance.

**Discussion**

**Critique of Methods**

Some potential limitations of the present study require comment. Studies in the aorta have demonstrated that the flow profile is almost flat across the diameter, but comparable studies in the pulmonary artery have not been as well documented so that potential errors could result if pulmonary volume flow were calculated directly. To circumvent this possibility and because we could not reliably and repeatedly measure the pulmonary artery diameter by echocardiography, we assumed that the pulmonary volume flow rate was equal to that in the aorta during steady-state conditions. Since oxygen saturations and indocyanine green dye-dilution curves indicated no evidence of intracar-
diac shunting in any patient, this assumption seems reasonable. Use of this method should give a good estimation of volume flow so that the resistance and impedance modulus measurements should be reliable. However, because the pulmonary artery diameter is derived, there could be errors in this parameter. The vessel diameter is indirectly taken into account in the kinetic power calculations, so there could be some uncertainty in these measures. However, the kinetic power components constituted such a small fraction of the total power (usually 1–2%) that the magnitude of any errors related to this uncertainty would be negligible.

In calculating aortic impedance phase angle, we did not correct for the physical separation between the pressure and flow sensors. Since there were minimal changes in the aortic pressure and no alterations in characteristic impedance, and since making this correction requires an assumption regarding the apparent phase velocity for which we had no data in our patients, we believed that neglecting this factor would not significantly affect our results or interpretations.

In addition, the absolute values of stroke volume are underestimations because coronary artery flow is not taken into account. Hence, our estimations of changes in resistance and impedance are likely to be underestimations of the true changes if nitroprusside, in this population of patients, has a direct effect to increase coronary blood flow.

One-dimensional echocardiographic measurements of left ventricular dimensions were used to index diastolic size. This single measurement is, at best, only a rough approximation that does not account for changes in shape or position of the walls. However, previous studies using nitroprusside and other nitrates in both normal volunteers and in patients with heart failure demonstrated no change in angiographically measured diastolic volumes. Thus, although we cannot say with certainty that the improved left ventricular performance occurred from an unchanged diastolic volume, the available evidence suggests that volume alterations, if present, were quite small. In fact, there was only an 8-ml change in stroke volume in our patients, so that any volume change would likely have been almost undetectable. Regardless, the presence or absence of diastolic ventricular volume changes does not alter our fundamental findings; these volume changes affect only our interpretations of the findings.

We analyzed five to eight nonconsecutive beats to obtain representative samples of steady-state changes and to avoid biasing the data because of cyclic variations. To assess the amount of beat-to-beat variability, the average and range of the coefficients of variations of selected variables under baseline conditions and during the nitroprusside 0.75 infusion are listed in Table 4. There was some beat-to-beat variability, as evidenced by the 2–13% coefficient of variation in the flows and pressures. The pulmonary artery resistance and characteristic impedance demonstrated the most variability with average coefficients of variations about twice that for the same aortic values.

The calculation of vascular resistance, particularly

**Table 2. Hemodynamic and Ventricular Pressure Responses to Nitroprusside in Patients with Heart Failure**

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR (beats/min)</th>
<th>Q (ml/sec)</th>
<th>CO (l/min)</th>
<th>SV (ml)</th>
<th>EDP (mm Hg)</th>
<th>Mean P (mm Hg)</th>
<th>+ dP/dt (mm Hg/sec)</th>
<th>− dP/dt (mm Hg/sec)</th>
<th>Max. accel (ml/sec/sec)</th>
<th>EDD (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>96.7 ± 6.9</td>
<td>64.6 ± 8</td>
<td>3.86 ± 0.5</td>
<td>40.1 ± 4.7</td>
<td>24.5 ± 1.9</td>
<td>52.7 ± 5.0</td>
<td>1225 ± 156</td>
<td>− 1205 ± 103</td>
<td>11809 ± 2308</td>
<td>6.7 ± 0.8</td>
</tr>
<tr>
<td>NP 0.25</td>
<td>96.5 ± 6.9</td>
<td>78.5 ± 11.6</td>
<td>4.52 ± 0.6</td>
<td>47.4 ± 4.4</td>
<td>20.8 ± 2.6</td>
<td>48.1 ± 4.9</td>
<td>1272 ± 160</td>
<td>− 1183 ± 111</td>
<td>13882 ± 3942</td>
<td>6.7 ± 0.8</td>
</tr>
<tr>
<td>NP 0.50</td>
<td>98.4 ± 6.6</td>
<td>80.4 ± 10.8</td>
<td>4.80 ± 0.6</td>
<td>47.7 ± 4.2</td>
<td>15.5 ± 3.0</td>
<td>44.1 ± 3.9</td>
<td>1266 ± 138</td>
<td>− 1196 ± 105</td>
<td>13928 ± 4129</td>
<td>6.6 ± 0.8</td>
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<tr>
<td>NP 0.75</td>
<td>100.4 ± 6.1</td>
<td>82.8 ± 11.2</td>
<td>4.93 ± 0.7</td>
<td>48.6 ± 5.2</td>
<td>11.2 ± 3.0</td>
<td>41.6 ± 3.8</td>
<td>1251 ± 148</td>
<td>− 1210 ± 99</td>
<td>13747 ± 3658</td>
<td>6.5 ± 0.8</td>
</tr>
</tbody>
</table>
P | Orth.con. | NS            | 0.0004      | 0.0001     | 0.01     | 0.0002      | 0.0002         | NS                  | NS                  | NS                    | NS      |
| Right ventricle |               |             |            |         |              |                |                     |                     |                       |         |
| Baseline   |                |             | 4.2 ± 0.9  | 18.3 ± 2.3 | 610 ± 114   | − 735 ± 101   | 12444 ± 1402      |                     |                       |         |
| NP 0.25    |                |             | 3.9 ± 1.5  | 15.7 ± 2.9 | 577 ± 84    | − 695 ± 65    | 15848 ± 1838      |                     |                       |         |
| NP 0.50    |                |             | 1.9 ± 1.8  | 12.0 ± 3.5 | 552 ± 74    | − 607 ± 68    | 17630 ± 2532      |                     |                       |         |
| NP 0.75    |                |             | 0.9 ± 1.3  | 9.7 ± 2.8  | 497 ± 79    | − 610 ± 65    | 14195 ± 2240      |                     |                       |         |
P | Orth.con. | 0.03          | 0.004       | NS         | NS         | 0.016       | 0.004(Q)       | NS                  | NS                  | 0.004(Q)  |

Data are mean ± SEM.

All orthogonal contrasts are linear except for the quadratic one denoted by (Q).

Abbreviations: HR = heart rate; Q = mean flow; CO = cardiac output; SV = stroke volume; EDP = end-diastolic pressure; Mean P = mean pressure; EDD = end-diastolic diameter; NP = nitroprusside; Orth.con. = orthogonal contrast; Max. accel = maximum volume flow acceleration.
in the pulmonary system, deserves further consideration. Because the pulmonary vessels are surrounded by alveolar pressure and can demonstrate a waterfall phenomenon when the alveolar pressure exceeds the pulmonary venous or left atrial pressure, the pulmonary vascular resistance by dividing the pulmonary arterial minus left atrial pressure gradient by the flow may not represent the true resistance. The downstream pressure that should be used to calculate the resistance depends on the absolute levels of the pulmonary venous and alveolar pressures. Under baseline conditions, it is unlikely that the alveolar pressure exceeded the high left atrial or pulmonary venous pressure, so our estimations of resistance based upon left atrial pressure as the downstream pressure are probably accurate. With vasodilatation, however, there is the possibility that the left atrial pressure fell below the alveolar pressure so that the resistance calculated by using the left atrial pressure may be too high. For instance, if the alveolar pressure at the highest dose of nitroprusside in patient 6 were 10 mm Hg, the true resistance would be 222 rather than 274 dyn-sec-cm, as we calculated based on a left atrial pressure of 7.2 mm Hg. Thus, during drug administration, our calculated resistances based on left atrial pressures are likely to be underestimations of the true resistance.

### Table 3. Vascular Impedance and External Power Response to Nitroprusside in Patients with Heart Failure

<table>
<thead>
<tr>
<th>Condition</th>
<th>$P_{ch}$ (mm Hg)</th>
<th>$P_{sys}$ (mm Hg)</th>
<th>$P_{dia}$ (mm Hg)</th>
<th>Resistance (dynam-sec-cm$^{-5}$)</th>
<th>$Z_0$ (dynam-sec-cm$^{-5}$)</th>
<th>$\Delta Z$ (dynam-sec-cm$^{-5}$)</th>
<th>$\phi_0$ (Hz)</th>
<th>$W_t$ (mW)</th>
<th>$W_p$ (mW)</th>
<th>$%W_0$</th>
</tr>
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<tbody>
<tr>
<td>Aorta</td>
<td>Baseline</td>
<td>110.9±13.2</td>
<td>65.5±2.7</td>
<td>83.9±6.1</td>
<td>1923±332</td>
<td>79.4±17.1</td>
<td>57.3±19.7</td>
<td>3.2±0.4</td>
<td>863±128</td>
<td>139.9±41.0</td>
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<td></td>
<td>NP 0.25</td>
<td>108.6±12.9</td>
<td>64.0±2.8</td>
<td>82.0±5.9</td>
<td>1571±268</td>
<td>94.8±27.1</td>
<td>66.0±30.5</td>
<td>3.4±0.5</td>
<td>1039±185</td>
<td>165.5±45.8</td>
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<tr>
<td></td>
<td>NP 0.50</td>
<td>104.4±11.6</td>
<td>62.9±3.2</td>
<td>79.4±5.7</td>
<td>1440±241</td>
<td>86.3±21.0</td>
<td>55.0±25.8</td>
<td>3.0±0.5</td>
<td>1036±180</td>
<td>172.0±45.2</td>
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<td></td>
<td>NP 0.75</td>
<td>101.8±11.4</td>
<td>61.9±3.3</td>
<td>77.5±5.8</td>
<td>1429±233</td>
<td>93.6±23.6</td>
<td>52.4±18.8</td>
<td>2.9±0.6</td>
<td>1054±186</td>
<td>176.7±47.2</td>
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<td>$p$</td>
<td>Orth.con.</td>
<td>0.05</td>
<td>NS</td>
<td>0.06</td>
<td>0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
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<tr>
<td></td>
<td>Orth.con.</td>
<td>0.06</td>
<td>NS</td>
<td>0.054</td>
<td>0.003(Q)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.07</td>
<td>NS</td>
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</table>

Pulmonary artery

<table>
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<tr>
<th>Condition</th>
<th>$P_{ch}$ (mm Hg)</th>
<th>$P_{sys}$ (mm Hg)</th>
<th>$P_{dia}$ (mm Hg)</th>
<th>Resistance (dynam-sec-cm$^{-5}$)</th>
<th>$Z_0$ (dynam-sec-cm$^{-5}$)</th>
<th>$\Delta Z$ (dynam-sec-cm$^{-5}$)</th>
<th>$\phi_0$ (Hz)</th>
<th>$W_t$ (mW)</th>
<th>$W_p$ (mW)</th>
<th>$%W_0$</th>
</tr>
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<tr>
<td>Baseline</td>
<td>55.6±4.3</td>
<td>25.8±2.2</td>
<td>37.6±3.0</td>
<td>457±91</td>
<td>49.4±9.8</td>
<td>45.1±12.4</td>
<td>3.8±0.4</td>
<td>417±60</td>
<td>83.9±10.2</td>
<td>21.4±2.2</td>
</tr>
<tr>
<td>NP 0.25</td>
<td>48.5±3.7</td>
<td>21.7±3.7</td>
<td>32.3±3.4</td>
<td>344±71</td>
<td>41.5±7.3</td>
<td>36.6±5.6</td>
<td>3.7±0.3</td>
<td>453±89</td>
<td>97.1±11.6</td>
<td>24.4±3.9</td>
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<td>NP 0.50</td>
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<td>18.7±3.4</td>
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<td>306±69</td>
<td>33.3±5.2</td>
<td>27.4±3.6</td>
<td>3.9±0.3</td>
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<tr>
<td>NP 0.75</td>
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<td>16.3±2.6</td>
<td>23.8±2.9</td>
<td>293±64</td>
<td>31.5±4.4</td>
<td>24.2±3.9</td>
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<td>344±65</td>
<td>77.3±10.7</td>
<td>24.7±3.5</td>
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<td>$p$</td>
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<td>NS</td>
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<td></td>
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<td>NS</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.036</td>
</tr>
</tbody>
</table>

Data are mean ± SEM.

All orthogonal contrasts are linear except for the quadratic one denoted by (Q).

Abbreviations: $Z_0$ = characteristic impedance; $\Delta Z$ = maximum minus minimum impedance modulus > 5 Hz; $\phi_0$ = first zero crossing of impedance phase angle; $W_t$ = total external power; $W_p$ = oscillatory external power.

### Table 4. Coefficients of Variation for Selected Parameters Listed in Tables 2 and 3

<table>
<thead>
<tr>
<th></th>
<th>Left ventricle</th>
<th>Aorta</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>EDP</td>
<td>Pressure</td>
</tr>
<tr>
<td>Baseline</td>
<td>Mean</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>7–16</td>
</tr>
<tr>
<td>NP 0.75</td>
<td>Mean</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>5–14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Right ventricle</th>
<th>Pulmonary artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pressure</td>
<td>Resistance</td>
</tr>
<tr>
<td>Baseline</td>
<td>Mean</td>
<td>22</td>
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<tr>
<td></td>
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<td>Mean</td>
<td>49.8</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>28–100</td>
</tr>
</tbody>
</table>

Abbreviations: CO = cardiac output; $Z_0$ = characteristic impedance; $W_t$ = total external power; EDP = end-diastolic pressure.
changes produced by nitroprusside. Hence, we feel that the directional changes, but not necessarily the magnitudes of the resistance changes, are valid indications of the effect of nitroprusside.

Either flow velocity or volume flow can be used as the flow measurement for calculations of impedance, but there is no accepted convention as to which is preferable. Velocity has been advocated because it makes the units of impedance the same as those used in other fields, such as acoustics, and this enables normalization with respect to body size since velocity, but not volume flow, is of similar magnitude in most animals. Use of velocity also characterizes the impedance of an entire vascular bed, since changes in velocity reflect changes in cross-sectional area of the entire bed. On the other hand, use of volume flow but not velocity renders the units of hydraulic power correct and may be more appropriate in assessing the impedance changes in a single vessel, such as the aorta or pulmonary artery.

We believed that nitroprusside should produce the same directional changes in impedance regardless of whether flow velocity or volume is used, because it reduces pressures in the vascular bed that would lead to passive decreases in cross-sectional area which, in turn, independent of volume changes would tend to increase the flow velocity. We found an actual increase in volume flow; therefore, it is likely that the estimates of impedance are underestimated if volume flow rather than flow velocity is used. We verified these above considerations by comparing the impedance changes produced by nitroprusside when they were calculated by using both volume flow and velocity on the same beats in two patients. In this study, we were primarily interested in assessing the effect of nitroprusside on the great vessels as well as on the load faced by the ventricles (a portion of which is indexed by the external power); therefore, we used volume flow in our calculations.

Implications of the Study

This study confirms that low doses of nitroprusside acutely improve left ventricular performance in terms of an increase in forward output together with a decrease in filling pressure from an unchanged end-diastolic size. At these doses, the present study shows that improved performance occurs concomitantly with the expected reduction in systemic arterial resistance and mean left ventricular pressure, but with no change in the high-frequency pulsatile components of hydraulic load. In contrast, in the pulmonary artery there is a pronounced direct effect of the drug to unload the right ventricle in terms of decreases in all of the nonpulsatile and pulsatile hydraulic load components.

Our results are in agreement with previous findings that left ventricular output is improved when arterial resistance is decreased. Our findings of a decrease in the lower-frequency components of impedance with nitroprusside are also similar to those in a recent study in a similar patient population. However, unlike that study, in which characteristic impedance decreased from 125 to 108 to 92 dyn-sec-cm⁻³ at doses of 9–19 and 20–38 μg/kg, we found no alteration in the aortic characteristic impedance. This apparent discrepancy may be a function of the slightly different methods used to estimate it. Ideally, the characteristic impedance should be estimated by averaging the highest frequency components of the spectrum. However, these harmonics are also the most susceptible to contamination by noise, particularly in the flow signal. Our method of estimating characteristic impedance was chosen to minimize artifacts due to noise, but consequently restricted us to the lower-frequency range of the spectrum and limited the number of terms that could be included in the average. Likewise, the choice of which frequency to use as the lower limit is arbitrary, but whichever one is chosen should be beyond the rapidly falling phase of the impedance modulus. Based on the individual spectra shown in figure 2 and taking the above considerations into account, we felt that 4 Hz was a reasonable compromise.

Previous studies demonstrate that passive alterations in the pulmonary vasculature secondary to alterations in left atrial pressure result in changes opposite in direction to those we found. Thus, our data suggest that the hemodynamic alterations in the pulmonary vasculature are the result of direct, active changes in physical properties produced by nitroprusside rather than merely being passive responses to a decrease in the chronically elevated left ventricular filling pressure. When epinephrine or norepinephrine was infused to increase pulmonary blood volume, pulmonary pressures and left atrial pressure in dogs, the resistance across the pulmonary bed was found to decrease, presumably because of recruitment of previously unperfused beds and passive distention. However, when left atrial pressure and pulmonary blood volume were decreased and pulmonary artery and venous pressures were actively increased by histamine, the pulmonary artery resistance increased. More recently, it was shown that an acute, mechanically induced increase of left atrial pressure resulted in a decrease in pulmonary vascular resistance and no change in characteristic impedance. Characteristic impedance was altered only when left atrial and pulmonary arterial pressures were chronically elevated, presumably because of changes in the mechanical properties of the wall itself. Even in this setting, when fluid was infused to passively restore left atrial pressure to its chronically elevated value of 15 mm Hg (after it had been lowered by α-adrenergic blockade), resistance decreased, pulmonary artery pressure increased back to its elevated value, and characteristic impedance still did not change. Another recent study suggests that volume alterations produced by hemorrhage or volume expansion in dogs altered characteristic impedance by changing smooth-muscle activation in the pulmonary artery. Thus, changes in pulmonary resistance appear to be inversely related to the left atrial pressure changes regardless of whether the atrial pressure changes are produced actively or passively and characteristic impedance is not altered by passive changes in left atrial pressure.
Therefore, we believe it unlikely that the hemodynamic responses we found in the pulmonary bed were passive and secondary to changes in left atrial pressure.

The response of the chronically altered pulmonary vasculature to nitroprusside in the doses used in this study, as manifested by decreases in both the pulsatile and nonpulsatile components of hydraulic load faced by the right ventricle, is similar to that seen in other studies in which vasodilators were administered in the face of increased pulmonary vascular tone. The baseline value of characteristic impedance of 49 dyn-sec-cm⁻⁶ that we found was similar to the value of 46 dyn-sec-cm⁻⁶ found in a population with pulmonary hypertension secondary to mitral stenosis (normal value was 23 dyn-sec-cm⁻⁶). The elevated total external and oscillatory power also decreased, reflecting the relatively greater decrease in pressure compared to the smaller increase in flow. This effect is in contrast to the increase in external power response in the systemic vasculature where the flow increase is relatively greater than the decrease in pressure.

It is difficult to attribute the parallel downward shift of the left ventricular diastolic pressure-volume curve observed in previous studies and inferred in this study to the systemic effect of vasodilators. Our data also do not allow us to ascertain unequivocally how vasodilators achieve this beneficial effect on left ventricular performance. However, since we demonstrated right ventricular unloading by nitroprusside and many prior studies have shown diastolic interaction between the ventricles, ventricular interaction may be one mechanism by which vasodilators achieve their beneficial effects. The left ventricular diastolic pressure-volume curve could be shifted by right ventricular unloading, resulting in both improvement in diastolic and systolic function even though the right ventricle is unlikely to directly influence left ventricular systolic function. One could argue that the small changes in right ventricular filling pressures that we found were insufficient to significantly alter left ventricular filling pressures. However, the study in which ventricular interdependence was proposed as the cause of the shift of the left ventricular pressure-volume curve with nitroglycerin in man found an amplification effect in that a 5-mm Hg fall in right ventricular end-diastolic pressure was associated with a 10-mm Hg fall in left ventricular end-diastolic pressure in a normal population. In a population with heart failure and presumably distended intrapericardial chambers, the amplification effect might be more pronounced than in a normal population. Additionally, small changes in right ventricular pressures could alter other external restraints on the left ventricle acting via stresses at the septal-ventricular junction or acting through changes in regional intrapericardial pressures. These have all been postulated as mechanisms of the parallel shift of the left ventricular pressure-volume curve.

Mechanisms other than ventricular interdependence could account for the drug-induced improvement in left ventricular performance. The decrease in filling pressures could have lowered the diastolic wall stress and, hence, diminished ongoing ischemia in those hearts in which ischemia played a role in the dysfunction. Additionally, coronary artery flow could have been increased either by direct action of the drugs or by an increase in the coronary perfusion pressure subsequent to the fall in ventricular filling pressures in the face of an unchanged aortic pressure. Whether subclinical ischemia plays any role in the ventricular function and whether there are alterations in either the demand or oxygen supply to these hearts remain to be determined. Alterations in ventricular relaxation produced by the drug could, theoretically, cause a shift of the pressure-volume curve. A previous study, however, showed no effect of nitroprusside on left ventricular relaxation, although no patients in heart failure were included.

Thus, although vasodilators improve left ventricular performance by decreasing the hydraulic load on the left ventricle, the quantitative contribution of this mechanism is unclear. Left ventricular performance may be altered independently or additively by unloading the right ventricle. Until maneuvers are found that uncouple the hemodynamic effects of the two vascular systems and ventricles in the intact organism, the independent influence of these two mechanisms will remain unclear.

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