Right Ventricular–Vascular Interaction in Congestive Heart Failure
Importance of Low-Frequency Impedance

William G. Kussmaul III, MD; Jonathan A. Altschuler, MD; William H. Matthai, MD; Warren K. Laskey, MD

Background. Vasodilator agents are widely used in congestive heart failure. These agents may have important effects on the pulsatile aspects of right ventricular hydraulic load.

Methods and Results. Fifteen patients with severe congestive heart failure were studied during cardiac catheterization by use of high-fidelity pressure transducers and a catheter-mounted flow velocity probe. Three graded doses of nitroprusside were infused as pulmonary artery (PA) pressure and flow were continuously recorded. From Fourier transforms of signal-averaged waves, PA impedance, hydraulic power, and wave reflection indices were derived. At the highest dose of nitroprusside (66±41 μg/min), cardiac output was significantly improved, whereas PA mean and wedge pressure, resistance, impedance at the first harmonic, characteristic impedance, and wave reflection amplitude were all reduced. At the dose (32±20 μg/min) at which cardiac output first showed improvement, only PA mean pressure and first-harmonic impedance were significantly reduced. Hydraulic power cost per unit of forward flow was also lowered at this dose, despite lack of significant change in pulmonary vascular resistance. At the lowest dose of nitroprusside (11±4 μg/min), six patients experienced a decrease in stroke volume, whereas the other nine were either unchanged (n=1) or showed an increase (n=8). Multiple regression revealed that only the change in first-harmonic impedance correlated with this effect, increasing when stroke volume decreased and decreasing when stroke volume increased (P=.02). The change in first-harmonic impedance at this dose appeared to be caused by alterations in the amplitude of PA wave reflections. At higher doses, changes in mean PA pressure (but not in pulmonary vascular resistance) correlated with changes in stroke volume.

Conclusions. Nitroprusside vasodilation at low doses alters PA hemodynamics in congestive heart failure primarily through changes in low-frequency impedance. In some patients, this effect is associated with decreased stroke output. At higher doses, favorable alterations in resistance, low- and high-frequency impedance, and wave reflections all contribute to increased forward flow and decreased power requirement per unit forward flow. These findings show that ventricular–vascular interaction is importantly affected by pulmonary vasodilation and that appreciation of pulsatile properties is required to understand the effects of pulmonary vasodilation on cardiac output. (Circulation. 1993;88:1010-1015.)

Key Words • nitroprusside • lung • right ventricle • vessels • arteries • waves • pulmonary artery

Vasodilator therapy is widely used in the treatment of congestive heart failure. Arteriolar dilating agents such as nitroprusside exert a favorable effect on left ventricular load by reducing systemic vascular resistance, low-frequency impedance, and the amplitude of arterial wave reflections.1-3 The role of right ventricular (RV) unloading in congestive heart failure remains largely unexplored, despite recognition that RV performance has both functional and prognostic importance in heart failure.4-6 Although some vasodilators reduce pulmonary vascular resistance, this is a steady-flow measurement that provides an incomplete description of pulsatile flow in a vascular bed characterized by low pressure and high compliance.

We studied the effects of graded doses of nitroprusside on pulmonary artery (PA) resistance, impedance, and wave reflection properties in patients with severe congestive heart failure to determine (1) whether favorable alterations in low- and high-frequency impedance occur in addition to the expected change in pulmonary resistance; (2) whether the behavior of PA wave reflections is modified by vasodilators; and (3) whether and by what mechanism improvement in the efficiency of RV-vascular interaction occurs during vasodilator administration.

Methods

Fifteen male patients with chronic congestive heart failure were studied. Their mean age was 56 years (range, 41 to 64 years). The patients all had severely limiting symptoms of congestive failure despite treat-
Catheterization Protocol

At the time of the study, all patients were fasted and premedicated with diazepam or diphenhydramine. Digoxin and diuretic therapy were continued, but all vasodilating drugs were discontinued for at least 12 hours before study. A balloon-tipped catheter was placed in the PA to record pressures and thermodilution cardiac output. With a long dilator/sheath set inserted via the femoral vein, an 8F high-fidelity catheter (Millar Instruments, Inc) was also positioned in the PA. This catheter has solid-state pressure transducers located 4 and 12 cm from the tip to allow simultaneous recording of PA and RV pressures. An electromagnetically driven flow velocity probe mounted at the same site as the distal pressure transducer is energized by a 500-Hz square-wave flowmeter (Carolina Medical Electronics). The sensitivity and frequency response of this system has been reported previously.7

Data Recording

All data were recorded with the patients supine and at rest and before administration of any iodinated contrast. At least 60 seconds of continuous baseline PA pressure and velocity data and the ECG were recorded on FM magnetic tape. Thermodilution cardiac outputs were obtained in triplicate. The results of those output determinations agreeing within approximately 10% were averaged, and the result was used to scale the velocity signal to volume flow during data analysis. Data were recorded, including repeat cardiac output determinations, during infusion of nitroprusside at a starting dose of 10 μg/min (25 μg/min in one patient). Four minutes were allowed to achieve a steady state as confirmed by repeated measurements of PA oxygen saturation before data recording was begun. Nitroprusside doses of 25, 50, 100, and in some patients 200 μg/min were then given, and data were recorded in the same manner. The protocol was terminated whenever cardiac output exhibited a >25% increase or the pulmonary wedge pressure fell by 50%. All patients tolerated the drug infusion well, and there were no complications during the study. At the completion of data gathering, the nitroprusside infusion was discontinued and coronary arteriography, ventriculography, and myocardial biopsy were carried out according to clinical indications.

Data Analysis

The methods for signal averaging, Fourier analysis of pressure and flow data, and computation of the impedance, power, and reflection spectra have been described previously.3,7,8 Characteristic impedance (Zc, dyne · s · cm−3) was calculated by averaging all impedance moduli between 2 and 12 Hz. This frequency range avoids the steep fall in impedance at the first harmonic as well as the possible effects of noise at higher frequencies. We eliminated from analysis pressure and flow harmonics that fell below Fourier-determined amplitudes of signal-averaged in vitro recordings (0.5 mm Hg pressure and 5 mL/s flow). Impedance at the first harmonic (Z1) represents low-frequency impedance. Pulmonary vascular resistance was calculated as mean PA minus mean pulmonary wedge pressure divided by cardiac output.

Measured pressure and flow waveforms were resolved in the time domain into their forward and reflected components as previously described.9,10 The reflection factor was defined as the ratio of the peak reflected wave amplitude divided by the peak forward amplitude.11 The timing of the return of the predominant reflected wave to the measuring site in the proximal PA is given both in milliseconds from the onset of ejection (BWAT, backward wave arrival time) and as a fraction of RV ejection time (BWAT/RVET).

Hydraulic (external) power was calculated ignoring the small kinetic terms.12 Mean power (Wm) is the product of mean PA pressure and mean PA flow (cardiac output [CO]). Total hydraulic power (WT) is the time-averaged integral of the instantaneous product P(t) × Q(t). Oscillatory power (Wosc), that fraction of power which produces oscillations but does not result in net forward flow, is the difference WT − Wm.

Since expression of total power does not convey utility in terms of forward flow produced, we calculated the quantity WT/CO as the hydraulic power cost per milliliter of forward flow. This ratio is considered an index of the efficiency of ventricular-vascular interaction.12 In the systemic circuit, Wosc is small compared with WT, and therefore the ratio WT/CO will approximate mean arterial pressure. However, Wosc in the pulmonary circuit represents a considerably larger proportion of WT. The ratio WT/CO then provides an index of the total hydraulic power required to move one unit of forward flow.

Statistical Analysis

Group data are expressed as mean±SD. Three nitroprusside doses were analyzed for each patient. For those patients in whom more than three doses were given, the first dose given was always used as dose 1, and dose 3 was taken as the lowest dose producing a 25% increment in cardiac output. If more than one intermediate dose remained, a single intermediate dose 2 was chosen randomly. Mean values for all four conditions (baseline, dose 1, dose 2, dose 3) were compared by one-way repeated-measures ANOVA. The Scheffe F test13 was used to make specific comparisons between baseline values and those at each drug dose.

Multiple linear regression was performed on the data at each nitroprusside dose level to find correlates of the change in stroke volume. Previous data on systemic arterial impedance have suggested that changes in Z1 may be caused by changes in the magnitude or timing of wave reflections as they return to the ventricle during late systole.5,14,15 To investigate this possibility for the pulmonary circulation, multiple regression using change in Z1 as the dependent variable was performed. All computations were carried out with STATVIEW statistical software (Abacus Concepts, Berkeley, Calif) on a Macintosh IIcx computer.
TABLE 1. Effects of Graded Nitroprusside Infusion on Group Mean Hemodynamics, Pulmonary Impedance, Wave Reflections, and Hydraulic Power

<table>
<thead>
<tr>
<th>Nitroprusside dose (µg/min)</th>
<th>Baseline</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>11±4</td>
<td>32±20</td>
<td>66±41</td>
</tr>
</tbody>
</table>

Hemodynamics

<table>
<thead>
<tr>
<th>Heart rate (bpm)</th>
<th>89±15</th>
<th>89±14</th>
<th>88±14</th>
<th>88±15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output (L/min)</td>
<td>3.8±0.9</td>
<td>3.8±0.9</td>
<td>4.1±0.9*</td>
<td>4.6±0.8*</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>40±11</td>
<td>41±11</td>
<td>45±14*</td>
<td>51±14*</td>
</tr>
<tr>
<td>RV end-diastolic pressure (mm Hg)</td>
<td>9.7±4.7</td>
<td>8.4±4.5</td>
<td>7.6±5.3</td>
<td>5.7±5.6*</td>
</tr>
<tr>
<td>Mean PA pressure (mm Hg)</td>
<td>38±6</td>
<td>36±7</td>
<td>33±8*</td>
<td>28±8*</td>
</tr>
<tr>
<td>PA wedge pressure (mm Hg)</td>
<td>25±7</td>
<td>24±9</td>
<td>21±8</td>
<td>15±8*</td>
</tr>
</tbody>
</table>

Pulmonary impedance data

| Resistance (dyne · sec · cm⁻²) | 287±105 | 262±83 | 239±89 | 221±62* |
| Z₁ (dyne · sec · cm⁻²) | 172±73 | 172±76 | 131±60* | 104±52* |
| Z₁ phase (radians) | -0.92±0.45 | -0.95±0.45 | -0.94±0.50 | -0.86±0.46 |
| Zₑ (dyne · sec · cm⁻²) | 54±14 | 52±15 | 46±12 | 41±13* |

Pulmonary artery wave reflection data

| Reflection factor | 0.66±0.21 | 0.66±0.22 | 0.62±0.20 | 0.57±0.22* |
| BWAT (msec) | 293±38 | 301±42 | 319±50 | 343±50* |
| BWAT/RVET | 0.68±0.14 | 0.72±0.18 | 0.76±0.21 | 0.86±0.23* |

Hydraulic power data

| Wₑₑ (mW) | 57±31 | 56±32 | 54±31 | 54±29 |
| Wₑₑ/Wₑ (%) | 16±5 | 18±5 | 16±5 | 17±5 |
| Wₑₑ/CO (mW · mL⁻¹ · sec) | 5.6±1.0 | 5.4±1.1 | 4.8±1.3* | 4.2±1.3* |

n= 15 patients. N1, N2, N3, during graded nitroprusside infusion at doses shown; bpm, beats per minute; RV, right ventricular; PA, pulmonary artery; Z₁, impedance at the first harmonic; Zₑ, characteristic impedance (average of moduli between 2 and 12 Hz); BWAT, backward wave arrival time measured from the QRS onset; RVET, right ventricular ejection time; Wₑₑ, oscillatory hydraulic power; Wₑ, total hydraulic power; CO, cardiac output.

*P<0.05; nitroprusside compared with baseline.

Results

Table 1 summarizes the effects of graded nitroprusside infusion on group mean hemodynamics, pulmonary impedance, wave reflections, and hydraulic power. For the group as a whole, no significant changes were seen at the lowest nitroprusside dose. At the second dose, stroke volume increased (40±11 to 45±14 mL), mean PA pressure fell (38±6 to 33±8 mm Hg), and Zₑ decreased (172±73 to 131±60 dyne · s · cm⁻²) (all P<.05). There were no group changes in resistance or in Zₑ at this dose level, but hydraulic power expenditure per unit forward flow decreased. At the highest dose, stroke volume increased further; reductions in RV filling pressure, resistance, Z₁, and Zₑ were seen, and wave reflection amplitude was reduced as its timing moved later in systole. There were no significant changes in the phase angle of the first impedance harmonic, although this tended to become less negative at higher doses of nitroprusside.

Fig 1 shows the effect of graded nitroprusside infusion on pulmonary impedance in a representative patient. Resistance (here approximated as the 0-Hz term) and impedance at the first harmonic exhibited the sharpest decreases, but impedance at all frequencies was diminished during vasodilation. In addition, the amplitude of impedance oscillations was less at the higher doses, suggesting less wave reflection. This was confirmed by the reflection analysis shown in Fig 2. At successively higher doses of nitroprusside (Fig 2, B, C, and D), the magnitude of the peak reflected wave can be seen to decrease as a fraction of the incident wave. In addition, the timing of the peak reflected wave moved progressively later in systole, ultimately falling at or just after the dicrotic notch.

Examination of individual data at the lowest nitroprusside dose revealed that although there were no group mean changes, disparate behavior was evident in that six patients actually experienced a decrease in stroke volume. Of these six, five demonstrated increased Zₑ at this dosage level, whereas the remaining nine patients (eight of whom had stroke volume increases) all showed decreased Zₑ. There was no discern-
ible relation between the change in stroke volume and changes in pulmonary vascular resistance, RV filling pressure, or mean PA pressure at this nitroprusside dose. Multiple regression using change in stroke volume as the dependent variable confirmed that only the change in Z₁ correlated (Table 2). At higher doses, changes in mean PA pressure correlated with altered stroke volume. Fig 3 plots the univariate regression of change in Z₁ and change in stroke volume at the lowest dose, showing a significant inverse relation. Of reflected wave amplitude, timing, and pulmonary vascular resistance, only reflected wave amplitude showed a significant correlation (P=.03) with the change in Z₁.

The two groups defined by the stroke volume response at the lowest nitroprusside dose (decrease in stroke volume, n=6; all others, n=9) were compared by Student’s t

**Table 2. Multiple Regression Results: Correlates of Change in Stroke Volume at Three Doses of Nitroprusside**

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Multiple regression P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N1</td>
</tr>
<tr>
<td>Mean PA pressure</td>
<td>0.80</td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
<td>0.97</td>
</tr>
<tr>
<td>RV end-diastolic pressure</td>
<td>0.71</td>
</tr>
<tr>
<td>Z₁</td>
<td>0.02</td>
</tr>
<tr>
<td>Z₃</td>
<td>0.42</td>
</tr>
</tbody>
</table>

N₁, N₂, N₃, during graded nitroprusside infusion at doses shown; PA, pulmonary artery; RV, right ventricular; Z₁, impedance at the first harmonic; Z₃, characteristic impedance (average of moduli between 2 and 12 Hz).

**FIG 3.** Graph showing change in stroke volume and change in first-harmonic impedance (Z₁) at the lowest nitroprusside dose plotted for all 15 patients. Although no change in either quantity was found for the group as a whole, it can be appreciated that this was because some patients showed a decrease in Z₁ and increase in stroke volume, whereas others exhibited the opposite pattern.
showing stroke volume decrease \([n=6]\) compared with \(337\pm 83\) dyne \(\cdot s \cdot cm^{-2}\) in the others \([n=9]\), \(P=.02\), but the overlap between the groups was considerable.

**Discussion**

**PA Impedance in Heart Failure: Previous Studies**

Elevated pulmonary resistance is commonly recognized to be present in chronic congestive heart failure. However, this quantity represents only an average, nonpulsatile property. There is less appreciation of the role of pulsatile components of impedance, which may also contribute importantly to the total RV hydraulic load. Other studies have shown an increase in pulmonary characteristic impedance under conditions of pulmonary hypertension, whether in the setting of mitral stenosis,\(^\text{16,17}\) congestive heart failure,\(^\text{1}\) or primary pulmonary hypertension.\(^\text{18}\) This evidence of increased PA stiffness, which augments RV power requirements, is corroborated in the present study by the early return of the reflected pressure and flow waves that occurred when RV ejection was only 68% complete. The amplitude of the reflected waves averaged 0.66 of the forward wave, indicating a high degree of reflection, exceeding that seen in the systemic circulation.\(^\text{3}\) Since reflected pressure waves add to the incident pressure and flow reflections subtract from forward flow,\(^\text{19}\) high-amplitude reflections returning during ventricular systole are likely to contribute significantly to total RV hydraulic load. Modification of these reflections by vasodilation should improve ventricular loading conditions and lower hydraulic power requirements, thus improving circulatory performance.

**Effects of Nitroprusside on RV-Vascular Interaction: Importance of Low-Frequency Impedance**

A primary finding of this study is that low-frequency impedance, represented by \(Z_1\), is a sensitive measure of the effects of vasodilators, especially at low doses. Hydraulic pulsatile power is proportional to the product of flow squared and impedance at each frequency. The first and second harmonics of flow are invariably of the greatest magnitude, exceeding even the mean flow term.\(^\text{20}\) The corresponding pulsatile power terms, although they do not contribute to net forward flow, therefore add significantly to the hydraulic power expended to produce it. Accordingly, reduction in the magnitude of low-frequency impedance induced by nitroprusside reduces the quantity \(W_f/CO\) even before pulmonary resistance is significantly changed. This indicates an improvement in the efficiency of ventricular-vascular interaction, since less of the total expended power is "wasted" in oscillations. The long-term effects of such improvement are unknown but are not likely to be negligible, since almost 20% of total hydraulic power was accounted for by pulsations.

In the only previous study of the effects of vasodilation on PA reflection, Yin et al\(^\text{1}\) and Brin and Yin\(^\text{2}\) found a statistically nonsignificant trend toward reduction in indices of reflection in six patients with congestive heart failure who received nitroprusside. Although they concluded that there were no effects on pulmonary wave reflections, examination of their results does show a trend favoring a decline in PA impedance oscillation (an indirect measure of wave reflection) with increasing doses of nitroprusside. Only five to eight nonconsecutive beats were averaged, and their timing with respect to respiration was not specified. The larger group of patients in the present report would be more likely to detect an effect on wave reflections. Our finding of a reduced reflection amplitude is corroborated by the finding of a dose-dependent lengthening of the reflection arrival time as well, as would be predicted from the decrease in pulmonary pressure and resistance. These findings parallel what has been found for the systemic circulation.\(^\text{3}\)

**Paradoxical Response to Low-Dose Nitroprusside**

No previous study has investigated the relation of pulsatile hydraulic properties to stroke volume during low-dose nitroprusside infusion. For the group as a whole, no change in any measured parameter was found. However, examination of the stroke volume data revealed that some patients actually experienced a decrease in stroke volume at the lowest dose. As detailed above and in Fig 3, this was associated closely with the change in first-harmonic impedance. The mechanism for this effect probably relates to alterations in wave reflections, which are responsible for the existence of impedance oscillations.\(^\text{21}\) We found that only the change in reflection factor correlated with the change in \(Z_1\). Therefore, changes in pulmonary pulsatile properties appear to account for the paradoxical response seen in some patients at low doses of nitroprusside. At higher doses, all patients experienced improvement in forward flow, since initial increases in \(Z_1\); seen in some patients were reversed. At these doses, changes in parameters at all frequencies (mean term: resistance; low frequencies: \(Z_1\), reflection factor, and backward wave arrival time; high frequencies: \(Z_2\)) occurred in favorable directions, and all therefore contributed to improved stroke output.

Although altered wave reflections can explain the reduction in \(Z_1\) that occurred during pulmonary vasodilation, there is another possible mechanism. Experimental studies have shown that decreased compliance in the aorta causes increased low-frequency impedance.\(^\text{22}\) Assuming that the same relation would apply in the PA, it is possible that reduction in mean PA pressure during nitroprusside administration led to increased compliance, hence decreased \(Z_1\). In the total group of 15 patients, both mean PA pressure and \(Z_1\) were unchanged at the lowest drug dose, and both decreased significantly at the second dose, in accord with this mechanism. However, as discussed above, there was no correlation between change in either stroke volume or \(Z_1\) and change in mean PA pressure at the lowest dose of nitroprusside. Therefore, although PA compliance changes may play a role in altered \(Z_1\) at higher doses, at the lowest dose, change in wave reflections appears to be the most likely explanation for decreased \(Z_1\).

Our findings show that in patients with congestive heart failure, very low doses of nitroprusside may induce a paradoxical response with a small decrease in stroke volume. However, at doses \(>25\) \(\mu g/min\), the response is uniformly favorable because of reductions in all components of impedance: resistance, low-frequency impedance, characteristic impedance, and wave reflections.
Limitations

A brief discussion of the technical limitations of this study is appropriate. Calculation of impedance from Fourier harmonics of pressure and flow assumes that the vascular system behaves in an approximately linear fashion, at least within physiological ranges of these variables. The errors introduced by potential nonlinear behavior have been analyzed and appear to be small.\textsuperscript{16,23,24} Determination of flow velocity by a catheter-mounted transducer assumes a relatively blunt velocity profile at the point of measurement. This assumption has been verified to a limited degree in the animal and human aorta and PA.\textsuperscript{25,26} Use in this study of a catheter inserted from the femoral vein and stabilized by a long sheath minimized catheter movement artifact.

Time-domain signal averaging can effectively attenuate the noise inherent in catheter flow velocity signals. This process also minimizes any effects of respiration by averaging across at least 25 beats. The noise levels of the pressure and flow measuring and recording systems used in this study have been determined, and harmonics of pressure and flow falling below these levels were not included in the analysis.

Calculation of pulmonary resistance using wedge pressure to estimate left atrial pressure may be subject to inaccuracy whenever alveolar or interstitial pulmonary pressures exceed left atrial pressure.\textsuperscript{27} This is unlikely to have occurred in the baseline state, when wedge pressure was elevated well above the normal range. At the higher nitroprusside doses, however, it is possible that this effect resulted in overestimation of pulmonary resistances. In this case, we might have failed to detect a significant decrease in resistance at dose 2.

Conclusions

The effects of nitroprusside vasodilation on pulmonary vascular properties in patients with chronic severe congestive heart failure are complex and vary depending on the dose given. At low doses, nitroprusside alters PA hemodynamics in congestive heart failure primarily through changes in low-frequency impedance. In some patients, this effect is associated with decreased stroke output. At higher doses, favorable alterations in resistance, low- and high-frequency impedance, and wave reflections all contribute to increased forward flow and decreased power requirement per unit forward flow. These findings show that ventricular-vascular interaction is importantly affected by pulmonary vasodilation and that appreciation of pulsatile properties is required to understand the effects of pulmonary vasodilation on cardiac output.

References

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