Effects of sodium nitroprusside in aortic stenosis associated with severe heart failure: pressure-volume loop analysis using a numerical model

Zoran B. Popović,1 Umesh N. Khot,2 Gian M. Novaro,1 Fernando Casas,1 Neil L. Greenberg,1 Mario J. Garcia,1 Gary S. Francis,1 and James D. Thomas1

1Department of Cardiovascular Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio; and 2Indiana Heart Physicians, Indianapolis, Indiana

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UNTIL RECENTLY, the use of vasodilators for aortic stenosis (AS) was strongly discouraged (4). The rationale behind this recommendation was the assumption that peripheral vasodilation in the presence of AS could lead to dissipation of energy by increasing the aortic valve gradient while minimally increasing stroke volume (SV), with the cost of hypotension and a decrease of coronary and renal perfusion pressure (4). However, we (12) have recently shown that short-term treatment with sodium nitroprusside (SNP) may be applicable to a subset of patients with severe AS and congestive heart failure with ventricular dysfunction. The patients with AS and left ventricular (LV) dysfunction improved while on this therapy, with cardiac index rising 56% and pulmonary capillary wedge pressure falling by 30%. However, the mechanisms for this improvement are quite unclear from a viewpoint of ventricular mechanics. SNP, an exogenous nitric oxide donor, has a well-documented direct arterial vasodilatory effect. Also, intracoronary infusion of SNP leads to a parallel downward shift of diastolic pressure-volume relationships (16, 18). Finally, although SNP has little direct effect on contractility, improvement of end-systolic pressure-volume relations may occur, e.g., by alleviation of ischemia (28). Direct assessment of parameters that determine ventricular contractility, or chamber compliance, in the clinical setting of decompensated heart failure is extremely difficult. However, our recently developed and validated numerical model of the cardiovascular system may give insight into possible mechanisms by evaluating the sensitivity of hemodynamic indexes to a change of relevant parameters and estimating the parameter change necessary to obtain output that corresponds to the observed hemodynamics (32).

The purpose of this study, therefore, was to 1) use a numerical model to identify ventricular or circulatory parameters that are responsible for improved hemodynamics by SNP and 2) determine the validity of our parameter selection by matching the pressure-volume data obtained by the numerical model with the data obtained from individual patients both before and during SNP infusion.

METHODS

AS Patient Population

We used previously published data from our original series of 25 patients that were obtained from a prospective study conducted at the Cleveland Clinic Foundation (12). The patients met the following inclusion criteria: admission to an intensive care unit for invasive hemodynamic monitoring of heart failure; ejection fraction ≤0.35; aortic valve area (AVA) ≤1 cm²; and cardiac index ≤2.2 l•min⁻¹•m⁻². The only criterion for exclusion was hypotension, defined as either the need for intravenous inotropic or pressor agents (dobutamine, dopamine, epinephrine, milrinone, norepinephrine, or phenylephrine) or a mean systemic arterial pressure <60 mmHg. Our institutional review board approved the study, and all the patients provided written informed consent to participate.

Invasive hemodynamic data were collected before and 24 h after the start of SNP infusion, including SV (by the Fick method), pulmonary capillary wedge pressure, right atrial pressure (by pulmonary artery balloon catheter), and systolic and diastolic systemic artery pressures (by arterial cannula) (12).
Individual Pressure-Volume Loop Reconstruction

Pressure-volume loops were reconstructed from the data obtained in five patients. Patient selection was based solely on the availability of complete good-quality digital echocardiographic studies performed both immediately before the beginning of SNP therapy and 24 h afterward, with the patients still undergoing continuous intravenous SNP treatment and hemodynamic monitoring. Similar to the overall study population, four of five patients had coronary artery disease, and three patients had been admitted with an acute coronary syndrome. Baseline and SNP hemodynamics of these patients did not differ from the data of the other 20 patients ($P = 0.002$ for all comparisons). The AVA was calculated by the continuity equation, whereas LV volumes were calculated by Simpson’s biplane method. Minimal LV volume was considered to be end systolic, whereas maximal LV volume was considered end diastolic.

End-diastolic volume and the volume at the beginning of ejection were considered equal. Similarly, end-systolic volume and the volume at the onset of filling were considered equal. To reconstruct the LV volume curve during ejection, we digitized the pulsed-wave Doppler signal of the LV outflow tract at a 5-ms resolution (Digitize, Yaron Danon) and calibrated it using echocardiographic LV SV. In this manner, we obtained the instantaneous volume change during systole.

To eliminate the variability due to different patient’s size, volumes were standardized to a body surface area of 1.7 m$^2$.

To reconstruct the LV pressure curve, we used the assumption that instantaneous LV pressure during systole may be derived if both instantaneous aortoventricular pressure gradients and aortic pressures are known. For this purpose, we first digitized the aortic valve CW Doppler signal in a 5-ms resolution and used it to calculate the instantaneous aortic valve gradient during systole by the simplified Bernoulli equation. The accuracy of instantaneous aortoventricular pressure gradients obtained in this manner has been reported to be within 1 mmHg (25). To reconstruct instantaneous aortic pressures during ejection, we assumed that, although the frequency domain of the aortic pressure tracings contain a multitude of harmonics (2), most of its power is contained in initial frequency. For this reason, we approximated the aortic pressure tracing with a simple sinusoidal function (Eq. 1) with the frequency $\omega$, amplitude that is equal to pulse pressure, and zero phase shift:

$$\text{AoP}(t) = \text{ArtP}_{\text{dia}} + \text{PP} \times \sin(\pi/4 \times \omega \times t_e)$$

where AoP is aortic pressure, ArtP$_{\text{dia}}$ and PP are diastolic arterial pressure and pulse pressure obtained invasively by radial artery cannulation, $\omega$ is an experimentally derived frequency constant, and $t_e$ is the time from the beginning of ejection normalized by LV ejection time. To obtain $\omega$ and to take into account that the aortic pressure waveform may be influenced by the presence of heart failure (15), we used data from a previous investigation of tachycardia-induced cardiomyopathy dogs (31). Aortic pressure tracings obtained during the ejection period were fitted to Eq. 1 to determine parameter $\omega$. The average value of parameter $\omega$ was $3.23 \pm 0.17$. When that value was used to estimate aortic pressure during ejection in our studies, the correlation between estimated and observed pressures was $0.98 \pm 0.02$, whereas the average absolute difference between estimated and observed pressures was $1.1 \pm 0.3$ mmHg. Finally, diastolic pressures were considered constant and equal to mean pulmonary capillary wedge pressure (13, 20).

Numerical Model Description

Our closed-loop, lumped parameter model has been described in previously (32). Briefly, it consists of 24 coupled differential equations relating flow throughout the circulation conceptualized as eight different chambers: the right atrium and ventricle, pulmonary arteries and veins, left atrium and ventricle, aorta, and systemic veins. For both the left and right ventricle, the systolic pressure-volume relation is linear [determined by the slope [end-systolic elastance ($E_{\text{syst}}$)] and x-axis intercept [volume axis intercept at zero pressure ($V_0$)]]. The diastolic pressure-volume relation is sigmoidal (17). The upper and lower parts of the sigmoid are, respectively, determined by the following equations:

$$P = A \times e^{(V - V_0)/(K_p^+)}$$

$$P = B \times e^{-V/(K_p^-)}$$

where $V_0$ is the inflection point, $A$ and $B$ are the exponential curve multipliers of the upper and lower part, $P_0^+$ and $P_0^-$ are pressure offsets of the upper and lower part, and $K_p^+$ and $K_p^-$ determine the curvatures of the curve.

The systemic circulation is composed of the aortic valve (represented by area, inertia, and resistance), aorta (represented by capacitance), and arterial (represented by resistance and inertia) and venous system (represented by resistance, capacitance, and inertia). The right ventricle and pulmonary circulation are composed in an analogous manner (1, 13, 32). A total of 96 parameters may be varied independently in the model. Time steps of 5 ms were used in all modeling exercises.

Simulation of Baseline Hemodynamics: Model Parameter Selection

Our aim was to select initial parameters such that the predicted model output resulted in hemodynamics of severe AS associated with poor LV systolic performance, as observed in our original series. To accomplish this, the average heart rate, systemic vascular resistance (SVR), pulmonary vascular resistance, and AVA of the original series were directly entered into the model. To model LV diastolic and systolic properties, we based our parameter selection on previously published data, as follows. The reported average $E_{\text{syst}}$ values (LV contractility parameter) ranged between 2.3 and 4.05 mmHg/ml in normal subjects (5, 19, 26, 27) and between 0.52 and 0.62 mmHg/ml in symptomatic dilated cardiomyopathy patients (10, 19). Although $E_{\text{syst}}$ is not affected by AS per se (9), our patients had depressed contractility, so we selected an $E_{\text{syst}}$ value of 1 mmHg/ml, a lower limit of a normal 95% confidence interval (CI) (26). Because our patients had dilated ventricles, the diastolic pressure-volume relationship followed only the upper part of the sigmoid. Of the four parameters that determine the sigmoid’s shape, physiologically, $K_p^+$, the chamber stiffness index, is the most important. The reported average values of $K_p^+$ for normal subjects are 0.021 and 0.031 mmHg/ml (6, 33), whereas it is 0.023 mmHg/ml in AS subjects, which is the value that we selected (33).

An iterative technique was used to tune additional model parameters to obtain the model output that optimally approximates average values of (7): 1) SV and LV filling pressures (obtained by Swan-Ganz catheter), 2) systolic and diastolic blood pressures (by arterial cannula), and 3) LV ejection fraction and aortic peak and mean gradients (by echocardiography).

This resulted in following values for these model parameters: 1) pressure offset of the diastolic pressure-volume relationship $P_0^- = 0$ mmHg, 2) total circulatory volume of 5,000 ml, and 3) $V_0$ of 9 ml [reported normal average values of 6 and $-15$ ml (5, 27)]. The observed and model-predicted hemodynamic data are presented in Table 1.

Simulation of SNP Treatment Hemodynamics

We sought to simulate the SNP effects by reducing the SVR and heart rate to values observed after 24 h of SNP infusion in our series of patients (Table 1). We then explored whether varying $E_{\text{syst}}$, $V_0$, and $P_0^+$ improves the concordance between observed and simulated hemodynamics. To achieve this, we performed parameter sensitivity and model residual analysis.

Sensitivity analysis. Local parameter sensitivity was evaluated by calculating the Jacobian matrix ($\delta P/\delta x$), defined as the change of the model’s individual hemodynamic index output ($y_i$) to an (small)
allowing for matched comparisons. Parameters were varied within a fixed to their initial values. Each time a parameter was changed, the usually randomly changed, whereas the other two parameters were kept of the end-systolic pressure-volume relationship (V₀) have opposite effects on model hemodynamics. Also, a diastolic pressure-volume relationship shift (Pb
\(_\text{es}\)) with parameter values used for simulation of AS with LV dysfunction
\([\text{Eq. } 4]\) after increasing 
\(E_\text{es}\) to the normal value of 3.5 mmHg/ml. Table
\([\text{Eq. } 4]\) Using numerical optimization methods (Mathematica 5.0, Wolfram Res.), we searched for the minima, or minimum local values, of the parameters in \([\text{Eq. } 4]\) with the constraints of \(E_\text{es}>1\), \(V_0<9\) mmHg, and \(P_b^*<0.15\) mmHg.

Estimation of uncertainty in predicting the model parameters. Prediction of model parameters depends on the CI of the Err for its value of 0, which in turns depends on the accuracy of the measurement of hemodynamic indexes. To obtain 95% CI for Err, we performed uncertainty analysis based on Monte Carlo simulations. For each iteration of the simulation, we generated three independent random numbers (range −1 to 1, normal distribution), corresponding to three hemodynamic indexes that were used to calculate Err. Each triplet of simulated hemodynamic values was calculated by adding the mean (reported in Table 1) to the product of the SE and the corre-
responding random number. Finally, Err was calculated as described.

Iterations were repeated 1,000 times, and 95% CI for Err was then calculated. On the basis of this interval, a 95% CI was sought for the parameters of \(E_\text{es}, V_0,\) and \(P_b^*\), corresponding to a minimum local value of Err, if applicable. For example, if \(E_\text{es}=1.33\) resulted in a minimal value of \(Err=0.01\) with a 95% CI of 0.005, we then sought the \(E_\text{es}\) values that corresponded to \(Err=0.015\).

Individual Pressure-Volume Simulation

Initial parameter selection. It was necessary to modify the initial AS parameters to obtain individualized model parameters that would correspond to each patient’s own pressure-volume loop at baseline. To obtain initial parameters, we first entered the patient’s SVR, AVA, and heart rate directly into the model. We then adjusted diastolic pressure-volume parameters, \(E_\text{es}, V_0,\) and \(P_b^*\) so that critical pressures and volumes (end-diastolic and end-systolic volume, peak systolic and end-diastolic pressure) of the model were within ±5% of the observed values.

Table 1. Comparison of observed and simulated hemodynamics in decompensated AS before and during SNP infusion

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>SNP Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Simulated</td>
</tr>
<tr>
<td></td>
<td>Observed</td>
<td>Simulated</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>91±9</td>
<td>91</td>
</tr>
<tr>
<td>AVA, cm²</td>
<td>0.58±0.04</td>
<td>0.58</td>
</tr>
<tr>
<td>SVR, dyn⋅cm⁻³</td>
<td>1.926±118</td>
<td>1.926</td>
</tr>
<tr>
<td>EF, %</td>
<td>21±2</td>
<td>21</td>
</tr>
<tr>
<td>SV, ml</td>
<td>33±2</td>
<td>35</td>
</tr>
<tr>
<td>Peak AVG, mmHg</td>
<td>64±8</td>
<td>55</td>
</tr>
<tr>
<td>Mean AVG, mmHg</td>
<td>38±4</td>
<td>35</td>
</tr>
<tr>
<td>Mean ArtP, mmHg</td>
<td>82±3</td>
<td>88</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>27±2</td>
<td>31</td>
</tr>
<tr>
<td>RAP, mmHg</td>
<td>15±2</td>
<td>11</td>
</tr>
</tbody>
</table>

Values are means ± SE. Hemodynamics of sodium nitroprusside (SNP) infusion were simulated by a simple systemic vascular resistance decrease. Note the discrepancy between observed and simulated hemodynamics during SNP infusion. AS, aortic stenosis; HR, heart rate; AVA, aortic valve area; SVR, systemic vascular resistance; EF, ejection fraction; SV, stroke volume; AVG, aortic valve gradient; ArtP, arterial pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure. *Obtained in a subgroup of patients (n = 5); †P < 0.001 for the comparison with observed data.

Table 2. Jacobian matrix of the model sensitivity to parameter variation in the setting of AS combined with normal or depressed contractility

<table>
<thead>
<tr>
<th></th>
<th>EDP</th>
<th>SV</th>
<th>ArtP</th>
<th>EDV</th>
<th>ESV</th>
<th>EF</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS with normal contractility (E₀ = 3.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(E_\text{es})</td>
<td>-0.95</td>
<td>2.81</td>
<td>3.23</td>
<td>-4.19</td>
<td>-7.01</td>
<td>4.23</td>
</tr>
<tr>
<td>(V_0)</td>
<td>0.15</td>
<td>-0.41</td>
<td>-0.51</td>
<td>0.48</td>
<td>0.89</td>
<td>-0.56</td>
</tr>
<tr>
<td>(P_b^*)</td>
<td>0.61</td>
<td>-0.97</td>
<td>-1.30</td>
<td>-1.11</td>
<td>-0.14</td>
<td>-0.23</td>
</tr>
<tr>
<td>AS with depressed contractility (E₀ = 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(E_\text{es})</td>
<td>-18.35</td>
<td>18.04</td>
<td>42.70</td>
<td>-28.81</td>
<td>-46.86</td>
<td>14.95</td>
</tr>
<tr>
<td>(V_0)</td>
<td>0.14</td>
<td>-0.14</td>
<td>-0.33</td>
<td>0.22</td>
<td>0.36</td>
<td>-0.11</td>
</tr>
<tr>
<td>(P_b^*)</td>
<td>0.30</td>
<td>-0.15</td>
<td>-0.36</td>
<td>-0.90</td>
<td>-0.75</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values represent the amount of change of the hemodynamic variable for an index change in parameter. For example, in AS with normal contractility, an end-systolic elastance (\(E_\text{es}\)) increase of 1 would lead to an end-diastolic pressure (EDP) decrease of 1.9 mmHg. As expected, \(E_\text{es}\) and the volume axis intercept of the end-systolic pressure-volume relationship (\(V_0\)) have opposite effects on model hemodynamics. Also, a diastolic pressure-volume relationship shift (\(P_b^*\)) increase increases EDP but decreases ventricular volumes. \(E_\text{es}\) influences model hemodynamics more if the contractility is decreased. EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; SV, stroke volume.
Pressure, and pulmonary capillary wedge pressure. For patient 5, we could not initially obtain a satisfactory Err decrease. Because the reconstructed pressure-volume loops suggested preload reduction (possible diuretic effect), we performed simulations after decreasing circulatory volume in 100-ml decrements. After circulatory volume was decreased by 300 ml, we obtained a satisfactory Err decrease. Finally, we conducted model residual analysis by constructing an Err versus model parameter function and solved it analytically for the local minima. The parameter values corresponding to the local minima were used to simulate the pressure-volume loop during SNP infusion.

**Statistical Methods**

Data are presented as means ± SE unless otherwise indicated. Observed data were compared with simulation data by single-sample t-test. Paired data were compared by a nonparametric Wilcoxon paired test. Simple linear regression was used to evaluate correlation between two parameters. P values <0.05 were deemed significant.

**RESULTS**

Effects on a pressure-volume loop of an isolated decrease of SVR to the same level as observed after 24 h of SNP infusion are presented in Table 1 and Fig. 2A. A simple decrease in SVR in the model increased SV by only 17% compared with the observed median SV increase of 52% (P = 0.001) (12). Also, mean aortic pressure in the model decreased by 29 mmHg compared with the median decrease of 12 mmHg in our original patient series (P = 0.001). Thus isolated arteriolar vasodilation in decompensated AS would induce severe hypotension with only a small SV increase and is not a dominant mechanism that explains the observed effects of SNP infusion.

The r value of the function relating Err to model parameters was r = 0.981, with all function parameters showing a P value of t-statistics of more than P < 0.0001. Table 3 shows that standardized β-coefficients of Err function were highest for V_0, V_0 × Ees interaction, and the squared value of Ees, signifying dominant effects of systolic parameters on Err function. The Err parameter function is presented in Fig. 1, A–C. Because the function is four dimensional, we represent it in by plotting Err against three pairs of parameter data. The local steepness of the surface indicates how much a change of parameters may improve model output, whereas the “valley” (local minimum value) indicates the optimal parameter combination. As can be seen, Err was mostly influenced by the combination of Ees and V_0 and least influenced by the combination of Ees and P_e.

**Model residual analysis of individual simulations of SNP effects.**

For each of the individual pressure-volume simulations, we did the following. We first entered the values of SVR and heart rate observed during SNP treatment. We then ran random simulations as described in *Model residual analysis.* However, the loss function Err was calculated using four (instead of three) hemodynamic parameters: end-diastolic volume, end-systolic volume, maximum LV systolic pressure, and pulmonary capillary wedge pressure. For patient 5, we could not initially obtain a satisfactory Err decrease. Because the reconstructed pressure-volume loops suggested preload reduction (possible diuretic effect), we performed simulations after decreasing circulatory volume in 100-ml decrements. After circulatory volume was decreased by 300 ml, we obtained a satisfactory Err decrease. Finally, we conducted model residual analysis by constructing an Err versus model parameter function and solved it analytically for the local minima. The parameter values corresponding to the local minima were used to simulate the pressure-volume loop during SNP infusion.

**Individual Patient Data**

Data of patients in whom echocardiography was performed both before and during SNP infusion are presented in Table 4,
whereas Fig. 3, left, shows reconstructed individual pressure-volume loops obtained before and after 24 h of SNP infusion. After SNP infusion, the peak and mean aortic valve gradient increased ($P < 0.045$ for both), whereas end-systolic volume decreased ($P < 0.045$). LV stroke work obtained by integration of reconstructed pressure-volume loops increased in all five patients ($P < 0.045$). There was no consistent trend in the change in end-diastolic volume after SNP infusion. Finally, no changes were noted in AVA.

In all patients, we analytically obtained the minima of the function of $\text{Err}$ versus parameter that satisfied the conditions of $E_{es}$ increase or no significant change and $V_0$ and $P_b$ decrease or no significant change. $E_{es}$ had to increase by an average of 32% in all subjects ($P < 0.045$) to obtain a realistic LV model, implying that a change of end-systolic pressure-volume properties occurred repeatedly and in the same direction (Table 4). $P_b$ decreased in four of five patients, implying that an improvement of LV diastolic function occurred in most patients. Finally, $V_0$ remained essentially unchanged. The apparent discrepancy between global and individual data stems from a different method of $\text{Err}$ calculation in individual data analysis. However, in both analyses, there was a dominance of systolic versus diastolic effects.

Figure 3, right, shows the pressure-volume loops derived from individual AS model applications, with the effects of SNP modeled using the parameters corresponding to the minima of the Err versus parameter function. There was an excellent correlation between observed and modeled LV stroke work ($r = 0.97$, $P < 0.0001$). However, modeled LV stroke work overestimated observed LV stroke work by $0.14 \pm 0.08 \text{J} (P = 0.001)$. This discrepancy was due to the assumption of flat diastolic pressure-volume relationships in observed pressure-volume loops.

DISCUSSION

In this study, we found that the observed beneficial effects of SNP (that is, increase of SV) in severe AS associated with heart failure and LV dysfunction cannot be attributed solely to the decrease of arterial resistance. Our data support the notion that SNP infusion results in improved systolic and diastolic performance and/or reduced myocardial ischemia in decompensated AS patients. Finally, this improvement was associated with an increase of the transaortic valve gradient in both model and observed data (34).
The results of our simulations suggest that to obtain observed improvement after 24 h of SNP infusion in patients with AS and systolic dysfunction, end-systolic pressure-volume relationships have to shift to the left and upward. This may result from 1) an increase in $E_{es}$, 2) a decrease in $V_0$, or 3) a combination of both factors. Our data cannot differentiate the exact mechanism of the improvement, because in these patients, with critically decompensated AS, we could not safely determine the change in the end-systolic pressure-volume relationship during preload reduction. Our modeling of individual pressure-volume loops suggests that the $E_{es}$ decrease more closely approximates the observed changes in pressure-volume loops. On the other hand, isolated $V_0$ changes, which may be induced by an increase of afterload or demand ischemia (21, 28), more closely mimicked global hemodynamics during SNP infusion. However, the $V_0$ decrease is often associated with an $E_{es}$ increase, and both changes act synergistically on LV systolic performance (7). Data obtained from our five modeled subjects also suggest that the specific hemodynamic effects of SNP may slightly vary among individuals.

### Possible Mechanisms of LV Performance Improvement During SNP Treatment

Effects of SNP on diastolic function have been well described. Intracoronary infusion of SNP leads to a downward shift of the diastolic pressure-volume relationship that is more pronounced in the setting of LV hypertrophy (16, 18). Matter et al. (16) have shown that intracoronary SNP infusion in AS patients with normal LV function leads to an end-diastolic pressure decrease of 10 mmHg. Also, SNP infusion may lead to an improved time constant of relaxation either through its direct effects (18) or indirectly through afterload reduction if LV dysfunction is present (24).

In contrast, little is known of the SNP effects on systolic function in the clinical setting. SNP acts as an exogenous nitric oxide donor and may have small positive inotropic properties (22) but not at the concentrations used in this study. Besides direct improvement of contractility, several possible mechanisms may have influenced the shift in the end-systolic pressure-volume relationship in patients with decompensated AS treated with SNP: ischemia relief, afterload decrease, preload...

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**Table 4.** Echocardiographic and model data from 5 patients in whom echocardiography was performed during maximal SNP infusion

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>SNP</td>
<td>Baseline</td>
<td>SNP</td>
<td>Baseline</td>
</tr>
<tr>
<td>EDV, ml</td>
<td>102</td>
<td>106</td>
<td>131</td>
<td>118</td>
</tr>
<tr>
<td>ESV, ml*</td>
<td>73</td>
<td>48</td>
<td>96</td>
<td>69</td>
</tr>
<tr>
<td>PG, mmHg*</td>
<td>68</td>
<td>101</td>
<td>117</td>
<td>197</td>
</tr>
<tr>
<td>MG, mmHg*</td>
<td>43</td>
<td>59</td>
<td>61</td>
<td>108</td>
</tr>
<tr>
<td>AVA, cm²</td>
<td>0.6</td>
<td>0.6</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>LVSW, J*</td>
<td>0.66</td>
<td>0.86</td>
<td>0.47</td>
<td>0.50</td>
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</table>

Model data

<table>
<thead>
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<th>$E_{es}$, mmHg/ml*</th>
<th>Patient 1</th>
<th>2.4</th>
<th>3.5</th>
<th>2.3</th>
<th>3.7</th>
<th>1.0</th>
<th>1.3</th>
<th>1.3</th>
<th>1.6</th>
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<td>$V_0$, ml</td>
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<td>14</td>
<td>20</td>
<td>13</td>
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<td>5</td>
<td>190</td>
<td>189</td>
<td>25</td>
<td>21</td>
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</tr>
<tr>
<td>$P_{es}$, mmHg</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.9</td>
<td>11.0</td>
<td>4.8</td>
<td>0.0</td>
<td>0.0</td>
<td>-4.0</td>
<td>13.0</td>
<td>24.4</td>
</tr>
<tr>
<td>LVSW, J*</td>
<td>0.72</td>
<td>0.88</td>
<td>0.60</td>
<td>0.68</td>
<td>0.48</td>
<td>1.8</td>
<td>0.65</td>
<td>1.32</td>
<td>0.98</td>
<td>1.51</td>
<td></td>
</tr>
</tbody>
</table>

MG, mean aortic gradient; PG, peak aortic gradient; LVSW, left ventricular stroke work. *$P = 0.045$ vs. baseline values.

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**Fig. 3.** Observed individual pressure-volume loops (left) compared with model-derived individual pressure-volume loops (right). Patients 1–5 are shown. The x-axis represents LV volume (in ml), whereas the y-axis represents LV pressure (in mmHg). Thin and thick lines represent data at baseline and during sodium nitroprusside treatment, respectively.
decrease, and the change of viscoelastic myocardial properties. Improvement through ischemia is more plausible mechanism, as Steendijk et al. (28) showed that demand ischemia in an animal model of coronary AS leads to an increase of $V_0$ from 0.5 to 5 ml (the average SV in this study was 7 ml). Of note, most of our patients had coronary artery disease. Moreover, even if epicardial coronary arteries are normal, subendocardial ischemia may be present in some patients because of inordinately high systolic and diastolic wall stress in decompensated AS (11). In our series, there were no differences in hemodynamic response between patients with coronary artery disease compared with other patients (12).

It is known that an abrupt increase in afterload leads to a leftward shift of the end-systolic pressure-volume relationship decrease in normal hearts; this shift is absent even in the very early stages of heart failure development (21) and may be reversed in later stages. SNP may act through this mechanism by decreasing peripheral vascular resistance. It is also possible that elimination of volume overload improved LV function. It has been shown that in patients with decompensated heart failure, a preload decrease improves LV stroke work (29).

Similarly, our AS patients showed a decrease of LV filling pressures with improved stroke work during SNP treatment. Finally, an additional mechanism may be the impact of SNP treatment on a viscous component of myocardial properties (23). A prolonged increase of ventricular volume may lead to a shift of pressure-volume relationships (14) and decreased LV contractility (8) acting through either viscoelastic material properties or by induction of creep (30). It should be emphasized that the beneficial effects of SNP analyzed in this study were documented after 24 h of continuous SNP infusion. The exact onset and time course of hemodynamic improvement cannot be determined from this study.

Limitations

There are several important methodological limitations of this study. First, in only the small fraction of subjects, adequate echocardiography data were obtained both before and after 24 h of SNP infusion. Second, LV pressures and volumes were not measured simultaneously. However, invasive hemodynamic and echocardiographic data were collected within <5 min. Third, instantaneous LV pressure tracings were obtained by summing aortic valve gradients with aortic pressure tracings that were reconstructed using equations validated by animal data. Assumptions underlying this procedure could lead to erroneous pressure curve estimates. Fourth, $V_0$ is a parameter extrapolated from a statistical procedure, and its physiological equivalent is not well understood. Finally, pressure-volume data were not acquired during acute changes in load that would enable direct assessment of $E_{es}$ and $V_0$. Thus our findings suggest, but do not prove, that changes in $E_{es}$ and $V_0$ occur during SNP treatment in this setting. However, our subjects were severely ill patients admitted to the critical care unit. Any change of hemodynamic milieu not driven by a specific therapeutic goal (such as improving cardiac output) could violate ethical research guidelines in such a population.

The study group was heterogeneous, with a varying severity of coronary artery disease. It is well recognized that AS is frequently associated with coronary artery disease (3). Our data do not allow us, therefore, to discriminate whether the observed effects are due to alleviation of myocardial ischemia or a direct improvement in LV contractility.

In conclusion, using a numerical model, we identified ventricular function parameters responsible for improved hemodynamics during SNP infusion in decompensated AS. We demonstrated that the hemodynamic improvement seen with SNP infusion in this setting is not due to a simple afterload decrease but to improved ventricular performance. Although the improvement is due to both systolic and diastolic effects of SNP, systolic effects dominate, probably through a combination of factors, such as improved myocardial oxygen supply/demand and afterload decrease.

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