Effects of Sodium Nitroprusside in Aortic Stenosis Associated with Severe Heart Failure:
Pressure-Volume Loop Analysis Using A Numerical Model


Running head: Nitroprusside and Aortic Stenosis

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Abstract

In the recently published clinical study (UNLOAD), sodium nitroprusside (NTP) improved cardiac function in patients with severe aortic stenosis (AS) and left ventricular (LV) systolic dysfunction. We explored possible mechanisms of these findings using a series of numerical simulations. A closed-loop lumped parameters model that consists of 24 differential equations relating pressure and flow throughout the circulation was used to analyze the effects of varying hemodynamic conditions in AS. Hemodynamic data from UNLOAD study subjects were used to construct the initial simulation. Systemic vascular resistance, heart rate and aortic valve area were directly entered into the model while end-systolic and diastolic pressure-volume (PV) relationships were adjusted using previously published data to match modeled and observed end-systolic and end-diastolic pressures and volumes. Initial simulation of NTP treatment by reduction of SVR was not adequate. In order to obtain realistic model hemodynamics that reliably reproduce NTP treatment effects, we performed a series of simulations while simultaneously changing end-systolic elastance (Ees), end-systolic volume at zero pressure (V0), and diastolic pressure volume shift. Our data indicate that either Ees increase or V0 decrease is necessary to obtain realistic model hemodynamics. In 5 patients, we corroborated our findings by using the model to duplicate individual PV loops obtained before and during NTP treatment. In conclusion, using a numerical model, we identified ventricular function parameters that are responsible of improved hemodynamics during NTP infusion in AS with LV dysfunction.

Key words: heart failure, ventricular mechanics, aortic stenosis, sodium nitroprusside
**Introduction**

Until recently, 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 aortic stenosis could lead to dissipation of energy by increasing the aortic valve gradient while minimally increasing stroke volume, with the cost of hypotension and a decrease of coronary and renal perfusion pressure (4). However, we have recently shown (12) that short-term treatment with sodium nitroprusside (NTP) may be applicable to a subset of patients with severe AS and congestive heart failure with ventricular dysfunction. The patients with AS and 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. Sodium nitroprusside, an exogenous NO donor, has a well-documented direct arterial vasodilatory effect. Also intracoronary infusion of NTP leads to a parallel downward shift of diastolic pressure-volume relationships.(16, 18) Finally, although NTP 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 sensitivity of hemodynamic indices to change of relevant parameters and estimate 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 of improved hemodynamics by NTP, and (2) determine the validity of our parameter selection by matching the pressure-volume data obtained by numerical model with the data obtained from individual patients both pre- and during NTP 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 $\leq 0.35$; aortic-valve area (AVA) $\leq 1$ cm$^2$; and a cardiac index $\leq 2.2$ L/min/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 $<60$ mm Hg. 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 hours after the start of NTP infusion, including stroke volume (by Fick method), pulmonary capillary wedge and right atrial pressures (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 5 patients. Patient selection was based solely on the availability of complete good quality digital echocardiographic studies performed both immediately prior to the beginning NTP therapy and 24 hours afterwards, with the patients still undergoing continuous intravenous NTP treatment and hemodynamic monitoring. Similar to the overall study population, 4/5 patients had coronary artery disease, and 3 had been admitted with an acute coronary syndrome. Baseline and NTP hemodynamics of these patients did not differ from the data of the other 20 patients (p = NS for all comparisons). The AVA was calculated by the continuity equation, while LV volumes were calculated by Simpson’s biplane method. Minimal LV volume was considered to be end-systolic while 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 PW Doppler signal of the LV outflow tract at a 5 ms resolution (Digitize, Yaron Danon Inc, Israel) and calibrated it using echocardiographic LV stroke volume. 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 the body surface area of 1.7 m². To reconstruct the LV pressure curve, we used the assumption that instantaneous LV pressure during systole may be derived if both instantaneous aorto-ventricular 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 instantaneous aortic valve gradient during systole by the simplified Bernoulli equation. The accuracy of instantaneous aorto-ventricular
pressure gradients obtained in this manner has been reported within 1 mmHg (25). To reconstruct instantaneous aortic pressures during ejection, we assumed that, while the frequency domain of the aortic pressure tracings contains 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 (Equation 1) with the frequency $\omega$, amplitude that is equal to pulse pressure and a zero phase shift:

$$AoP(t) = ArtP_{dia} + PP \times sin(\pi / 4 \times \omega \times t_n)$$

(1)

where $ArtP_{dia}$ and $PP$ are diastolic arterial pressure and pulse pressure obtained invasively by radial artery cannulation, $\omega$ is an experimentally derived frequency constant, and $t_n$ 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 ejection period were fitted into the equation (1) to determine parameter $\omega$. The average value of the parameter $\omega$ was 3.23 ± 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 ± 0.02, while the average absolute difference between estimated and observed pressures was 1.1 ± 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 8 different chambers: the right atrium and ventricle, pulmonary arteries and
veins, left atrium and ventricle, aorta, and systemic veins. For both left and right ventricle, the systolic pressure-volume relation is linear (determined by the slope $E_{es}$ and x axis intercept $V_0$). The diastolic pressure-volume relation is sigmoidal, (17). The upper and lower parts of the sigmoid are respectively determined by the equations (2):

$$
P = A \cdot e^{(V - V_{d0})K_{p}^+} + P_{b}^+ \quad V \geq V_{d0}$$

$$
P = P_{b}^- - B \cdot e^{(V_{d0} - V)K_{p}^-} \quad V \leq V_{d0}$$

where $V_{d0}$ is the inflection point, $A$ and $B$ are the exponential curve multipliers of the upper and lower part, $P_{b}^+$ and $P_{b}^-$ are pressure offsets of the upper and lower part, while $K_{p}^+$ and $K_{p}^-$ determine the curvatures of the curve.

The systemic circulation is composed of the aortic valve (represented by area, inertance, and resistance), aorta (represented by capacitance), and arterial (represented by resistance and inertance) and venous system (represented by resistance, capacitance, and inertance). The right ventricle and pulmonary circulation are composed in 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 $E_{es}$ 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 0.6 mmHg/ml in symptomatic dilated cardiomyopathy patients (10, 19). While $E_{es}$ is not affected by AS *per se*, (9) our patients had depressed contractility, so we selected $E_{es}$ value of 1 mmHg/ml, a lower limit of a normal 95% confidence interval (26). Since our patients had dilated ventricles, the diastolic pressure-volume relationship followed only the upper part of the sigmoid. Of the 4 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 l/ml (6, 33), while it is 0.023 l/ml in AS subjects, which is the value 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): a) stroke volume and LV filling pressures (obtained by Swan-Ganz catheter), b) systolic and diastolic blood pressures (by arterial cannula), and c) LV ejection fraction and aortic peak and mean gradients (by echocardiography).

This resulted in following values for these model parameters: a) pressure offset of the diastolic pressure-volume relationship $P_{b^+} = 0$ mmHg, b) total circulatory volume of 5000 ml, and c) x-axis intercept of end-systolic pressure volume relationships of 9 ml (reported normal average values 6 and –15 ml (5, 27)). The observed and model-predicted hemodynamic data are presented in Table 1.

**Simulation of NTP treatment hemodynamics**

We sought to simulate the NTP effects by reducing the SVR and heart rate to values observed after 24hr of NTP infusion in our series of patients (Table 1). Then we explored if varying $E_{es}$,
V₀, and Pᵇ⁺ may improve the concordance between observed and simulated hemodynamics. To achieve this we performed parameter sensitivity and model residuals analysis.

**Sensitivity analysis.** Local parameter sensitivity was evaluated by calculating the Jacobian matrix (\( \partial y_i / \partial x_j \)), defined as the change of the model’s individual hemodynamic index output (\( y_i \)) to an (small) individual simulation parameter change (\( x_j \)). In order to determine the impact of parameter changes on hemodynamics of model output, we performed 300 simulation runs with either \( E_{es} \), \( V₀ \), or \( Pᵇ⁺ \) being individually randomly changed, while the other two parameters were kept fixed to their initial values. Each time a parameter was changed, the random number generator was reinitialized with the same seed, thus allowing for matched comparisons. Parameters were varied within a ±5% interval for \( E_{es} \) and \( V₀ \), and by ±1 mmHg for \( Pᵇ⁺ \). We assessed local parameter sensitivity with two sets of initial parameter sets: a) with parameter values used for simulation of AS with LV dysfunction, and b) after increasing \( E_{es} \) to the normal value of 3.5 mmHg/ml. Table 2 summarizes these findings.

**Model residuals analysis.** To further optimize and tune the model’s predictive capabilities we performed a model residuals analysis. The objective was to assess how a discrete parameter combination affected the model’s hemodynamics when compared to the observed values. For this purpose we ran 2100 simulations, while randomly and simultaneously varying \( E_{es} \) (range 0.95 - 2 mmHg/ml), \( V₀ \) (range -50 to 10 ml) and shift of \( Pᵇ⁺ \) (range - 20 to 1 mmHg). The discrete parameter combination influence on resulting hemodynamics was quantified by a loss function based on the least squares criterion. The loss function \( Err \) represents the sum of the standardized squared residuals of the differences between observed and model-derived hemodynamic indices (3):

\[
Err = \sum \left[ \frac{(I_m - I_o)}{I_o} \right]^2
\] (3)
Where \( I \) is the individual hemodynamic index to be assessed (i.e. stroke volume, mean arterial pressure, and pulmonary capillary pressure) while sub indices \( o \) and \( m \) indicate observed and model-derived values. The discrete parameter combination(s) with corresponding \( Err = 0 \) represent ideal parameter set. To find these optimal model parameter values that would result in the calculated \( Err \) that is equal to zero, we modeled \( Err \) as a dependent variable of \( E_{es}, V_0, \) and \( P_b^+ \) and fitted that to a second–order polynomial function of the form as presented in Equation 4, using standard multiple regression procedure:

\[
Err = a + b \cdot E_{es} + c \cdot E_{es}^2 + d \cdot V_0 + e \cdot V_0^2 + f \cdot E_{es} \cdot V_0 + g \cdot P_b^+ + h \cdot P_b^{+2} + i \cdot E_{es} \cdot V_0 \cdot P_b^+ \quad (4)
\]

Using numerical optimization methods (Mathematica 5.0, Wolfram Res) we searched for the minima, or minimum local values of the parameters in equation [4] with the constraints of \( E_{es} > 1, V_0 < 9 \text{ mmHg}, \) and \( P_b^+ < 0 \text{ mmHg} \).

**Estimation of uncertainty in predicting the model parameters.** Prediction of model parameters depends on the confidence interval (CI) of the \( Err \) for its value of 0, which in turns depends on the accuracy of the measurement of hemodynamic indices. 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 indices 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 standard error of the mean and the corresponding random number. Finally, \( Err \) was calculated as described.
Iterations were repeated 1000 times, and 95% CI for $Err$ was then calculated. Based on this interval, 95% CI were sought for parameters of $E_{es}$, $V_0$, and $P_b^+$, corresponding to minimum local value of $Err$, if applicable. For example, if $E_{es} = 1.33$ resulted in minimal value of $Err = 0.01$ with 95% CI of 0.005, we then sought the $E_{es}$ values which 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. Then, we adjusted diastolic pressure-volume parameters, $E_{es}$, and $V_0$ 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.

**Model residual analysis of individual simulations of NTP 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 NTP treatment. Then, we ran random simulations as described in “Model residuals analysis” paragraph. 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 satisfactory $Err$ decrease. As the reconstructed pressure volume loops suggested preload reduction (possible diuretic effect), we performed simulations after decreasing circulatory volume in 100 ml decrements. After decreasing circulatory volume by 300 ml we obtained a satisfactory $Err$ decrease. Finally, we conducted model residuals analysis by constructing $Err$ vs. model parameters function, and solved it analytically for the local minima. The parameter values
corresponding to the local minima were used to simulate pressure-volume loop during NTP infusion.

**Statistical Methods**

Data are presented as average ± SEM, unless otherwise indicated. Observed data were compared to simulation data by single-sample t-test. Paired data were compared by nonparametric Wilcoxon paired test. Simple linear regression was used to evaluate correlation between two parameters. p values less than 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 hours of NTP infusion are presented in Table 1 and Figure 2A. A simple decrease in SVR in the model increased stroke volume by only 17%, as compared to the observed median stroke volume increase of 52% (P = 0.001) (12). Also, mean aortic pressure in a model decreased by 29 mmHg, as compared to median decrease of 12 mmHg in our original patients’ series (p = 0.001). Thus, isolated arteriolar vasodilation in decompensated AS would induce severe hypotension with only a small stroke volume increase and is not a dominant mechanism that explains the observed effects of NTP 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 beta coefficients of $Err$ function were highest for $V_0$, $V_0^*E_{es}$ interaction and squared value of $E_{es}$, signifying dominant effects of systolic parameters on $Err$ function. The
Err-parameter function is presented in Figure 1A to C. As the function is four dimensional, we represent it in by plotting Err against 3 pairs of parameter data. The local steepness of the surface indicates how much a change of parameters may improve model output, while the “valley” (local minimum value), would indicate optimal parameter combination. As can be seen, Err was mostly determined by the values of Ees and V0, whose combination clearly showed a distinct and consistent association. To optimize Err in the presence of Ees increase, V0 had to be increased. In contrast, this dependency was less pronounced in the plot of Ees vs P_b^+, and even more so in the plot of V0 vs P_b^+ data, indicating the dominance of systolic function parameters for the model optimization.

While no minima of Err function within given constraints was found, Err function had minimal value for V0 of -34 ml (95% CI -2 to -57 ml)(Figure 2B). Assuming that P_b^+ decreased to -10 mmHg with NTP infusion (as previously reported), Err function had minimal value for the Ees of 1.33 mmHg/ml (95% CI 1.12 to 1.57 mmHg/ml) (Figure 2C). Figure 2D shows the hypothetic hemodynamics of both V0 and P_b^+ decrease to ~34ml and ~10mmHg, respectively.

**Individual patient data**

Data of patients in whom echocardiography was performed both before and during NTP infusion are presented in Table 4, while left panels in Figure 3 represent reconstructed individual pressure-volume loops obtained before and after 24 hours of NTP infusion. After NTP infusion, peak and mean aortic valve gradient increased (p = 0.045 for both), while end-systolic volume decreased (p = 0.045). LV stroke work (LVSW) 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 following NTP infusion. Finally, no changes were noted in AVA.

In all patients, we analytically obtained the minima of the function of $Err$ vs. 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 a change of end-systolic pressure volume properties occurred repeatedly and in the same direction (Table 4). $P_b^+$ decreased in 4/5 patients implying 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 $Err$ calculation in individual data analysis. However, in both analyses, there was a dominance of systolic vs. diastolic effects.

Right panels in Figure 3. represent the pressure volume loops derived from individual AS model applications, with the effects of NTP modeled using the parameters corresponding to the minima of the $Err$ vs. parameter function. There was an excellent correlation between observed and modeled LVSW ($r = 0.97$, $p <0.0001$). However, modeled LVSW overestimated observed LVSW by $0.14 \pm 0.08$ J ($p = 0.001$). This discrepancy was due to assumption of flat diastolic pressure volume relationships in observed PV loops.

**Discussion**

In this study, we have found that the observed beneficial effects of NTP (that is, increase of stroke volume) in severe AS associated with heart failure and LV dysfunction cannot be attributed solely to the decrease of arterial resistance. Our data supports that NTP 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 transaortic valve gradient in both model and observed data (34).

The results of our simulations suggest that in order to obtain observed improvement after 24 hours of NTP 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, since in these patients, with critically decompensated AS, we could not safely determine the change in 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 increase of afterload or demand ischemia (21, 28 ), more closely mimicked global hemodynamics during NTP infusion. However, $V_0$ decrease is often associated with $E_{es}$ increase, and both changes act synergistically on LV systolic performance (7 ). Data obtained from our 5-modeled subjects also suggest that the specific hemodynamic effects of NTP may slightly vary among individuals.

**Possible mechanisms of LV performance improvement during NTP treatment**

Effects of NTP on diastolic function have been well described. Intracoronary infusion of NTP leads to downward shift of diastolic pressure volume relationship that is more pronounced in the setting of LV hypertrophy. (18) (16). Matter et al. have shown that intracoronary NTP infusion in AS patients with normal LV function leads to end-diastolic pressure decrease of 10 mmHg. Also,
NTP infusion may lead to 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 NTP effects on systolic function in the clinical setting. NTP acts as exogenous NO donor and may have small positive inotropic properties (22), but not at concentrations used in this study. Besides direct improvement of contractility, several possible mechanisms may have influenced the shift in end-systolic pressure volume relationship in patients with decompensated AS treated with NTP: ischemia relief, afterload decrease, preload decrease, and the change of viscoelastic myocardial properties. Improvement through ischemia is more plausible mechanism, as Steendijk et al. showed that demand ischemia in an animal model of coronary artery stenosis leads to an increase of $V_0$ from 0.5 ml to 5 ml (the average stroke volume in this study was 7 ml) (28 ). 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 when compared to other patients (12 ).

It is known that abrupt increase in afterload leads leftward shift of 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. NTP 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 preload decrease improves LV stroke work (29 ). Similarly, our AS patients showed a decrease of LV filling pressures with improved stroke work during NTP treatment. Finally, an additional mechanism may be impact of NTP treatment on viscous component of myocardial
properties (23). 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 NTP analyzed in this paper were documented after 24 hours of continuous NTP infusion. The exact onset and time course of hemodynamic improvement cannot be determined from this study.

Limitations

There are several important methodologic limitations of this study. First, in only the small fraction of subjects, adequate echocardiography data were obtained both before and after 24 hours of NTP infusion. Second, LV pressures and volumes were not measured simultaneously. However, invasive hemodynamic and echocardiographic data were collected within less than 5 minutes. 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 physiologic 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 NTP 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 heterogenous, with varying severity of coronary artery disease. It is well recognized that AS is frequently associated with coronary artery disease (3). Our data does not allow us, therefore, to discriminate whether the observed effects are due to alleviation of myocardial ischemia or direct improvement in LV contractility.

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

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References:


Table 1. Comparison of observed and simulated hemodynamics in decompensated aortic stenosis before and during nitroprusside infusion. Hemodynamics of nitroprusside infusion was simulated by simple systemic vascular resistance decrease. Note the discrepancy between observed and simulated hemodynamics during nitroprusside.

<table>
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<th>Baseline</th>
<th>NTP infusion</th>
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<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Simulated</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>91 ± 9</td>
<td>91</td>
</tr>
<tr>
<td>AVA (cm²)</td>
<td>0.58 ± 0.04</td>
<td>0.58</td>
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<tr>
<td>SVR (dyn•s•cm⁻⁵)</td>
<td>1926 ±118</td>
<td>1926</td>
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<tr>
<td>EF (%)</td>
<td>21 ± 2</td>
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<tr>
<td>SV (ml)</td>
<td>33 ± 2</td>
<td>35</td>
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<tr>
<td>Peak AVG (mmHg)</td>
<td>64 ± 8</td>
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<tr>
<td>mean AVG (mmHg)</td>
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<td>35</td>
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<tr>
<td>Mean ArtP (mmHg)</td>
<td>82 ± 3</td>
<td>88</td>
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<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>
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*: obtained in a subgroup of patients (n = 5). †: p = 0.001 for the comparison with observed data.

ArtP: Arterial pressure; AVA: Aortic valve area; AVG: aortic valve gradient; EF: ejection fraction; HR: heart rate; NTP: nitroprusside; PCWP: pulmonary capillary wedge pressure; RAP: right atrial pressure; SV: stroke volume; SVR: systemic vascular resistance
Table 2. Jacobian matrix of the model sensitivity to parameter variation in the setting of aortic stenosis (AS) combined with normal or depressed contractility. The values represent the amount of change of hemodynamic variable for an index change in parameter. For example, in AS with normal contractility, an $E_{es}$ increase of 1 would lead to EDP decrease of 1.9 mmHg. As expected, $E_{es}$ and $V_0$ have opposite effects on model hemodynamics. Also, $P_b^+$ increase increases end-diastolic pressure but decreases ventricular volumes. $E_{es}$ influence model hemodynamics more if the contractility is decreased.

<table>
<thead>
<tr>
<th></th>
<th>EDP</th>
<th>SV</th>
<th>ArtP</th>
<th>EDV</th>
<th>ESV</th>
<th>EF</th>
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<tbody>
<tr>
<td><strong>AS with normal contractility ($E_{es} = 3.5$)</strong></td>
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<tr>
<td>$E_{es}$</td>
<td>-0.95</td>
<td>2.81</td>
<td>3.23</td>
<td>-4.19</td>
<td>-7.01</td>
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<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>
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<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>
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<td><strong>AS with depressed contractility ($E_{es} = 1$)</strong></td>
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<td>$E_{es}$</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>

ArtP: Mean systemic arterial pressure; EDV: end-diastolic volume EDP: end-diastolic pressure; $E_{es}$ : end-systolic elastance; EF: ejection fraction; ESV: end-systolic volume; $P_b^+$: diastolic pressure-volume relationship shift; SV: stroke volume; $V_0$: volume axis intercept of end-systolic pressure volume relationships.
Table 3. Standardized (non-dimensional) beta coefficients from regression analysis of $Err$-ventricular parameters function. Beta coefficients describe relative contribution of individual parameter to the final value $Err$. Note that the highest beta coefficients corresponded to systolic parameters of $V_0$, $E_{es} \cdot V_0$, and $(E_{es})^2$.

<table>
<thead>
<tr>
<th></th>
<th>Beta</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{es}$</td>
<td>-3.46</td>
<td>0.10</td>
</tr>
<tr>
<td>$(E_{es})^2$</td>
<td>3.47</td>
<td>0.10</td>
</tr>
<tr>
<td>$V_0$</td>
<td>4.06</td>
<td>0.05</td>
</tr>
<tr>
<td>$(V_0)^2$</td>
<td>0.49</td>
<td>0.01</td>
</tr>
<tr>
<td>$E_{es} \cdot V_0$</td>
<td>-3.91</td>
<td>0.05</td>
</tr>
<tr>
<td>$P_b^+$</td>
<td>-0.21</td>
<td>0.02</td>
</tr>
<tr>
<td>$(P_b^+)^2$</td>
<td>-0.25</td>
<td>0.02</td>
</tr>
<tr>
<td>$E_{es} \cdot V_0 \cdot P_b^+$</td>
<td>0.40</td>
<td>0.01</td>
</tr>
</tbody>
</table>

$P<0.0001$ for all beta coefficients. $E_{es}$: end-systolic elastance; $P_b^+$: diastolic pressure-volume relationship shift; SE: standard error of beta; $V_0$: volume axis intercept of end-systolic pressure-volume relationships.
Table 4. Echocardiographic and model data from five patients in whom echocardiography was performed during maximal sodium nitroprusside infusion

<table>
<thead>
<tr>
<th></th>
<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></td>
<td>Base NTP</td>
<td>Base NTP</td>
<td>Base NTP</td>
<td>Base NTP</td>
<td>Base NTP</td>
</tr>
<tr>
<td>Observed data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>102</td>
<td>106</td>
<td>131</td>
<td>118</td>
<td>171</td>
</tr>
<tr>
<td>ESV (ml)*</td>
<td>73</td>
<td>48</td>
<td>96</td>
<td>69</td>
<td>136</td>
</tr>
<tr>
<td>PG (mmHg)*</td>
<td>68</td>
<td>101</td>
<td>117</td>
<td>197</td>
<td>48</td>
</tr>
<tr>
<td>MG (mmHg)*</td>
<td>43</td>
<td>59</td>
<td>61</td>
<td>108</td>
<td>29</td>
</tr>
<tr>
<td>AVA (cm²)</td>
<td>0.6</td>
<td>0.6</td>
<td>0.4</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>LVSW (J)*</td>
<td>0.66</td>
<td>0.86</td>
<td>0.47</td>
<td>0.50</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ees (mmHg/ml)*</td>
<td>2.4</td>
<td>3.5</td>
<td>2.3</td>
<td>3.1</td>
<td>1.0</td>
</tr>
<tr>
<td>V₀ (ml)</td>
<td>14</td>
<td>14</td>
<td>20</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Pb+(mmHg)</td>
<td>0.0</td>
<td>-6.0</td>
<td>0.0</td>
<td>0.9</td>
<td>11.0</td>
</tr>
<tr>
<td>LVSW (J)*</td>
<td>0.72</td>
<td>0.88</td>
<td>0.68</td>
<td>0.68</td>
<td>0.48</td>
</tr>
</tbody>
</table>

*: p = 0.045 vs Baseline values. AVA: Aortic valve area; EDV: end-diastolic volume; Eₑₑₐ: minimal diastolic elastance; Eₑₑₛ: end-systolic elastance; ESV: end-systolic volume; LVSW: left ventricular stroke work; MG: mean aortic gradient; PG: peak aortic gradient; V₀: x-axis intercept of end-systolic pressure-volume relationships.
Legend for Figures:

Figure 1. Three dimensional plots of the loss function $Err$ vs. $E_{es}$ and $V_0$ (A), $V_0$ and $P_b^+$ (B), and $E_{es}$ and $P_b^+$ (C). The interpolated surface is represents the second-order polynomial fit of $Err$ vs. all 3 parameters. As can be seen, $Err$ was most influenced by the combination of $E_{es}$ and $V$, and least influenced by the combination of $E_{es}$ and $P_b^+$.

Figure 2. Pressure volume loops generated from the decompensated AS model at baseline (thin line) and A) after isolated systemic vascular resistance (SVR) decrease; B) combined optimal $V_0$ decrease (from 9 ml to –34 ml) and SVR decrease; C) combined SVR decrease and optimal $E_{es}$ increase (from 1 to 1.33 mmHg/ml) in the setting of $P_b^+$ decrease to -10 mmHg; D) combined SVR decrease and optimal $V_0$ decrease (to – 34 ml) in the setting of -10 mmHg $P_b^+$ decrease.

Figure 3. Observed individual pressure-volume loops (Left panels) compared to model-derived individual pressure volume loops (Right panels). Rows represent patients 1 to 5. $x$ axis represents LV volume, while $y$ axis represents LV pressure. Thin and thick lines represent data at baseline and during sodium nitroprusside treatment, respectively.
Figure 1A.
Figure 1B.
Figure 1C.
Figure 2.
Observed vs. Model for Patients 1 to 5.

Figure 3.