

# A Theoretic Analysis of the Effect of Pulmonary Vasodilation on Pulmonary Venous Pressure: Implications for Inhaled Nitric Oxide Therapy

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**Background:** Although the use of inhaled nitric oxide offers certain advantages over more traditional pulmonary vasodilators, concerns have emerged because of reports of acute pulmonary edema during nitric oxide administration in patients with chronic heart failure. It is unclear whether the pulmonary vasodilating action of nitric oxide could, by itself, cause venous pressures to rise in the lung and why patients with preexisting chronic heart failure are at greatest risk for the development of pulmonary edema during inhaled nitric oxide therapy.

**Methods:** The cardiovascular system was modeled as time-varying elastances; the pulmonary and systemic vascular systems were each modeled as a series of resistive and compliance elements. Protocols were devised to examine the effects of a decrease in pulmonary vascular resistance on pulmonary venous pressure under different conditions of contractile state and volume status.

**Results:** Under all conditions studied, pulmonary venous pressure increased as pulmonary vascular resistance decreased. Increases in pulmonary venous pressure were caused by volume shifts between pulmonary arterial and venous compartments. These volume shifts were accentuated by high volume status. The impact of alterations in contractile state was minimal.

**Conclusions:** Pulmonary vasodilation by itself can lead to an increase in pulmonary venous pressure that is mediated by shifts of blood between arterial and venous compartments of the pulmonary bed. Furthermore, impairment in ventricular contractile state by itself has relatively little effect on pulmonary venous pressure. The magnitude of the increase in pulmonary venous pressure is largely determined by the volume status and the initial value of pulmonary vascular resistance. *J Heart Lung Transplant* 1996;15:715-21.

The use of inhaled nitric oxide ( $\text{NO}_1$ ) as a pulmonary vasodilator is being investigated in many spheres of clinical medicine. The common uses of  $\text{NO}_1$  include (1) intraoperative treatment of elevated pulmonary vascular resistance in patients undergoing heart operations,<sup>1</sup> (2) the assessment of pulmonary vascular reactivity in patients with heart failure undergoing evaluation for heart transplan-

tation,<sup>2,3</sup> and (3) treatment of persistent pulmonary hypertension in the newborn infant.<sup>4,5</sup> Although  $\text{NO}_1$  offers certain advantages over more traditional pulmonary vasodilators, concerns have emerged because of reports of elevations of pulmonary capillary pressures<sup>2,3</sup> and acute pulmonary edema<sup>6</sup> during  $\text{NO}_1$  administration in patients with chronic heart failure.

Under some circumstances NO may act as a negative inotropic agent.<sup>7-10</sup> However, because  $\text{NO}_1$  is rapidly bound and sequestered by hemoglobin in the blood,<sup>11</sup> it has been argued that  $\text{NO}_1$  cannot exert negative inotropic actions in vivo. This raises questions as to the mechanism by which elevations in pulmonary artery occlusion pressure and pulmonary edema can occur during  $\text{NO}_1$  treatment. It is unclear whether the pulmonary vasodilating action

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**TABLE** Parameter values chosen for use in model: specific parameters were varied in ranges specified

	Right ventricle	Left ventricle
<b>Heart parameters</b>		
Maximum elastance ( $E_{max}$ ) (mm Hg/ml)	0.7 (0.35-0.70)	3.0 (1.5-3.0)
Unstressed volume (ml)	0	0
Time to end systole ( $T_{es}$ ) (msec)	175	175
Time constant of relaxation ( $\tau$ ) (msec)	25	25
Scaling factor for EDPVR (mm Hg)	0.35	0.35
Exponent for EDPVR ( $ml^{-1}$ )	0.023	0.023
Heart rate (beats/min)	75	75
<b>Vascular parameters</b>	<b>Pulmonary</b>	<b>Systemic</b>
Arterial resistance (Wood units)	1.0 (0.1-8.3)	15.5
Characteristic resistance (Wood units)	0.3	0.5
Venous resistance (Wood units)	0.25	0.25
Vascular resistance (Wood units)	0.4-8.6	16.0
Arterial capacitance ( $ml \cdot mm\ Hg^{-1}$ )	13	1.32
Venous capacitance ( $ml \cdot mm\ Hg^{-1}$ )	8	70
<b>Blood volume</b>		
Stressed ( $V_s$ ) (ml)	750 (750-2075)	
Unstressed ( $V_u$ ) (ml)	4750	

$E_{max}$  is the maximum value of the  $\epsilon(t)$  function defined in the appendix. Vascular resistance is the sum of arterial and characteristic resistances; venous resistance represents the resistance to ventricular filling. Wood units =  $mm\ Hg \cdot min \cdot L^{-1}$ . EDPVR, End-diastolic pressure volume relationship.

of  $NO_1$  could, by itself, cause pulmonary capillary pressure to rise in the lung; furthermore, proposing such a mechanism would challenge more traditional views that acute elevations in pulmonary capillary pressure leading to acute pulmonary edema are for the most part a consequence of acute left ventricular dysfunction. It is also unknown why patients with preexisting chronic heart failure are at greatest risk for the development of pulmonary edema with  $NO_1$ . Improved understanding of the hemodynamic factors that lead to elevation of pulmonary capillary pressure during  $NO_1$  administration would be helpful in designing means of predicting, preventing, and treating this serious side effect.

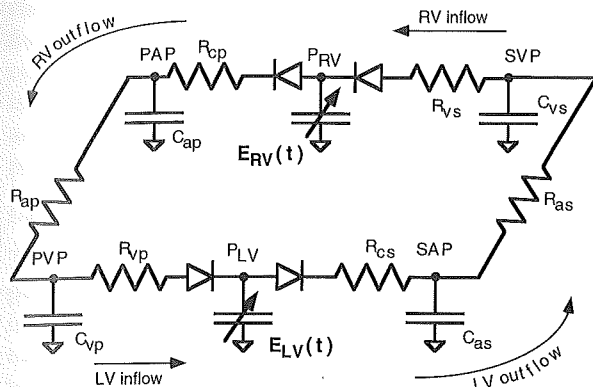
Because the interactions between the ventricles and vascular beds are complex, and because of the closed-loop nature of the cardiovascular system, it is often difficult to delineate the dominant mechanism underlying an observed hemodynamic phenomenon. This is particularly the case with the often limited information available from clinical studies. Computer simulations of the cardiovascular system have proved useful in helping investigators to gain insight into such complex problems.<sup>12</sup> We therefore took a similar approach to explore the theoretic hemodynamic consequences of  $NO_1$  therapy. The purpose of this theoretic analysis was to determine whether a decrease in pulmonary vascular resistance alone could cause pulmonary capillary pressure to rise in

the absence of any reduction in left ventricular (LV) contractile state. Furthermore, this question was evaluated in the setting of varying degrees of baseline heart failure to clarify why some of these patients are at increased risk. The results are interpreted within the context of previous clinical experience.

## MATERIAL AND METHODS

### Cardiovascular Model

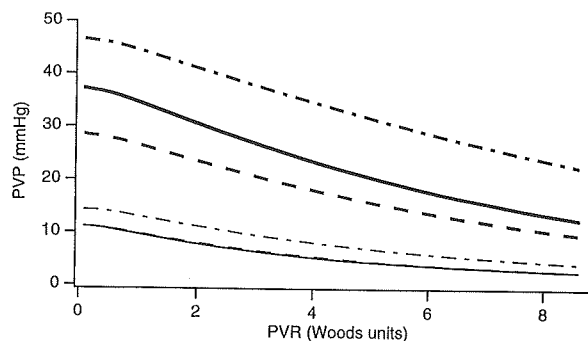
The model of the cardiovascular system used in this study has been described previously<sup>13</sup> and the major features are described in the appendix. Briefly, ventricular function was represented by a time-varying elastance model that interrelates ventricular pressure and volume. Contractility was indexed by the maximum ventricular elastance,  $E_{max}$ . Diastolic function was indexed by the stiffness coefficient of an exponential function that describes the end-diastolic pressure volume relationship. The systemic and pulmonary vascular systems were each modeled as a series of resistance and compliance elements as shown in Figure 1. In this model, pulmonary venous pressure is identical to pulmonary capillary pressure. Each of the capacitive compartments represents the stressed volume contained in its respective vascular bed; only volume that contributed to pressure generation (that is, stressed volume) was considered in the model. The sum of the stressed



**FIGURE 1** Diagram of electric circuit used for simulation. Details of this model are presented in appendix.  $E_{LV}(t)$  and  $E_{RV}(t)$  are time-varying elastance functions for left and right ventricles, respectively;  $P_{LV}$  and  $P_{RV}$  are pressures generated by left and right ventricles, respectively;  $C_{as}$  and  $C_{ap}$  are lumped systemic and pulmonary arterial capacitances, respectively;  $C_{vs}$  and  $C_{vp}$  are lumped systemic and pulmonary venous capacitances, respectively;  $R_{cs}$  and  $R_{cp}$  are proximal characteristic systemic and pulmonary resistances;  $R_{as}$  and  $R_{ap}$  are lumped systemic and pulmonary arterial resistances, respectively.  $R_{vs}$  and  $R_{vp}$  are resistances to return of blood from systemic and pulmonary venous capacitances to heart, respectively. *RV*, Right ventricle; *LV*, left ventricle; *PAP*, pulmonary arterial pressure; *SVP*, systemic venous pressure; *PVP*, pulmonary venous pressure; *SAP*, systemic arterial pressure.

blood volumes contained within each of the capacitive compartments equals total body stressed blood volume ( $V_s$ ). The distribution of  $V_s$  among the individual volume compartments changes when vascular parameters are changed.

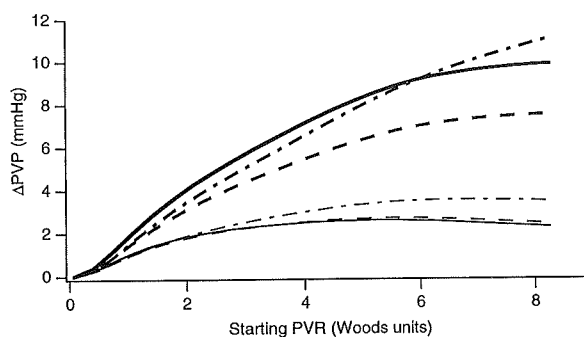
The normal value of each parameter of the model was set to be appropriate for a 75 kg man. These normal values were adapted from previous reports in the literature<sup>14-16</sup> and are listed in the Table. Parameter values were independently altered to model pulmonary hypertension and simulate the changes that would occur in response to pulmonary vasodilation. Six pulmonary hypertensive conditions were modeled: volume-compensated and uncompensated acute pulmonary hypertension, volume-compensated and uncompensated pulmonary hypertension in the setting of failure of the left side of the heart, and volume-compensated and uncompensated pulmonary hypertension in the setting of biventricular heart failure. The specific modeling of these conditions is described more fully later.



**FIGURE 2** Impact of changing pulmonary vascular resistance (*PVR*) on pulmonary venous pressure (*PVP*) in absence of changes in other cardiovascular parameters. Six lines show data from each of protocols; specific conditions are summarized in Table I. *Thin solid line*, Normal right ventricular (*RV*) and left ventricular (*LV*) maximum ventricular elastance (*E<sub>max</sub>*), normal stressed volume; *thin dashed line*, low *RV* and *LV E<sub>max</sub>*, normal stressed volume; *thin dotted/dashed line*, normal *RV E<sub>max</sub>*, low *LV E<sub>max</sub>*, normal stressed volume; *thick solid line*, normal *RV* and *LV E<sub>max</sub>*, high stressed volume; *thick dashed line*, low *RV* and *LV E<sub>max</sub>*, high stressed volume; *thick dotted/dashed line*, normal *RV E<sub>max</sub>*, low *LV E<sub>max</sub>*, high stressed volume. At any particular value of pulmonary vascular resistance, pulmonary venous pressure was highest in protocol 4, in which *RV* elastance was normal, *LV* elastance was reduced, and  $V_s$  was high.

### Protocols

Protocols were devised to examine the effects of a decrease in pulmonary vascular resistance on pulmonary venous pressure, pulmonary arterial pressure, and cardiac output. Pulmonary vascular resistance ramp decreases (from 8.7 to 0.4 Wood units in 32 steps) were examined under six different conditions of right ventricular (*RV*) function, *LV* function, and volume status. In the first protocol, all the other parameters were set at their normal values. In the second protocol,  $V_s$  was increased from a normal value of 750 ml to 2075 ml to raise the starting cardiac output to normal in the face of the markedly elevated pulmonary vascular resistance of 8.7 Wood units. To model pulmonary hypertension that is a result of long-standing failure of the left side of the heart, *LV E<sub>max</sub>* was reduced by 50% in the third and fourth protocols, with  $V_s$  at the baseline value in the third and increased to 2075 ml in the fourth. To evaluate the impact of a global reduction in contractile state, both *RV* and *LV E<sub>max</sub>* were reduced by 50% in protocols five and six. Again,  $V_s$  was

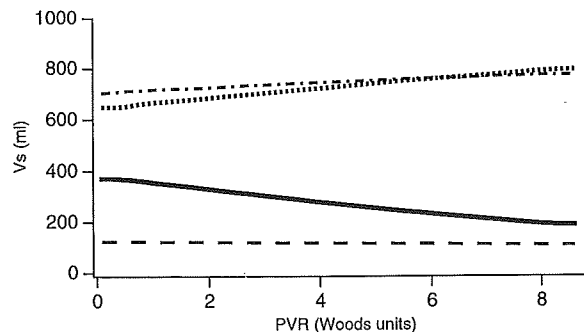


**FIGURE 3** Resultant change in pulmonary venous pressure ( $\Delta PVP$ ) as result of 50% reduction in pulmonary vascular resistance ( $PVR$ ) as function of starting pulmonary vascular resistance. Six lines show data from each of protocols; specific conditions are summarized in Table I, and lines styles are as defined in legend of Figure 2. At low stressed volumes (represented by set of three *thin lines* in lower portion of graph) and at starting pulmonary vascular resistance values higher than 2 Wood units, change in pulmonary venous pressure shows little dependence on starting pulmonary vascular resistance or on ventricular contractile state. Greatest change in pulmonary venous pressure was seen under conditions of high stressed volumes (represented by set of three *thick lines* in upper portion of graph).

normal in protocol five and was raised to 2075 ml in protocol six.

## RESULTS

The relationships between pulmonary vascular resistance and pulmonary venous pressure for the six conditions outlined herein are illustrated in Figure 2. Under all conditions studied, pulmonary venous pressure increased as pulmonary vascular resistance decreased. At any particular value of pulmonary vascular resistance, pulmonary venous pressure was highest in condition four, in which RV elastance was normal, LV elastance was reduced, and  $V_s$  was high. The three *thick lines* at the top portion of the graph represent the three conditions of high  $V_s$  (conditions 2, 4, and 6). When these three conditions are compared, it is apparent that pulmonary venous pressure was lowest with biventricular reduction in contractile state (condition 6) and intermediate with normal RV and LV contractile state (condition 2). The three conditions with normal  $V_s$  are represented by the *thin lines* in the bottom portion of the graph (conditions 1, 3, and 5). Comparison of these conditions revealed that pulmonary venous pressure



**FIGURE 4** Redistribution of volume that occurred during pulmonary vascular resistance ( $PVR$ ) run in protocol 4. Pulmonary venous volume (*thick, solid line*) increased markedly as pulmonary vascular resistance was decreased, whereas pulmonary arterial (*dotted line*) and systemic venous (*dotted/dashed line*) volumes decreased.  $V_s$ , Stressed blood volume.

was relatively unaffected by changes in LV and RV contractile state.

These same data were reanalyzed to illustrate the effect of a 50% reduction in pulmonary vascular resistance on pulmonary venous pressure for each starting value of pulmonary vascular resistance (Figure 3). As expected, when starting pulmonary vascular resistance was low, the impact of halving its value on pulmonary venous pressure was negligible. In the three conditions of normal blood volume (again represented by the *thin lines*), the increase in pulmonary venous pressure was relatively constant when the starting pulmonary vascular resistance was greater than 4 Wood units. In contrast, when  $V_s$  was elevated, the increase in pulmonary venous pressure was more pronounced and continued to increase at higher starting values of pulmonary vascular resistance. Note, however, that among the three conditions of high  $V_s$ , a reduction in biventricular contractile state (condition 6) attenuated the increase in pulmonary venous pressure. The impact of alterations in contractile state otherwise was minimal.

Examination of several variables in the simulation revealed that increases in pulmonary venous pressure associated with decreases in pulmonary vascular resistance were a result of volume shifts between pulmonary arterial and venous compartments. Figure 4 illustrates the redistribution of volume that occurred during the pulmonary vascular resistance run in protocol 4. Pulmonary venous volume (*thick, solid line*) increased markedly as pulmonary vascular resistance was decreased, whereas pulmonary arte-

rial (*dotted line*) and systemic venous (*dotted/dashed line*) volumes decreased. It is apparent that a reduction in pulmonary vascular resistance resulted in a shift of stressed volume out of the pulmonary arterial and systemic venous systems and into the pulmonary venous system.

## DISCUSSION

The results of this theoretic analysis suggest that pulmonary vasodilation by itself can lead to an increase in pulmonary venous pressure that is mediated by shifts of blood between arterial and venous compartments of the pulmonary bed. Furthermore, as suggested previously,<sup>12</sup> impairment in ventricular contractile state by itself has relatively little effect on pulmonary venous pressure. The magnitude of the increase in pulmonary venous pressure is largely determined by the volume status and the initial value of pulmonary resistance; the higher the stressed volume and initial pulmonary vascular resistance values, the greater the increase in pulmonary venous pressure because of a decrease in pulmonary vascular resistance. This is consistent with the notion advanced by some investigators that the elevations of pulmonary vascular resistance in chronic heart failure protect the pulmonary capillary networks from high pressures.<sup>17</sup>

NO<sub>1</sub> is unique among the class of pulmonary vasodilators inasmuch as it is considered to have no effect on the systemic vasculature.<sup>18,19</sup> Other pulmonary vasodilators such as prostacyclin and sodium nitroprusside also reduce systemic vascular resistance, and their use, therefore, is often limited by systemic hypotension. However, in addition to reducing systemic vascular resistance, the "nonselective" pulmonary vasodilators also increase the systemic venous capacitance by increasing the unstressed volume and thereby reducing the stressed volume. Therefore the two main actions of the nonselective pulmonary vasodilators would offset each other: pulmonary vasodilation would lead to an increase in pulmonary venous pressure, whereas decreasing stressed volume would lead to a reduction in pulmonary venous pressure. In contrast, because NO<sub>1</sub> does not cause a change in systemic capacitance, the increase in pulmonary venous pressure would be unopposed.

Recent reports of acute pulmonary edema as result of NO<sub>1</sub> administration have raised concerns regarding the hemodynamic effects of NO<sub>1</sub> in patients with heart failure.<sup>6</sup> It has been suggested that the rise in pulmonary venous pressure is a direct consequence of a decrease in LV contractile state

and that the latter is brought about by NO<sub>1</sub> acting as a negative inotropic agent.<sup>20</sup> Although some studies have shown that NO is capable of reducing contractile force in isolated myocytes,<sup>8,9</sup> it has been argued to be unlikely that when it is administered via the inhaled route there are any appreciable effects on the intact heart; NO has been shown to be rapidly sequestered by hemoglobin in the blood<sup>11</sup> and thereby inactivated long before it reaches the systemic circulation. The present analysis suggests that it is not necessary for this agent to work as a negative inotrope to cause pulmonary venous pressure to rise: its pulmonary vasodilating actions alone are sufficient to explain all of the clinical observations, including why patients with preexisting heart failure are at greatest risk for pulmonary edema.

The relationship between ventricular function and pulmonary venous pressure has been explored in a previous theoretic analysis aimed at determining why pulmonary venous pressure rises after the onset of LV ischemia.<sup>12</sup> Because it is known that LV ischemia is associated with acute impairment of LV function and activation of the sympathetic nervous system, the model analysis afforded the opportunity to examine the independent contributions of these responses to alterations in pulmonary venous pressure. Results of that study suggested that significant elevations of pulmonary venous pressure do not occur as a direct consequence of ventricular dysfunction, but instead result from a shift of blood volume from the unstressed to the stressed compartments. As in the present study, the importance of shifts of blood volume among the individual systemic and pulmonic compartments for modulation of pulmonary venous pressure was underscored.

In addition to having depressed ventricular function, patients with long-standing heart failure also have increased total body water and sodium levels and have elevations in sympathetic tone.<sup>21</sup> As a result of the latter, systemic vascular capacity is reduced.<sup>22</sup> The net effect of these factors is equivalent to increasing the V<sub>s</sub>. Therefore results of the present analysis would suggest that patients with heart failure are at increased risk for development of pulmonary edema during NO<sub>1</sub> therapy because of the high effective volume status. Reductions in V<sub>s</sub> by the addition of an agent with systemic vasodilatory effects (such as sodium nitroprusside or nitroglycerine) may be an important adjunct to NO<sub>1</sub> therapy in this population.

This study represents a purely theoretic analysis of the impact of NO<sub>1</sub> therapy on pulmonary venous pressure. As such, the results of this analysis should

be interpreted with the limitations of the model in mind. The analysis is based on a relatively simple closed-loop model of the cardiovascular system. Individual parameter values were similar to previously published measurements for normal, as well as pulmonary hypertensive, physiologic conditions. Other possible mechanisms for development of pulmonary edema, such as changes in pulmonary capillary permeability, were beyond the scope of this model; the purpose of this model was to assess the hemodynamic consequences of pulmonary vasodilation and to explain the increases in pulmonary venous pressure seen during NO<sub>1</sub> therapy in patients with heart failure. The model ignored ventricular interaction and pericardial constraint; however, these effects have been shown to be slight and would not be expected to alter the conclusions of this study. Reflex vascular changes were ignored; it was assumed that NO<sub>1</sub> has a single effect, that is, a reduction in pulmonary vascular resistance. It is important to appreciate that the power of this type of analysis lies in the ability to make such an assumption. The central question in this study was whether a reduction in pulmonary vascular resistance alone could account for the clinically observed increase in pulmonary venous pressure. The goal of this type of analysis is thus to provide a theoretic foundation for guiding future experimental research in this area. The results suggest findings that might be considered a change in the way clinicians think about the determinants of pulmonary venous pressure. Though not definitive because of its theoretic nature, we present a comprehensive theory that accounts for a wide range of hemodynamic phenomena observed when NO<sub>1</sub> is administered.

#### REFERENCES

- Rich GF, Murphy GD Jr, Roos CM, Johns RA. Inhaled nitric oxide: selective pulmonary vasodilation in cardiac surgical patients. *Anesthesiology* 1993;78:1028-35.
- Semigran MJ, Cockrill BA, Kacmarek R, et al. Hemodynamic effects of inhaled nitric oxide in heart failure. *J Am Coll Cardiol* 1994;24:982-8.
- Kieler-Jensen N, Ricksten S, Stenqvist O, et al. Inhaled nitric oxide in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance. *J Heart Lung Transplant* 1994;13:366-75.
- Kinsella JP, Neish SR, Sheffer E, Abram SH. Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 1992;340:819-20.
- Roberts JD, Polaner DM, Lang P, Zapol WM. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 1992;340:818-9.
- Bocchi EA, Bacal F, Auler JOC, Carmone MJC, Bellotti G, Pileggi F. Inhaled nitric oxide leading to pulmonary edema in stable severe heart failure. *Am J Cardiol* 1994;74:70-2.
- Finkel MS, Oddis CV, Jacob RD, Watkins SC, Hattler BG, Simmons RL. Negative inotropic effects of cytokines on the heart mediated by nitric oxide. *Science* 1992;257:387-9.
- Brady AJB, Poole-Wilson PA, Harding SE, Warren JB. Nitric oxide production within cardiac myocytes reduces their contractility in endotoxemia. *Am J Physiol* 1992;263:H1963-6.
- Brady AJB, Warren JB, Poole-Wilson PA, Williams TJ, Harding SE. Nitric oxide attenuates cardiac myocyte contraction. *Am J Physiol* 1993;265:H176-82.
- Balligand J, Ungureanu D, Kelly RA, et al. Abnormal contractile function due to induction of nitric oxide synthesis in rat cardiac myocytes follows exposure to activated macrophage-conditioned medium. *J Clin Invest* 1993;91:2314-9.
- Ignarro LJ. Biological actions and properties of endothelium-derived nitric oxide formed and released from artery and vein. *Circ Res* 1989;65:1-21.
- Burkhoff D, Tyberg JV. Why does pulmonary venous pressure rise after onset of LV dysfunction: a theoretical analysis. *Am J Physiol* 1993;34:H1819-28.
- Santamore WP, Burkhoff D. Hemodynamic consequences of ventricular interaction as assessed by model analysis. *Am J Physiol* 1991;260:H146-57.
- Milnor WR. *Hemodynamics*. Baltimore: Williams and Wilkins, 1982.
- Nichols WW, O'Rourke MF. *McDonald's blood flow in arteries*. Philadelphia: Lea and Febiger, 1990.
- Sagawa K, Maughan WL, Suga H, Sunagawa K. *Cardiac contraction and the pressure-volume relationship*. Oxford, United Kingdom: Oxford University Press, 1988.
- Shirai M, Ninomiya I, Sada K. Constrictor response of small pulmonary arteries to acute pulmonary hypertension during left atrial pressure elevation. *Jpn J Physiol* 1991;41:129-42.
- Frostell C, Fratacci M, Wain JC, Jones R, Zapol WM. Inhaled nitric oxide: a selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. *Circulation* 1991;83:2038-47.
- Fratacci MD, Frostell CG, Chenty TY, Wain JC, Robinson DR, Zapol WM. Inhaled nitric oxide: a selective pulmonary vasodilator of heparin protamine vasoconstriction in sheep. *Anesthesiology* 1991;75:990-9.
- Loh E, Stampler JS, Hare JM, Colucci WS. Cardiovascular effects of inhaled nitric oxide in patients with left ventricular dysfunction [Abstract]. *Circulation* 1993;88:S6122.
- Packer M. Role of the sympathetic nervous system in chronic heart failure: a historical and philosophical perspective. *Circulation* 1990;82:II-6.
- Bennett TD, Wyss CF, Scher AM. Changes in vascular capacity in awake dogs in response to carotid sinus occlusion and administration of catecholamines. *Circ Res* 1984;55:440-53.

#### APPENDIX

The equations describing the model depicted in Figure 4 are reviewed in this section. The ventricles were modeled as time-varying elastances (elastance,  $\mathcal{E}$ , as a function of time,  $t$ ) with linear end-systolic ( $E_{es}$ ) and nonlinear end-diastolic pressure-volume relations. LV pressures ( $P_{LV}$ ) and volume ( $V_{LV}$ ) were interrelated by the following equations, which we have used before.<sup>13</sup>

$$P_{LV}(t) = [P_{es,LV}(V_{LV}) - P_{ed,LV}(V_{LV})\mathcal{E}_{LV}(t)] + P_{ed,LV}(V_{LV})$$



where

$$\varepsilon_{LV}(t) = \frac{1}{2} \left[ \sin \left( \frac{\pi}{T_{es}} t - \frac{\pi}{2} \right) + 1 \right] \text{ for } t \leq 3T_{es}/2$$

$$\varepsilon_{LV}(t) = 0.5 \exp[(t - 3T_{es}/2)/t] \text{ for } t \geq 3T_{es}/2$$

$$P_{es,LV}(V_{LV}) = E_{es,LV}(V_{LV} - V_{0,LV})$$

$$P_{ed,LV}(V_{LV}) = A_{LV} [\exp[B_{LV}(V_{LV} - V_{0,LV})] - 1]$$

$P_{es}$  and  $P_{ed}$  are the pressures at end-systole and end-diastole, respectively.  $E_{es}$  is the value of  $E$  at end-systole, or  $E$  max.  $A$  is the scaling factor and  $B$  is the exponent for the non-linear EDPVR.  $T_{es}$  is the time to end-systole.

A comparable set of equations was used to describe RV function; all of the parameters describing RV and LV function were independent of each other except for  $T_{es}$  (duration of systole) and  $t$ , which were set at the same values for both ventricles; thus  $\varepsilon_{LV}(t)$  and  $\varepsilon_{RV}(t)$  were identical functions.

The capacitance of the systemic circulation was divided into arterial and venous capacitances,  $C_{as}$  and  $C_{vs}$ , respectively. Similarly, the pulmonic circulation had arterial and venous capacitive elements,  $C_{ap}$  and  $C_{vp}$ , respectively. Pressures (systemic arterial pressure [SAS], systemic venous pressure [SVP], pulmonary arterial pressure [PAP], and pulmonary venous pressure [PVP]) and their respective volumes ( $V_{Cas}$ ,  $V_{Cvs}$ ,  $V_{Cap}$ ,  $V_{Cvp}$ ) in each capacitance were related by the following linear relations:

$$SAP = V_{Cas}/C_{as}$$

$$SVP = V_{Cvs}/C_{vs}$$

$$PAP = V_{Cap}/C_{ap}$$

$$PVP = V_{Cvp}/C_{vp}$$

In each of these equations, the volume represents the stressed volume in the capacitance. The total unstressed volume of the system equals the sum of the unstressed volumes of all four capacitances. Therefore total unstressed volume could be considered as a single parameter ( $V_U$ ), without the need to be broken down into unstressed volumes of individual compartments. Therefore total body blood volume ( $V_{tot}$ ), unstressed volume, and volumes on individual capacitances are interrelated by

$$V_{tot} = V_{Cas} + V_{Cvs} + V_{Cap} + V_{Cvp} + V_U + V_{LV} + V_{RV}$$

A set of six differential equations described changes in volumes in the four capacitors and the two ventricles as functions of time in terms of the pressure across of each element and the value of the resistance connecting between different elements (see Table I and Figure 4 for

abbreviations; subscripts  $s$  and  $p$  denote systemic and pulmonic, respectively).

$$\frac{dV_{LV}(t)}{dt} = \frac{PVP(t) - P_{LV}(t, V_{LV})}{R_{vp}} \alpha_{LV} - \frac{P_{LV}(t, V_{LV}) - SAP(t)}{R_{cs}} \beta_{LV}$$

$$\frac{dV_{Cas}(t)}{dt} = \frac{P_{LV}(t, V_{LV}) - SAP(t)}{R_{cs}} \beta_{LV} - \frac{SAP(t) - SVP(t)}{R_{as}}$$

$$\frac{dV_{Cvs}(t)}{dt} = \frac{SAP(t) - SVP(t)}{R_{as}} - \frac{SVP(t) - P_{RV}(t, V_{RV})}{R_{vs}} \alpha_{RV}$$

$$\frac{dV_{RV}(t)}{dt} = \frac{SVP(t) - P_{RV}(t, V_{RV})}{R_{vs}} \alpha_{RV} - \frac{P_{RV}(t, V_{RV}) - PAP(t)}{R_{cp}} \beta_{RV}$$

$$\frac{dV_{Cap}(t)}{dt} = \frac{P_{RV}(t, V_{RV}) - PAP(t)}{R_{cp}} \beta_{RV} - \frac{PAP(t) - PVP(t)}{R_{ap}}$$

$$\frac{dV_{Cvp}(t)}{dt} = \frac{PAP(t) - PVP(t)}{R_{ap}} - \frac{PVP(t) - P_{LV}(t, V_{LV})}{R_{vp}} \alpha_{LV}$$

The values of  $\alpha$  and  $\beta$  in these equations are set at either 0 or 1 depending on whether ventricular filling or ejection is occurring as follows:

$$\alpha_{LV} = 1 \text{ if } P_{LV}(t) < P_{Cvp}(t) \\ = 0 \text{ otherwise}$$

$$\alpha_{RV} = 1 \text{ if } P_{RV}(t) < P_{Cvs}(t) \\ = 0 \text{ otherwise}$$

$$\beta_{LV} = 1 \text{ if } P_{LV}(t) < P_{Cas}(t) \\ = 0 \text{ otherwise}$$

$$\beta_{RV} = 1 \text{ if } P_{RV}(t) < P_{Cap}(t) \\ = 0 \text{ otherwise}$$

These simultaneous differential equations were solved by numeric methods.