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A human cardiopulmonary system model applied to the analysis of the Valsalva maneuver

K. LU, J. W. CLARK, JR., F. H. GHORBEL, D. L. WARE, and A. BIDANI. A human cardiopulmonary system model applied to the analysis of the Valsalva maneuver. Am J Physiol Heart Circ Physiol 281: H2661–H2679, 2001.—Previous models combining the human cardiovascular and pulmonary systems have not addressed their strong dynamic interaction. They are primarily cardiovascular or pulmonary in their orientation and do not permit a full exploration of how the combined cardiopulmonary system responds to large amplitude forcing (e.g., by the Valsalva maneuver). To address this issue, we developed a new model that represents the important components of the cardiopulmonary system and their coupled interaction. Included in the model are descriptions of atrial and ventricular mechanics, hemodynamics of the systemic and pulmonic circulations, baroreflex control of arterial pressure, airway and lung mechanics, and gas transport at the alveolar-capillary membrane. Parameters of this combined model were adjusted to fit nominal data, yielding accurate and realistic pressure, volume, and flow waveforms. With the same set of parameters, the nominal model predicted the hemodynamic responses to the markedly increased intrathoracic (pleural) pressures during the Valsalva maneuver. In summary, this model accurately represents the cardiopulmonary system and can explain how the heart, lung, and autonomic tone interact during the Valsalva maneuver. It is likely that with further refinement it could describe various physiological states and help investigators to better understand the biophysics of cardiopulmonary disease.

cardiopulmonary modeling; ventricular interaction; closed-loop hemodynamics; baroreflex control; airway mechanics; gas exchange

THE DIAGNOSIS AND TREATMENT of cardiopulmonary disease may be improved by using mathematical models of the cardiovascular and pulmonary systems. With this in mind, we developed a model of the cardiopulmonary system of the normal human subject that not only represents the system accurately but also predicts its response to a variety of commonly used diagnostic procedures. To our knowledge, this is the first example of a truly integrative model of the cardiopulmonary system.

Recently, our group (5, 25) developed a multicomartment model of the canine circulation. We have now modified and extended this cardiovascular model to encompass human heart mechanics, a circulatory loop, baroreflex control of arterial pressure, airway mechanics, and gas transport at the alveolar-capillary membrane.

Distributed circulatory models of the systemic and pulmonic circulations have been developed (1, 3, 12, 37). However, the mechanics of the lung and airways were not detailed in any of these, and the heart was modeled rather simply. The gas exchange at the alveolar-capillary membrane (an obvious link between cardiovascular and pulmonary system) was considered only in the model of Hardy et al. (12). Of these models, baroreflex control of arterial pressure was included only in the work of Ursino et al. (37).

Distributed airway mechanics models [e.g., Elad et al. (7) and Lambert et al. (16)] can be too complex for a combined cardiopulmonary model, making lumped lower-order compartment models [such as that of Lutchen et al. (19)] preferred. The lumped compartment model we (18) developed describes ventilation, perfusion, mechanics, and gas transport over the full range of normal lung volumes. A modified version of this model was used in the current study.

Our heart model was based on our previous work in dogs (5, 25). The parameters of that model were adjusted to better fit the flow, volume, and temporal relationships of the human cardiac cycle. Similar adjustments were made in the systemic and pulmonic component models of the canine circulatory loop (25). The resulting model is of intermediate complexity and simulates pressure, volume, and flow distribution of the human subject in the supine position.

To better simulate the cardiovascular response to perturbation, we added nonlinear descriptions of the venous system and a description of how the baroreflexes influence heart rate, myocardial contractility, and vasomotor tone. We based our baroreceptor control model on the work of Spickler et al. (35) and Wesseling et al. (38) and included descriptions of both parasympathetic (vagal) and sympathetic pathways.

Our new lung model combines models previously developed by our group, namely, an airway mechanics model [from Athanasiades et al. (2)] and a gas exchange model. Our combined model with realistic pressure, volume, and flow waveforms. With the same set of parameters, the nominal model predicted the hemodynamic responses to the markedly increased intrathoracic (pleural) pressures during the Valsalva maneuver.
change model [modified from Liu et al. (18)]. It characterizes the nonlinear resistive-compliant properties of the airways and the nonlinear pressure-volume characteristics of the lung. A distributed pulmonary circulatory model containing 35 contiguous capillary segments characterizes gas exchange at the alveolar-capillary membrane and yields good fits to expired O₂ and CO₂ data measured at the mouth.

This integrated cardiopulmonary model describes heart-lung interactions and the timing of baroreflex changes in heart rate, myocardial contractility, and vasomotor tone. Its parameters fit available cardiovascular and pulmonary data obtained during tidal breathing and can predict the responses to large-scale perturbations in pleural pressure, such as those occurring in the forced vital capacity and Valsalva maneuvers.

Glossary

Activation functions

\[ e(t) \] Time-varying activation function
\[ e_a(t) \] Activation function of the atrium
\[ e_v(t) \] Activation function of the ventricle

Airflows

\[ Q_{CA} \] Airflow from collapsible airways to alveolar region
\[ Q_{DC} \] Airflow from upper supported airway to collapsible airway
\[ Q_{ED} \] Airflow from environment to upper supported airway

Blood flows

\[ Q_{Ao} \] Aortic flow
\[ Q_{PA} \] Pulmonary arterial flow

Compliances

\[ C_{Ao,P} \] Aortic root compliance
\[ C_{Ao,D} \] Distal aortic compliance
\[ C_{PA} \] Pulmonary artery compliance
\[ C_{PA,D} \] Distal pulmonary artery compliance
\[ C_{PC} \] Pulmonary capillary compliance
\[ C_{PV} \] Pulmonary venous compliance
\[ C_{SA,D} \] Distal systemic artery compliance
\[ C_{SC} \] Systemic capillary compliance

Constants and scaling parameters

\[ a \] Time constant
\[ a_{\text{min}} \] Dimensionless constant
\[ a_x \] Normalized frequency offset
\[ A_i \] Parameter of activation function of the heart
\[ b_{\text{min}} \] Dimensionless constant
\[ b_x \] Dimensionless constant
\[ B_i \] Parameter of activation function of the heart
\[ C_i \] Parameter of activation function of the heart
\[ C_{LT} \] Lung tissue elastic constant

\[ D_0 \] Volume parameter
\[ D_1 \] Stressed pressure offset
\[ D_2 \] Unstressed pressure offset
\[ h_1 \] Constant
\[ h_2 \] Constant
\[ h_3 \] Constant
\[ h_4 \] Constant
\[ h_5 \] Constant
\[ h_6 \] Constant
\[ K \] Gain
\[ K_1 \] Stressed scaling pressure
\[ K_2 \] Unstressed scaling pressure
\[ K_a \] Scaling parameter
\[ K_b \] Scaling parameter
\[ K_c \] Scaling parameter
\[ K_{p1} \] Constant scaling parameter
\[ K_{p2} \] Constant scaling parameter
\[ K_R \] Resistance scaling factor
\[ K_{r} \] Scaling factor for pressure
\[ \lambda \] Diastolic elastance coefficient
\[ \tau_p \] Passive exponential constant
\[ \tau_c \] Time constant

Gas diffusion and flux

\[ C_{bi}^{(j)} \] Gas species \( i \) blood concentration in the \( j \)th capillary
\[ D_{i} \] Diffusion capacity for the \( i \)th gas species
\[ D_{L,CO_2} \] Lung diffusion capacity of CO₂
\[ D_{L,N_2} \] Lung diffusion capacity of N₂
\[ D_{L,O_2} \] Lung diffusion capacity of O₂
\[ \Phi_{tot} \] Total gas flux rate

Inertances

\[ L_{Ao,D} \] Distal aortic inertance
\[ L_{Ao,P} \] Aortic root inertance
\[ L_{PA} \] Pulmonary arterial inertance

Neural control

\[ F_{con} \] Normalized sympathetic efferent discharge frequency controlling contractility
\[ F_{Hr,S} \] Normalized sympathetic controlling HR frequency
\[ F_{Hr,V} \] Normalized vagal controlling HR frequency
\[ F_{symp} \] Sympathetic discharge frequency
\[ F_{vagus} \] Vagal discharge frequency
\[ F_{vaso} \] Normalized sympathetic efferent discharge frequency controlling vasomotor tone
\[ F_x \] Discharge frequency
\[ x \] Generic output index representing heart rate, contractility, or vasomotor tone
\[ N_1 \] Baroreceptor firing frequency
\[ N_2 \] Derivative of baroreceptor firing frequency
\[ N_{con} \] Sympathetic discharge at central nervous system controlling contractility
N_{hr,S} \text{ Sympathetic discharge at central nervous system controlling heart rate} \\
N_{hr,V} \text{ Vagal discharge at central nervous system controlling heart rate} \\
N(s) \text{ Laplace transform of } N(t) \\
N(t) \text{ Baroreceptor discharge frequency} \\
N_{vaso} \text{ Sympathetic discharge at central nervous system controlling vasomotor tone} \\
N_{vaso}(s) \text{ Laplace transform of } N_{vaso} \\
N_{x,0} \text{ Base frequency} \\
N_{x}(t) \text{ Discharge frequency of neural pathways of the central nervous system} \\

\textbf{Physiology} \\
A_{D} \text{ Distal aorta} \\
A_{P} \text{ Proximal aorta} \\
BR \text{ Baroreceptor element} \\
CNS \text{ Central nervous system} \\
LA \text{ Left atrium} \\
LV \text{ Left ventricle} \\
LVF \text{ Left ventricular free wall} \\
PA \text{ Pulmonary arterioles} \\
PA_{D} \text{ Distal pulmonary arterioles} \\
PA_{P} \text{ Proximal pulmonary arterioles} \\
PC \text{ Pulmonary capillaries} \\
PCD \text{ Pericardium} \\
PV \text{ Pulmonary veins} \\
RA \text{ Right atrium} \\
RV \text{ Right ventricle} \\
RVF \text{ Right ventricular free wall} \\
SA_{D} \text{ Distal systemic arterioles} \\
SA_{P} \text{ Proximal systemic arterioles} \\
SC \text{ Systemic capillaries} \\
SPT \text{ Septum} \\
SV \text{ Systemic veins} \\
VC \text{ Vena cava} \\

\textbf{Pressures} \\
P_{0} \text{ Diastolic pressure magnitude} \\
P_{\text{atm}} \text{ Atmospheric pressure} \\
P_{\text{atm},i} \text{ Partial pressure of gas species } i \text{ in the atmosphere} \\
P_{A} \text{ Partial pressure of gas species } i \text{ in the small airway} \\
P_{A} \text{ Alveolar pressure} \\
P_{A,CO_{2}} \text{ Alveolar CO}_{2} \text{ partial pressure} \\
P_{A,O_{2}} \text{ Alveolar } O_{2} \text{ partial pressure} \\
P_{A0} \text{ Aortic arch pressure} \\
P_{b,CO_{2}} \text{ CO}_{2} \text{ partial pressure in the blood} \\
P_{b,O_{2}} \text{ } O_{2} \text{ partial pressure in the blood} \\
P_{C} \text{ Partial pressure of gas species } i \text{ in the middle airway} \\
P_{C} \text{ Pressure in the lumen of the midairway segment} \\
P_{C,CO_{2}} \text{ CO}_{2} \text{ partial pressure in the collapsible airway} \\
P_{C,O_{2}} \text{ } O_{2} \text{ partial pressure in the collapsible airway} \\
P_{CW} \text{ Recoil pressure of the chest wall} \\
P_{CO_{2}} \text{ Partial pressure of } CO_{2} \\
P_{D} \text{ Partial pressure of gas species } i \text{ in the upper airway} \\
P_{D} \text{ Pressure in the lung dead space} \\
P_{D,CO_{2}} \text{ CO}_{2} \text{ partial pressure in the lung dead space} \\
P_{D,O_{2}} \text{ } O_{2} \text{ partial pressure in the lung dead space} \\
P_{EL} \text{ Lung elastic recoil pressure} \\
P_{ES}(V) \text{ End-systolic pressure} \\
P_{k}^{(j)} \text{ Partial pressure of gas species } i \text{ in the } j\text{th capillary} \\
P_{LA} \text{ Left atrial pressure} \\
P_{LV} \text{ Left ventricular pressure} \\
P_{muss} \text{ Pressure of the respiratory muscles} \\
P_{O_{2}} \text{ Partial pressure of } O_{2} \\
P_{PL} \text{ Pleural pressure} \\
P_{SA}^{a} \text{ Systemic arterial pressure in the active state} \\
P_{SA}^{p} \text{ Systemic arterial pressure in the passive state} \\
P_{SV} \text{ Transmural pressure of systemic veins} \\
P_{TM} \text{ Transmural pressure of collapsible midairway} \\
P_{VC} \text{ Transmural pressure of the vena cava} \\

\textbf{Resistances} \\
R_{0} \text{ Offset parameter} \\
R_{A_{D},P} \text{ Aortic root flow resistance} \\
R_{A_{D},D} \text{ Distal aortic flow resistance} \\
R_{C} \text{ Resistance of collapsible midairway} \\
R_{COR} \text{ Coronary flow resistance} \\
R_{CRB} \text{ Cerebral flow resistance} \\
R_{LA} \text{ Left atrial flow resistance} \\
R_{LT} \text{ Lung tissue resistive constant} \\
R_{M} \text{ Mitral valve flow resistance} \\
R_{PA} \text{ Pulmonary arteriolar flow resistance} \\
R_{PA,D} \text{ Distal pulmonary arterial flow resistance} \\
R_{PC} \text{ Resistance of pulmonary capillaries} \\
R_{PC,0} \text{ Magnitude of pulmonary capillary resistance} \\
R_{PS} \text{ Pulmonary shunt flow resistance} \\
R_{PV} \text{ Pulmonary venous flow resistance} \\
R_{RA} \text{ Right atrial flow resistance} \\
R_{S} \text{ Small airways resistance} \\
R_{SA} \text{ Resistance of systemic arteries} \\
R_{SA,D} \text{ Systemic arteriolar flow resistance} \\
R_{SC} \text{ Systemic capillary flow resistance} \\
R_{SV} \text{ Systemic venous flow resistance} \\
R_{TA_{0}} \text{ Viscoelastic resistance of proximal aorta wall} \\
R_{TA_{0},D} \text{ Viscoelastic resistance of distal aorta wall} \\
R_{TA} \text{ Tricuspid valve flow resistance} \\
R_{TPA} \text{ Pulmonary artery wall viscoelastic resistance} \\
R_{unw} \text{ Upper supported airway resistance} \\
R_{VC} \text{ Resistance of the vena cava}
Variables and measurements

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E_{ES})</td>
<td>End-systolic elastance</td>
</tr>
<tr>
<td>EDPVR</td>
<td>End-diastolic pressure-volume relationship</td>
</tr>
<tr>
<td>ESPVR</td>
<td>End-systolic pressure-volume relationship</td>
</tr>
<tr>
<td>FRC</td>
<td>Functional residual capacity</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>P-V</td>
<td>Pressure-volume (relationship)</td>
</tr>
<tr>
<td>s</td>
<td>Laplace variable</td>
</tr>
<tr>
<td>STPD</td>
<td>Standard temperature, pressure, dry weight</td>
</tr>
<tr>
<td>t</td>
<td>Time</td>
</tr>
<tr>
<td>TLC</td>
<td>Total lung capacity</td>
</tr>
<tr>
<td>(v_{j}^{z})</td>
<td>Blood flow velocity in the (j)th capillary</td>
</tr>
<tr>
<td>(z)</td>
<td>Length coordinate of the pulmonary capillary</td>
</tr>
</tbody>
</table>

Volumes

- \(V_0\): Unstressed volume
- \(V_A\): Alveolar volume
- \(V_{A,max}\): Maximal alveolar volume
- \(V_C\): Collapsible airway volume
- \(V_{CW}\): Chest wall volume
- \(V_D\): Systolic volume offset
- \(V_{ED}\): End-diastolic volume
- \(V_{ES}\): End-systolic volume
- \(V_{b,j}\): Blood volume contained in the \(j\)th capillary
- \(V_L\): Lung volume
- \(V_{LV}\): Left ventricular volume
- \(V_{max}\): Maximal volume
- \(V_{min}\): Minimum volume
- \(V_{PC}\): Blood volume of pulmonary capillaries
- \(V_{PC,max}\): Maximal blood volume of pulmonary capillaries
- \(V_{SA}\): Blood volume of systemic arteries
- \(V_{SA,0}\): Minimal volume of systemic arteries
- \(V_{SA,max}\): Maximal lumen volume of systemic arteries
- \(V_{SV}\): Luminal volume of systemic veins
- \(V_{VC}\): Luminal volume of the vena cava
- \(V_{VE}\): Viscoelastic volume

MODEL DEVELOPMENT

Ventricular Model

Our ventricular model is based on the work of Chung et al. (5), wherein each ventricular compartment is characterized by a time-varying elastance function (Tables 1–3). The elastance function is developed by three curves, as established in Ref. 5, namely, the end-systolic P-V relationship (ESPVR), the end-diastolic P-V relationship (EDPVR), and a time-varying activation function \(e(t)\). The activation function \(e(t)\) consists of a series of Gaussian curves and serves to produce a smooth transition between the EDPVR and the ESPVR. A detailed description of the ventricular model can be found in Ref. 5.

Circulatory Model

The general framework of our human circulatory loop model (Fig. 1 and Table 4) is similar to that of Olansen et al. (25) with certain extensions and modifications. We included 1) nonlinear P-V relationships to describe the peripheral venous system, 2) a nonlinear collapsible description of the P-V relationship for the vena cava, and 3) separate descriptions of baroreceptor-mediated control of heart rate, myocardial contractility, and vasomotor tone.

Nonlinear P-V Characteristics of Systemic Veins and the Vena Cava

Systemic veins. The nonlinear P-V relationship of veins has been modeled previously by Kresch (15) and by Snyder and Rideout (34). As volume increases, the vessels stiffen. The resulting P-V curve can be represented as follows

\[
P_{SV} = -K_s \times \log \left( \frac{V_{max}}{V_{SV}} - 0.99 \right)
\]

where \(P_{SV}\) and \(V_{SV}\) are the transmural pressure and luminal volume of systemic veins, \(K_s\) is a scaling factor (in mmHg), and \(V_{max}\) is the maximal volume (in ml) of the lumped systemic veins (Table 5).

Vena cava. Under some conditions, the vena cava may collapse. For example, when pleural pressure is greater than the luminal pressure of the vena cava, total caval volume decreases substantially, and the resistance to flow is increased. To account for this, we described the P-V relationship as follows

\[
\text{if } V_{VC} = V_0, \text{ then } P_{VC} = D_1 + 1 \times (V_{VC} - V_0) \\
\text{if } V_{VC} < V_0, \text{ then } P_{VC} = D_2 + K_2 \times \log(V_{VC} - V_0)
\]

where \(P_{VC}\) and \(V_{VC}\) denote the transmural pressure and luminal volume of the vena cava, respectively, \(V_0\) is the unstressed volume, and \(V_{min}\) is the minimum volume. We adjusted the parameters \(K_1, K_2, D_1, \text{ and } D_2\) to produce P-V curves similar to those used in the human venous model of Snyder and Rideout (34).

### Table 1. Parameter values of the ventricular model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>LVF</th>
<th>RVF</th>
<th>PCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E_{ES}), mmHg/ml</td>
<td>4.3</td>
<td>0.6</td>
<td>N/A</td>
</tr>
<tr>
<td>(P_0), mmHg</td>
<td>1.7</td>
<td>0.67</td>
<td>0.5</td>
</tr>
<tr>
<td>(V_0), ml</td>
<td>25</td>
<td>25</td>
<td>200</td>
</tr>
<tr>
<td>(V_{DP}), ml</td>
<td>40</td>
<td>40</td>
<td>N/A</td>
</tr>
<tr>
<td>(\lambda), ml⁻¹</td>
<td>0.015</td>
<td>0.015</td>
<td>0.005</td>
</tr>
</tbody>
</table>

For abbreviations, see Glossary and text.

### Table 2. Parameter values of the atrial model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>LA</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E_{ES}), mmHg/ml</td>
<td>0.2</td>
<td>2</td>
</tr>
<tr>
<td>(P_0), mmHg</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>(V_0), ml</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>(V_{D}), ml</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>(\lambda), ml⁻¹</td>
<td>0.025</td>
<td>0.025</td>
</tr>
</tbody>
</table>

For abbreviations, see Glossary and text.
The resistance of the vena cava ($R_{VC}$) is a nonlinear function of its luminal blood volume ($V_{VC}$) according to the following equation

$$R_{VC} = K_R \left( \frac{V_{max}}{V_{VC}} \right)^2 + R_0 \quad (4)$$

where $K_R$ is a scaling factor (in mmHg·s·ml$^{-1}$), $V_{max}$ denotes the maximum volume, and $R_0$ is an offset parameter (in mmHg·s·ml$^{-1}$) (Table 5).

### Arterial Baroreflex Control

Our previous study (25) did not consider baroreflex control of heart rate, myocardial contractility, and vasomotor tone. We have now included lumped characterizations of the baroreceptors and their reflex pathways in the present study, according to the general structure used by Wesseling et al. (38).

**Baroreceptors.** Figure 2 includes four functional blocks that represent the baroreceptor, the central nervous system (CNS), the efferent pathways, and the effector organ. The input to the baroreceptor element (BR) is central arterial pressure [aortic arch pressure ($P_{Ao}$)], and the output $[N(t)]$ is the instantaneous firing frequency of the BR. Following Spickler et al. (35), we characterized the input-output relationship in terms of the following transfer function

$$\frac{N(s)}{P_{Ao}(s)} = \frac{K \times (1 + 0.036s)}{(1 + 0.0018s)(1 + as)} \quad \text{where} \ a < 0.0018 \quad (5)$$

### Table 3. Parameter values for the activation function

<table>
<thead>
<tr>
<th>Parameters</th>
<th>$\varepsilon_i(t)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_i$</td>
<td>$i = 1$ 0.3, $i = 2$ 0.35, $i = 3$ 0.5, $i = 4$ 0.55, 0.9</td>
</tr>
<tr>
<td>$B_i$, s$^2$</td>
<td>0.045, 0.035, 0.037, 0.036, 0.018</td>
</tr>
<tr>
<td>$C_i$, s</td>
<td>0.175, 0.23, 0.275, 0.3, 0.025</td>
</tr>
</tbody>
</table>

Parameter $A_i$ is dimensionless. For abbreviations, see Glossary and text.

### Table 4. Nominal parameter values in the systemic and pulmonary circulations

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{Ao,D}$</td>
<td>0.015</td>
</tr>
<tr>
<td>$R_{Ao,P}$</td>
<td>0.005</td>
</tr>
<tr>
<td>$R_{COR}$</td>
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<tr>
<td>$R_{CRB}$</td>
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<tr>
<td>$R_{LA}$</td>
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<tr>
<td>$R_{LM}$</td>
<td>0.008</td>
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<tr>
<td>$R_{PA}$</td>
<td>0.005</td>
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<tr>
<td>$R_{PA,D}$</td>
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</tr>
<tr>
<td>$R_{PA,P}$</td>
<td>0.002</td>
</tr>
<tr>
<td>$R_{PC}$</td>
<td>0.008</td>
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<tr>
<td>$R_{PS}$</td>
<td>4.5</td>
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<tr>
<td>$R_{PV}$</td>
<td>0.008</td>
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<tr>
<td>$R_{RA}$</td>
<td>0.05</td>
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<tr>
<td>$R_{SA,D}$</td>
<td>0.8</td>
</tr>
<tr>
<td>$R_{SC}$</td>
<td>0.6</td>
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<tr>
<td>$R_{SV}$</td>
<td>0.17</td>
</tr>
<tr>
<td>$R_{TAo}$</td>
<td>0.06</td>
</tr>
<tr>
<td>$R_{TAo,D}$</td>
<td>0.0125</td>
</tr>
<tr>
<td>$R_{TC}$</td>
<td>0.015</td>
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<tr>
<td>$R_{TPA}$</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Compliances, ml/mmHg**
- $C_{Ao,D}$ 0.2
- $C_{Ao,P}$ 1.6
- $C_{PA}$ 0.5
- $C_{PA,D}$ 0.05
- $C_{PA,P}$ 0.8
- $C_{PC}$ 1.0
- $C_{PV}$ 4.0
- $C_{SA,D}$ 0.069
- $C_{SC}$ 0.2

**Inertances, mmHg·s$^2$·ml$^{-1}$**
- $L_{Ao,D}$ 0.0017
- $L_{Ao,P}$ 0.01226
- $L_{PA}$ 0.00018

For abbreviations, see Glossary and text.

**Fig. 1.** A hydraulic equivalent representation of the closed-loop circulatory model. For abbreviations, see Glossary.
The corresponding differential equation is as follows

\[ 0.0018 a \frac{d^2 N}{dt^2} + (0.0018 + a) \frac{dN}{dt} + N(t) = K \left[ P_{Ao}(t) + 0.036K \frac{dP_{Ao}(t)}{dt} \right] \tag{6} \]

where \( K \) is the gain and \( a \) is a time constant \([35]\).

Central nervous system. The medullary cardiovascular control center is modeled in terms of four noninteracting pathways, each characterized by filtering, gain, and a delay as per the modeling concept of Wessling et al. \([38]\). One vagal (fast) and one sympathetic (slow) pathway each controls heart rate, whereas two other sympathetic pathways control myocardial contractility and vasomotor tone. The fast vagal pathway has a 0.2-s delay, whereas each sympathetic pathway has a 3-s delay.

Efferent pathways. We described each efferent pathway according to the following generic equation in normalized form (Table 6)

\[ F_x(t) = a_x + \frac{b_x}{e^{v[N(x(t)) - N_{c,x}] + 1}} \tag{7} \]

The generic parameter \( x \) represents heart rate, contractility, or vasomotor tone. The parameters \( \tau_x \) and \( N_{c,x} \) were fitted to the representative data. This equation provides a sigmoidal input-output relationship (threshold and saturation) between central neuron activity (output of central delay box) and the discharge frequency of the particular motor neuron \((6, 11, 22, 29, 35)\).

Because increases in BR firing frequency increase vagal discharge frequency, \( \tau_x \) in the vagal efferent pathway is negative, producing a monotonically increasing input-output relationship for the linear part of the curve (Fig. 2). Sympathetic pathways use positive \( \tau_x \) values, because BR and sympathetic discharge frequencies change in opposite directions. Figure 2 shows that the discharge frequency \( F_x(t) \) of each efferent pathway inputs to the final block of the diagram, which contains characterization of the input-output response of the effector organ itself (the heart or vessel).

Effectors organs. Heart rate is controlled by vagal and sympathetic neural activity and has been characterized by Sunagawa as a three-dimensional response surface \([36]\). We developed the following equation to characterize the human heart rate response surface to vagal and sympathetic input (Table 7)

\[ \text{HR} = h_1 + h_2 \times F_{HR,S} - h_3 \times F_{HR,V} - h_4 \times F_{HR,V} + h_5 \times F_{HR,V} - h_6 \times F_{HR,V} \times F_{HR,S} \tag{8} \]

where \( \text{HR} \) (in beats/min) represents heart rate, \( F_{HR,V} \) and \( F_{HR,S} \) are the normalized vagal and sympathetic frequencies, and \( h_1 \)–\( h_6 \) are constants. This formula generates a normalized heart rate response surface analogous to that of Sunagawa et al. \([36]\).

For abbreviations, see Glossary and text.

Table 5. Parameter values for nonlinear P-V curves of systemic veins and the vena cava

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic Veins</strong></td>
<td></td>
</tr>
<tr>
<td>( K_v ), mmHg</td>
<td>40</td>
</tr>
<tr>
<td>( V_{max} ), ml</td>
<td>3,500</td>
</tr>
<tr>
<td><strong>Vena Cava</strong></td>
<td></td>
</tr>
<tr>
<td>( D_1 ), mmHg</td>
<td>0.0</td>
</tr>
<tr>
<td>( D_2 ), mmHg</td>
<td>-5.0</td>
</tr>
<tr>
<td>( K_1 ), mmHg</td>
<td>0.15</td>
</tr>
<tr>
<td>( K_2 ), mmHg</td>
<td>0.4</td>
</tr>
<tr>
<td>( K_R ), mmHg( \cdot )ml(^{-1} )</td>
<td>0.001</td>
</tr>
<tr>
<td>( R_0 ), mmHg( \cdot )ml(^{-1} )</td>
<td>0.025</td>
</tr>
<tr>
<td>( V_0 ), ml</td>
<td>130</td>
</tr>
<tr>
<td>( V_{max} ), ml</td>
<td>350</td>
</tr>
<tr>
<td>( V_{min} ), ml</td>
<td>50</td>
</tr>
</tbody>
</table>

Fig. 2. Block diagram of baroreflex control of arterial pressure. A fast vagal (dashed arrow) pathway and 3 slow sympathetic pathways are included to control heart rate, myocardial contractility, and vasomotor tone. The overall control scheme is based on the modeling concept of Wesseling et al. \([38]\). For abbreviations, see text.
Table 6. Parameter values for the baroreflex pathway

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Vagal</th>
<th>Heart rate</th>
<th>Contractility</th>
<th>Vasomotor tone</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a_x)</td>
<td>0</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>(b_x)</td>
<td>1.0</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>(N_{x,0}), Hz</td>
<td>110</td>
<td>100</td>
<td>110</td>
<td>110</td>
</tr>
<tr>
<td>(\tau_x), s</td>
<td>-0.04</td>
<td>0.09</td>
<td>0.04</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Parameters \(a_x\) and \(b_x\) are dimensionless. For abbreviations, see Glossary and text.

In our study, the heart period (calculated as 60/HR, in s) is explicitly determined by the vagal-sympathetic mechanism according to Eq. 8, and the systolic period is mediated by the sympathetic frequency (Fig. 3). The diastolic filling time is the difference between the two and is thus controlled indirectly.

Greater sympathetic tone increases myocardial elastance and shortens ventricular systole. Therefore, we modified the ventricular activation function to describe the change in ventricular elastance \(e(t)\) as a function of sympathetic efferent discharge frequency \((F_{con})\) (see Fig. 3).

A rise in \(F_{con}\) increases maximum elastance and shortens the systolic period. The expression for the end-systolic P-V relationship \(P_{ES}(V)\) becomes (notation from Ref. 25 and Table 1)

\[
P_{ES}(V) = a(F_{con}) \times E_{ES} \times (V - V_D) \tag{9}
\]

and the activation function \(e(t,F_{con})\) becomes

\[
e(t,F_{con}) = \sum_{i=1}^{n} A_i e^{-\frac{1}{2} \left( \frac{b(F_{con})}{a(F_{con})} \right)^2} \tag{10}
\]

where

\[
a(F_{con}) = a_{min} + K_a \times F_{con} \tag{11}
\]

\[
b(F_{con}) = b_{min} + K_b \times F_{con} \tag{12}
\]

Here, \(a_{min}\) and \(b_{min}\) are dimensionless constants representing the minimum values of the functions \(a\) and \(b\), respectively, and \(K_a\) and \(K_b\) are scaling parameters.

Arteries and arterioles are the major resistance vessels. When their smooth muscle contracts, lumen diameter decreases, axial resistance to flow increases, and the muscle wall stiffens. Therefore, a change in vasomotor tone involves a change in both axial resistance and in wall compliance. We transformed the passive and fully activated length-tension relationships previously described by Gore and Davis (10) into an equivalent P-V relationship for a cylindrical vessel. Figure 4 shows the passive and fully activated P-V curves used in our model, which are represented as follows. Fully activated

\[
P_{SA}^a(V_{SA}) = K_e \times \log \left( \frac{V_{SA} - V_{SA,0}}{D_0} + 1 \right) \tag{13}
\]

and passive

\[
P_{SA}^p(V_{SA}) = K_{p1} \times e^{e\tau_p/(V_{SA} - V_{SA,0})} + K_{p2} \times (V_{SA} - V_{SA,0})^2 \tag{14}
\]

where \(P_{SA}^a\) and \(P_{SA}^p\) represent the arterial pressures in the fully activated and passive states, respectively, \(V_{SA}\) is the blood volume contained in systemic arteries, and \(V_{SA,0}\) (in ml) is the minimal volume. We assume \(V_{SA} \approx V_{SA,0}\) in Eqs. 13 and 14. \(K_e\), \(K_{p1}\), and \(K_{p2}\) (in mmHg) are constant scaling parameters, \(D_0\) (in ml) is a volume parameter, and \(\tau_p\) (in \(s^{-1}\)) is constant. During sympathetic stimulation, the compliance of the vessel is characterized by Eq. 13; when the sympathetic tone is abolished, the compliance of vessel wall is described by Eq. 14. The normalized sympathetic efferent frequency \((F_{vaso})\) serves as a scaling factor for the transition between these states

\[
P_{SA}(V_{SA}) = P_{vaso}^a \times P_{SA}^a(V_{SA}) + (1 - F_{vaso}) \times P_{SA}^p(V_{SA}) \tag{15}
\]

Axial resistance is also affected by sympathetic activity. Resistance \((R_{SA}\); in mmHg·s·ml\(^{-1}\)) and sympathetic efferent frequency \((F_{vaso})\) are related by

\[
R_{SA} = K_s \times e^{4 \times F_{vaso}} + K_s \times \left( \frac{V_{SA,max}}{V_{SA}} \right)^2 \tag{16}
\]

The first term is regulated by the sympathetic frequency and the second term is a function of lumen volume \((V_{SA})\). \(V_{SA,max}\)

![Fig. 3. Model representation of the sympathetically regulated activation function e(t). Four different levels of contractility corresponding to different sympathetic efferent frequencies (F_con) are shown.](image-url)
is the maximal lumen volume and $K_r$ (in mmHg) is a pressure scaling constant.

### Airway/Lung Mechanics Model

The pulmonary portion of our cardiopulmonary model combines two models previously developed. One focuses on airway/lung mechanics (2) and the other focuses on gas exchange (18). Figure 5 shows an equivalent pneumatic circuit model of the airways and lung of the normal human. The lung mechanics model (2) includes nonlinear characterizations of airway resistance, airway and chest wall compliance, and lung tissue viscoelasticity. This particular model (2) has also been used in a related context to analyze the “work of breathing” during clinical breathing maneuvers [see Athanasiades et al. (2) for details].

In the supine human, the lungs and their airways are subject to the same time-varying intrathoracic pleural pressure ($P_{PL}$). Figure 5 indicates that this pressure is generated by the respiratory muscles ($P_{mus}$) and the recoil pressure of the chest wall ($P_{CW}$). Measured $P_{PL}$ is also the driving pressure for our airway mechanics model. The upper airway is assumed rigid and is characterized by a nonlinear flow-dependent resistor (Rohrer resistor). The midairways are assumed collapsible and are characterized by a nonlinear volume-dependent resistance [$R_C(V_C)$] and a nonlinear P-V relationship [$P_{TM}(V_C)$], where $V_C$ is the collapsible segment volume (Fig. 5). Pressure in the lumen of the midairway segment of the model is denoted as $P_C$, and the transmural pressure across the wall is denoted as $P_{TM}$. $P_A$ is the alveolar pressure and $P_{EL}$ is the lung elastic recoil pressure. Small airways resistance ($R_S$) is characterized as a nonlinear function of the alveolar volume ($V_A$).

From an analysis of the pneumatic circuit according to Newton’s first law

\[ P_A = P_{EL} + R_u V_A + P_{PL} \]  

\[ P_C = P_{TM} + P_{PL} \]  

\[ P_{PL} = P_{CW} + P_{mus} \]  

The component air flows (in ml/s) in the airway system are computed according to the equations below, which are derived from the continuity equation applied to each node of the pneumatic network. The resulting differential equations are as follows

\[ Q_{CA} = \frac{P_C - P_A}{R_S} \]  

\[ Q_{DC} = \frac{P_D - P_C}{R_C} \]  

\[ Q_{CA} = \frac{P_{atm} - P_D}{R_{uaw}} = Q_{ED} \]

As such, the rate of the volume changes in the airway may be written as follows

\[ V_C = Q_{DC} - Q_{CA} \]  

\[ V_A = Q_{CA} - \Phi_{tot} \]

where $\Phi_{tot}$ denotes the total gas flux rate (in ml/s) of all gaseous species across the alveolar-capillary membrane, as given by Eq. 31.

---

**Fig. 4.** Active and passive P-V curves of systemic arteries. $P_{SA}$ and $V_{SA}$ represent the pressure and volume in the systemic arteries. $F_{vaso}$ is the normalized sympathetic discharge frequency controlling the vasomotor tone.

**Fig. 5.** Airway/lung mechanics model. A: components of airway mechanics, pulmonary circulation, and gas exchange. B: equivalent pneumatic circuit representation of airway/lung mechanics and gas exchange [modified from Athanasiades et al. (2)]. For abbreviations, see Glossary and text.
Gas Exchange Model

Gas exchange between air and blood occurs across the alveolar-capillary membrane. For modeling purposes, we assumed 1) inspired air is instantly warmed to body temperature and saturated with water vapor, 2) gaseous content obeys the ideal gas law, 3) blood is characterized as a uniform homogeneous medium, and 4) reactions between the gaseous species and blood are assumed to equilibrate instantaneously. The empirical $O_2$ and $CO_2$ dissociation curves relate the content of each species with their corresponding partial pressures in blood. The diffusing capacity for the $i$th gaseous species ($D_{li}$) characterizes its diffusion across the alveolar-capillary membrane. $O_2$ is taken up by the blood, $CO_2$ is removed, and $N_2$ diffuses either way depending on the direction and saturated with water vapor,

2
1
2
1

2
1
2
1

where $V_{PC,max}$ is the maximal blood volume in the pulmonary capillaries.

Cardiopulmonary Interactions

Any combined cardiovascular and pulmonary model must account for interactions that can occur between these systems. These interactions take a variety of forms and frequently are quite subtle. In general, to test for system interaction, a variable in one system is perturbed and the effects on both systems are assessed. We accomplished this by using only perturbations in pleural pressure ($P_{Pl}$). The following sections provide simple examples of this coupled interaction.

How $P_{Pl}$ mediates cardiac and vascular mechanics. $P_{Pl}$ affects both intracardiac pressures and the pressures within the large intrathoracic vessels, but alveolar pressure has the greatest effect on pulmonary capillaries (18, 23). Consequently, in our model, the capillary transmural pressure is mediated by the alveolar pressure, whereas the pressures of the pulmonary arteries and veins are changed by $P_{Pl}$.

How lung air volume changes lung perfusion. The pulmonary capillary bed forms an extensive network of vessels, which surround the alveolar region. During lung inflation, these vessels are stretched and constricted by the expanding alveolar volume. This increases capillary resistance and reduces blood flow, thus facilitating gas exchange. The relationship we used to describe the capillary resistance ($R_{PC}$) changes with alveolar volume ($V_A$) is as follows

$$R_{PC}(V_A) = R_{PC,0} \left( \frac{V_A}{V_{A,max}} \right)^2$$

Here, $R_{PC,0}$ is a constant chosen to set the magnitude of capillary resistance and $V_{A,max}$ represents the maximum alveolar volume.

COMPUTATIONAL ASPECTS

To summarize, we modified and combined previous cardiac and pulmonary models developed by our group to form a cardiopulmonary model of the normal human (Tables 8–10). The pulmonary models employed (2, 18) were originally developed as human models and were verified using data obtained from normal human subjects. However, the cardiovascular model used as a basis for designing our human circulatory model (25) was validated using data from the dog. To develop the human model, we first scaled up our canine model to

\[
\frac{\partial C_i}{\partial t} = -\frac{\partial P_i C_i}{\partial z} + \frac{D_{li} [P_A - P_{li}]}{V_{PC}}
\]
provide an initial model of the normal human cardiovascular system. This has been done by others (see, e.g., Ref. 17). Because human and canine blood pressures and blood velocities are similar, scaling factors are related closely to the ratios of blood volume. (Blood volume is directly related to body weight and body surface area.) In a second phase, we manually adjusted the parameters of the initial human circulatory model to yield a reasonable fit to typical human pressure data and hemodynamic indexes available in the literature.

First, we determined that the cardiac output of a 70-kg human is 2.5 times that of a 25-kg dog. Because the mean systemic arterial pressures in the human and dog are similar, we calculated a set of human cardiovascular parameters by decreasing all the resistive and inertial parameters of the canine model by 2.5 and by similarly increasing the compliant parameters. This scaling provided a reasonable initial representation of the human cardiovascular system, although additional adjustments were necessary for better regional representations of typical hemodynamic waveforms.

The representations used for certain elements of the canine and human circulatory models were different. Specifically, the linear representations of venous compliance in the canine model were replaced by nonlinear P-V relationships in the human model. Nonlinear active and passive P-V curves were also incorporated to describe arterial compliance.

The structure of the human circulatory model also differs in that several parallel circulation pathways were added. In the pulmonary circulation, the average pulmonary shunt flow is 2% of the pulmonary blood flow, whereas in the systemic circulation, the mean coronary and cerebral flows are set to 6% and 14%, respectively, of the cardiac output. The nominal distribution of blood volume in the pulmonic and systemic circulations are set at a level of 8.8% and 84%, respectively. The remaining 7.2% of the blood is contained in the heart. These figures agree with the results shown in Ref. 24 (p. 30 and 124).

We approximated the first-order spatial derivative in Eq. 32 using a four-point biased quadratic interpolation formula (31) and eliminated fictitious points at the entrance of the capillary bed using constant inlet conditions (i.e., partial pressures of 40 mmHg for O2 and 46 mmHg for CO2).

The PPL data reported previously by Liu et al. (18) were used to directly drive the pulmonary model. Therefore, the respiratory frequency was determined directly from the experimental data. The model begins at end expiration, when there is no flow and air volume in the lung equals the functional residual capacity (FRC), which is set to the typical value of 2,200 ml.

The combined model has 77 nonlinear differential equations and 116 parameters associated with its component models. In all, 149 outputs were generated simultaneously. Table 11 shows the distribution of the state variables and model parameters in the combined cardiopulmonary model.

The model was programmed in C programming language and solved using the variable step-size Runge-Kutta-Merson algorithm, with a maximum time step size of $2 \times 10^{-2}$ s and an error tolerance of $1 \times 10^{-6}$. On average, it takes 20 min of CPU time on a Pentium

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Pressure, mmHg</th>
<th>Volume, ml</th>
<th>Flow, ml/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td>90</td>
<td></td>
<td></td>
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<tr>
<td>LV</td>
<td>130</td>
<td></td>
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</tr>
<tr>
<td>PCD</td>
<td>440</td>
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<td></td>
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<td>RA</td>
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<td>RV</td>
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<td>75.3</td>
</tr>
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<td>174</td>
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<tr>
<td>SC</td>
<td>18.6</td>
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<tr>
<td>SV</td>
<td>6.4</td>
<td>3,000</td>
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<td>VC</td>
<td>6.3</td>
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<tr>
<td>Pulmonary Circulation</td>
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<td>PA</td>
<td>15.6</td>
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<tr>
<td>PAD</td>
<td>16.3</td>
<td>35</td>
<td>67.5</td>
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<tr>
<td>PAO</td>
<td>17.6</td>
<td>18</td>
<td>67.5</td>
</tr>
<tr>
<td>PC</td>
<td>14.2</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>PV</td>
<td>12.3</td>
<td>200</td>
<td></td>
</tr>
</tbody>
</table>

For abbreviations, see Glossary and text.
II 333-MHz machine to simulate 35 s of cardiopulmonary events.

**Simulation Results**

**Hemodynamics.** Figure 6 compares a model-generated and human systemic pressure waveform (Fig. 22.15 in Ref. 20). The left ventricular end-systolic pressure is 125 mmHg and the systolic duration is 0.3 s, or about one-third of the cardiac cycle (0.8 s). The aortic root pressure ranges from 80 to 120 mmHg. The diastolic notch can be clearly seen in both the simulation and the data.

Figure 7 compares experimental data to the model-generated left ventricular volume and aortic and pulmonary arterial flow waveforms (Fig. 6-1 in Ref. 24). The left ventricular volume ranged from 150 ml [end-diastolic volume (VED)] to 70 ml [end-systolic volume (VES)], giving a stroke volume of 80 ml and an ejection fraction of 80/150, or 0.533. The volume added as the result of atrial systole ($D_V$) was 30 ml, 20% of the VED. The peak aortic flow rate was 750 ml/s and the peak pulmonary arterial flow rate was 400–500 ml/s. The aortic flow rate has a higher peak value and shorter time span compared with the pulmonic flow rate because of the stronger contractile force and higher afterload of the left ventricle. Numerical integration of the aortic and pulmonic flow waveforms over one cycle showed that the mean values of the area enclosed by the two waveforms were the same, although during individual cardiac cycles they may be different from each other due to variations of intrathoracic pressure.

Table 12 compares indexes of the model-predicted and measured data. Our model predicts that at peak inspiration, the stroke volume of the left heart decreases, whereas the stroke volume of the right heart increases. At peak expiration, the opposite occurs. These changes agreed well with measured data (4, 9, 13, 26, 28). Our model helps explain the mechanism underlying this physiological relationship.

Right and left ventricular volumes respond to $P_{PL}$ because of both direct and series ventricular interaction. When $P_{PL}$ are negative (e.g., with inspiration), an increase in venous return augments right ventricular filling and stroke volume. The increased right ventricular filling causes the septum to encroach upon the left ventricle, because the pericardium limits total cardiac volume. As a result, left ventricular stroke volume is reduced. Simulations that ignore this ventricular interaction (rigid septum) underestimate the percent fall in left ventricular stroke volume occurring during inspiration (2.5% vs. 5% with ventricular interaction). Without pericardial constraint, there is little respiratory variation in left ventricular stroke volume (1%).

Expiration causes a volume shift from the pulmonary to the systemic circulation. The blood pooling in the systemic vascular bed then increases left ventricular afterload with the next inspiration. Simulations show that both the end-systolic transmural pressure and volume of the left ventricle are highest at early inspiration, consistent with increased afterload (27, 30, 32). During inspiration, both decreased filling and increased afterload decrease left ventricular stroke volume. The same mechanism explains why the left and right ventricles respond differently to elevated $P_{PL}$ during expiration.

**Airway Mechanics and Gas Exchange**

Figure 8 depicts the airway pressures and lung volumes predicted by our model. During inspiration, subatmospheric $P_{PL}$ is transmitted to the alveoli, facilitating air flow into the lungs. As this occurs, lung elastic recoil increases and the alveolar and atmospheric pressures equalize, marking the end of inspiration and the start of expiration. During expiration, the less negative $P_{PL}$ and the resulting changes in lung elastic recoil cause positive alveolar pressure, pushing air from the

Table 11. Distribution of state variables, parameters, and outputs in the combined human cardiopulmonary model

<table>
<thead>
<tr>
<th></th>
<th>Number of State Variables</th>
<th>Number of Parameters</th>
<th>Number of Outputs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular system</td>
<td>32</td>
<td>52</td>
<td>76</td>
</tr>
<tr>
<td>Airway mechanics</td>
<td>4</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Gas exchange</td>
<td>36</td>
<td>24</td>
<td>50</td>
</tr>
<tr>
<td>Baroreflex control</td>
<td>5</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
<td>116</td>
<td>149</td>
</tr>
</tbody>
</table>

Fig. 6. Model-predicted systemic pressure waveforms (A) compared with the textbook figure [McClintic (20); B] showing left ventricular pressure ($P_{LV}$), aortic root pressure ($P_{Ao}$), and left atrial pressure ($P_{LA}$).
lungs. The inspiratory and expiratory changes in lung volume are depicted in Fig. 8B. Here, total lung volume is the sum of the air volumes contained in the alveoli, collapsible airways, and dead space. The model predicts an average tidal volume of 500 ml and a functional residual capacity (FRC) of 2.2 l, which agreed with measured values.

Inspiration fills the alveoli with O₂-enriched air, whereas expiration removes CO₂. Figure 9 depicts the model-generated variation in airway gas composition in terms of changes in the partial pressures of O₂ and CO₂ (PO₂ and PCO₂, respectively). Alveolar PO₂ and PCO₂ are relatively constant. Alveolar PO₂ varies from 95 to 105 mmHg, and alveolar PCO₂ varies from 35 to 40 mmHg. With inspiration, PO₂ in the upper airways (dead space) rises sharply, whereas PCO₂ drops sharply. However, not all inhaled air enters the alveoli, and inhaled and residual air mix, making variations in alveolar PO₂ and PCO₂ much smaller than those in the dead space. Expiration lowers the PO₂ and raises the PCO₂ in the dead space, whereas gases continuously diffuse across the alveolar-capillary membrane.

Table 12. Comparison of hemodynamic indexes drawn from model-predicted and measured data

<table>
<thead>
<tr>
<th>Hemodynamic Variables</th>
<th>Model-Predicted Data</th>
<th>Measured Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic root pressure, mmHg</td>
<td>80–125</td>
<td>80–120</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>53.3</td>
<td>56.7</td>
</tr>
<tr>
<td>LV end-diastolic volume, ml</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>LV end-systolic pressure, mmHg</td>
<td>125</td>
<td>120</td>
</tr>
<tr>
<td>LV end-systolic volume, ml</td>
<td>70</td>
<td>65</td>
</tr>
<tr>
<td>Peak aortic flow, ml/s</td>
<td>780</td>
<td>720</td>
</tr>
<tr>
<td>Peak pulmonary arterial flow, ml/s</td>
<td>500</td>
<td>450</td>
</tr>
</tbody>
</table>

Measured data values are from McClintic (20) and Mountcastle (24).
sequently, alveolar $P_{O_2}$ decreases and alveolar $P_{CO_2}$ increases.

*Alveolar capillary gas exchange.* Figure 10 depicts the flux of $O_2$ and $CO_2$ at the alveolar-capillary membrane, which is modeled as 35 contiguous segments. For each segment, there is a gaseous flux waveform that pulsates with capillary blood flow. Most gaseous diffusion occurs at the initial capillary segments but later diminishes when blood and alveolar gas content has equilibrated. Thus, the flux rates decrease exponentially from the first (entrance) to the last segment (exit). We tested our model against the known changes that occur during the FVC and Valsalva maneuvers.

**Forced Vital Capacity Maneuver**

The FVC maneuver is a commonly used pulmonary function test. The subject fully exhales and then inhales to total lung capacity (TLC) without pausing. Immediately, the subject exhales as rapidly as possible, until airflow is no longer detected at the mouth. We applied the measured FVC $P_{PL}$ data reported in Ref. 18 to our model.

Figure 11 compares the model predictions to data measured from a human. During the rapid inspiration phase, lung volume increased to full capacity (Fig. 11A) and $P_{PL}$ decreased (Fig. 11B). At the beginning of forced expiration, $P_{PL}$ increases sharply, and lung volume decreased until it reached residual volume. The predicted and measured data correlated nicely.

During the FVC maneuver, the expired $P_{O_2}$ decreased constantly and reached a minimum value of 118 mmHg. In contrast, $P_{CO_2}$ increased steadily until its maximum value of 38 mmHg. Figure 12 compares the predicted temporal profile of $P_{O_2}$ and $P_{CO_2}$ in expired air with data from Liu et al. (18). Again, the model prediction agreed well with the measured data.

Hemodynamic changes are seldom recorded during the FVC maneuver, but our model can predict them. Figure 13 shows the predicted change in left and right heart stroke volumes. As in normal respiration, the left
and right ventricles showed opposite responses during inspiration and the early part of the forced expiration. However, after a few beats into the prolonged second phase of forced expiration, the stroke volumes of both ventricles decreased quickly and then returned to baseline after an overshoot (Fig. 13). Stroke volume decreases because elevated PPL decreases venous return. The recovery and the overshoot may be caused by neural factors (discussed below).

Figure 14 demonstrates a similar recovery and overshoot in the systemic arterial pressure waveform (A) and the temporal variations in heart rate (B), vagal discharge (C), and sympathetic discharge (D). Heart rate increases slowly during the maneuver. Vagal efferent activity slows, and a burst of sympathetic activity occurs later. These findings are consistent with the faster and slower activity of the vagal and sympathetic pathways, respectively. The decreasing vagal and increasing sympathetic outputs correlated with the observed increases in heart rate, myocardial contractility, and vasomotor tone and explained the partial recovery of arterial blood pressure that occurs during and shortly after the maneuver.

Valsalva Maneuver

During the Valsalva maneuver, the subject forcefully exhales against a closed glottis (or nose and mouth). The maneuver markedly elevates intrathoracic pressure and affects venous return, myocardial contractility, vasomotor tone, and baroreflex heart rate control. It is a widely used test of baroreceptor reflexes (6).

The hemodynamic response to the Valsalva maneuver has four distinct phases: phase 1 (an initial increase in arterial pressure), phase 2 (a rapid fall in arterial pressure, followed by a partial recovery and tachycardia), phase 3 (a reduction in arterial pressure upon the sudden termination of breath holding, accompanied by a continued tachycardia), and phase 4 (an
overshoot in arterial pressure accompanied by a slowing of heart rate).

In our model, we simulated the Valsalva maneuver by elevating PPL to a higher value for 15 s, starting at the end of both inspiration and diastole. PPL of 10, 20, 30, and 40 mmHg were used in the simulation to represent different levels of expiratory effort. Airflow in the airways was set to zero during the maneuver to simulate the closed glottis.

Figure 15 compares the model-generated changes in arterial pressure and heart rate when PPL is 40mmHg during the Valsalva maneuver with the experimental data from Bannister (33). The predicted increase in arterial pressure during phase 1 (120% of baseline), recovery of the arterial pressure during phase 2, and overshoot during phase 4 (20% above baseline) fitted well with the measured data, as did the predicted heart rate changes. Heart rate peaked at 110 beats/min and dropped to 62 beats/min after the maneuver. However, the predicted heart rate changes before and after the maneuver were much smoother than the measured data. This may be because an idealized square PPL waveform was used in the Valsalva maneuver simulation. In reality, PPL recordings show fluctuations before and after the maneuver.

Figure 16 shows heart rate, cardiac output, and mean arterial pressure as a function of PPL during the Valsalva maneuver. Experimental data from Korner et al. (14) were superimposed on the plot. Both heart rate and mean arterial pressure increased nearly linearly as PPL increased. Because of reduced venous return, cardiac output declined with the increase in PPL.

Table 13 shows that a variety of calculated hemodynamic indices evaluated from the model predictions during the Valsalva maneuver agreed well with those obtained from humans [Fox et al. (8)].

Baroreflex control during the Valsalva maneuver. The Valsalva maneuver changes autonomic tone, central nervous system activity, arterial blood pressure, and heart rate. Figure 17 illustrates how heart rate, myocardial contractility, and vasomotor tone responded to baroreflex control during each phase of the Valsalva maneuver.

Phase 1 elevation of arterial pressure occurs without baroreflex control, suggesting that the elevation is due only to the mechanical forces of increased intrathoracic pressure (6), which compresses the heart chambers and augments output to the periphery.

Phase 1 lasts about one to two heartbeats. As venous return is reduced by the elevated intrathoracic pressure, diastolic filling and stroke volume decrease. Therefore, in phase 2, blood pressure decreases and heart rate increases, with baroreflexes helping maintain arterial pressure and cardiac output. Simulations demonstrate the importance of baroreflex control.
When baroreflex control was abolished (Fig. 17A), arterial pressure dropped during this phase. When the sympathetic vasomotor tone was added (Fig. 17B), the reduction in arterial pressure leveled off after five to six beats, and arterial pressure stabilized. When myocardial contractility was added (Fig. 17C), a slow and gradual recovery of arterial pressure toward baseline occurred after six beats. The delay corresponded to the late increase in sympathetic efferent traffic (Fig. 18C), which constricts arterial resistive vessels and augments myocardial contractility. When baroreflex control of heart rate was included (Fig. 17D), heart rate increased. These simulations demonstrate the importance of baroreflex control during phase 2 of the Valsalva maneuver.

During phase 3, the model predicts a fall in arterial pressure without baroreflex input (Fig. 17A). The decrease in intrathoracic pressure decreased intracardiac pressure and stroke volume. Heart rates remained high due to the increased sympathetic tone (Fig. 18C).

During phase 4, venous return became normal. However, the delayed sympathetic response maintained the heightened myocardial contractility, tachycardia, and vasoconstriction. With no baroreflex control (Fig. 17A), arterial pressure slowly returned to baseline. With vasoconstriction (Fig. 17B), there was a small overshoot in arterial pressure even though arterial pressure returned to normal. This overshoot was more prominent (120% of the baseline level) when baroreflex control of myocardial contractility was added (Fig. 17C). Adding heart rate control (Fig. 17D) augmented this overshoot to a lesser degree.

The variations of vagal and sympathetic discharge frequencies during the maneuver are shown in Fig. 18. During phase 2, vagal discharges diminished and sympathetic discharges increased. The increase in sympathetic tone occurred after vagal tone decreased. Immediately after the release of the strain, vagal discharge frequency quickly returned toward control, whereas the elevated sympathetic tone continued into the late part of phase 4.

Figure 19 summarizes how the individual baroreflex pathways maintain arterial pressure. In phase 2, vasoconstriction prevented arterial pressure from dropping at a constant rate, whereas increased myocardial contractility and tachycardia helped restore arterial pressure and cardiac output. Continued increases in myocardial contractility and vasomotor control contrib-

Fig. 16. Relationships between $P_{PL}$ and heart rate (A), cardiac output (B), and mean arterial pressure (C) during the Valsalva maneuver. [Data source: Korner et al. (14).]
Table 13. Summary of model-predicted changes in hemodynamic indexes during the Valsalva maneuver

<table>
<thead>
<tr>
<th></th>
<th>Model-Predicted Data</th>
<th>Measured Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Output</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control, l/min</td>
<td>5.0</td>
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<tr>
<td>Phase 1, %Control</td>
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<td>97</td>
</tr>
<tr>
<td>Phase 2, %Control</td>
<td>45</td>
<td>39</td>
</tr>
<tr>
<td>Phase 3, %Control</td>
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<td>36</td>
</tr>
<tr>
<td>Phase 4, %Control</td>
<td>120</td>
<td>107</td>
</tr>
<tr>
<td><strong>Heart Rate, beats/min</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>68</td>
<td>72</td>
</tr>
<tr>
<td>Phase 1</td>
<td>66</td>
<td>65</td>
</tr>
<tr>
<td>Phase 2</td>
<td>105</td>
<td>97</td>
</tr>
<tr>
<td>Phase 3</td>
<td>107</td>
<td>105</td>
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<td>Phase 4</td>
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<td>57</td>
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<tr>
<td><strong>Pulmonary Arterial Pressure, mmHg</strong></td>
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<td></td>
</tr>
<tr>
<td>Control</td>
<td>30/5</td>
<td>23/12</td>
</tr>
<tr>
<td>Phase 1</td>
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<tr>
<td>Phase 2</td>
<td>55/43</td>
<td>50/44</td>
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<tr>
<td>Phase 3</td>
<td>19/2</td>
<td>22/11</td>
</tr>
<tr>
<td>Phase 4</td>
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<td>28/15</td>
</tr>
<tr>
<td><strong>Systemic Arterial Pressure, mmHg</strong></td>
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<td></td>
</tr>
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<td>143/88</td>
</tr>
<tr>
<td>Phase 1</td>
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<td>90/60</td>
<td>97/73</td>
</tr>
<tr>
<td>Phase 4</td>
<td>170/110</td>
<td>178/100</td>
</tr>
</tbody>
</table>

Index values were compared with measured data values in each of the 4 stages (phases 1–4). Measured data values are from Fox et al. (8).

Fig. 17. Model-generated arterial pressure waveforms during the Valsalva maneuver under four baroreflex control conditions. A: no baroreflex control present; B: only the vasomotor tone control; C: vasomotor tone + myocardial contractility control; D: all 3 control components (vasomotor tone, myocardial contractility, and heart rate). The arrows indicate the start and the end of the maneuver.

Fig. 18. Model-generated sympathetic and parasympathetic (vagal) efferent bursts during the Valsalva maneuver. A: $P_{SA}$ response. B: vagal discharge frequency [showing both the spike representation ($a$) and the relative changes of the frequency value ($F_{vagus}; b$)]. C: sympathetic discharge frequency [showing both the spike representation ($a$) and the relative changes of the frequency value ($F_{symp}; b$)]. The arrows indicate the start and the end of the maneuver.

Fig. 19. Schematic representation of the contribution of the individual baroreflex pathway to the $P_{SA}$ response during the Valsalva maneuver. HR, heart rate; CON, myocardial contractility; VASO, vasomotor tone.

**DISCUSSION**

We presented a mathematical model of the human cardiopulmonary system that combines several component models previously developed by our group. Physiological data predicted by this combined model agreed well with data taken from resting and normal subjects in the supine position. The model was further validated by accurately predicting the sudden and large physio-
logical changes that occurred during the FVC test and all four stages of the Valsalva maneuver.

Although the Valsalva maneuver is well understood, it remains a relatively complicated physiological response, with mechanical and autonomic components that are difficult to separate when used clinically. This limits what information might be obtained from a test that otherwise is very helpful, easy to perform, and commonly used to assess patients with a wide variety of cardiovascular disorders. Because our cardiopulmonary system can mimic a combined response from separate pulmonary, circulatory, and neural components, actual (clinical) responses to the Valsalva maneuver might be analyzed in terms of these components (see Fig. 18 and its accompanying discussion), and a specific physiological defect may be more easily identified. It is also possible that variations between or within groups may be more amenable to statistical analysis, because of the purely quantitative nature of the model. Good statistical backing would certainly improve the meaning and significance of future studies using the Valsalva maneuver.

The utility of our cardiopulmonary model should not be limited to the Valsalva maneuver, however. With further modification and extension, it might help diagnose or analyze other normal or disordered physiological responses, such as orthostatic hypotension, and could characterize disease states such as atherosclerosis, valvular stenosis, and the pulmonary effects of congestive heart failure and the adult respiratory distress syndrome. It could also be helpful in assessing the prognosis of patients with congestive heart failure and/or coronary artery disease, because in these patients both autonomic and mechanical dysfunction are major determinants of premature death.

Model Limitations

All models have limitations, and ours is no exception. The following are a discussion of the limitations of our model:

We employed a circulatory model of intermediate complexity for use in the larger cardiopulmonary model. It mimics the hemodynamics of the circulation quite well. The objectives of the study are general, however, and if questions such as flow in a particular circulation or pulse wave propagation were asked of this model, its foundational assumptions would be too crude to provide adequate predictions (e.g., wave propagation delay is approximated by a phase shift). In addition, as a supine model, it cannot simulate the hemodynamic responses related to changes in body position or gravitational forces, e.g., when subjects stand up from the supine position or enter different gravitational environments as in space flight. To address such problems, additional bandwidth (structural changes) would have to be provided in the form of the adoption of a more distributed model or certain nonlinear elements would have to be included. This, however, is the subject matter of another study.

Ventricular elastance is defined as the instantaneous transmural pressure-to-ventricular volume ratio. At each point in time, it represents a linear relationship between pressure and volume. Therefore, it provides only an approximation to the curvilinear Frank-Starling relationship (5). This approximation works well around the operational point of the human heart, but with large increase in volume, it would overestimate the pressure developed by the ventricle. To represent the Frank-Starling mechanism more faithfully, the expression for elastance should be modified and made a function of both end-diastolic volume ($V_{ED}$) and time, as in Ref. 10a.

The lung was characterized as a single compartment, and homogeneous ventilation was assumed. This is unsuitable when the lungs have regional disease. A multiple-compartment model would be required in that case.

The neural control scheme currently employed in the cardiopulmonary model includes only the baroreceptor-mediated control of heart rate, myocardial contractility, and vasomotor tone. It does not contain an explicit description of the splanchnic circulation, which in humans has a venous bed richly innervated by adrenergic nerve fibers. To develop quantitative descriptions of venoconstriction in humans, more data are needed. Therefore, we neglected venoconstriction as an important baroreceptor-mediated effect in the Valsalva maneuver. Other important factors, such as the cardiopulmonary baroreceptors, hormonal effects, central and peripheral chemoreceptor-mediated ventilation, and autoregulation of special circulations, are not considered in the current model. These factors can also exert important effects on the heart, circulatory hemodynamics, pulmonary mechanics, and ventilatory control.

The model characterizes gas exchange only at the alveolar-capillary membrane. However, gaseous partial pressures in pulmonary arterial blood at the inlet to this membrane are not constant, because gas exchange occurs at other tissue sites in the body. Modifying the model to characterize this additional tissue gas exchange would affect the gaseous content of the pulmonary arterial blood presented to the alveolar membrane.

Finally, the model must be refined by comparing its predictions with clinical data obtained prospectively.

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