Age-dependent cardiopulmonary interaction during airway obstruction: a simulation model

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Goldman E. Age-dependent cardiopulmonary interaction during airway obstruction: a simulation model. Am J Physiol Heart Circ Physiol 299: H1610–H1614, 2010. First published August 13, 2010; doi:10.1152/ajpheart.00176.2010.—Inspiratory fall in arterial blood pressure (Pa) during airway obstruction was ascribed to ventricular interdependence, afterload, and transmission of intrathoracic pressure swings. We have shown this effect significantly reduced in the elderly, but the underlying reasons remain unclear. Here we compare the results of inspiratory loading in young and older subjects with a mathematical model that simulated beat-by-beat fluctuations in cardiopulmonary variables. By increasing arterial and left ventricular elastance parameters in the older group, simulations strongly correlated with the experimental Pa and identified a linear increase of left ventricular transmural pressures with negative intrathoracic pressure that was nearly 38% larger than that in the younger group. The apparent perfusion preservation by less Pa decline with obstruction in the elderly could be misleading, since it reflects an increased afterload and diastolic dysfunction.

cardiopulmonary model

WELL-KNOWN HEMODYNAMIC CHANGES during the Mueller maneuver (5, 8) and airway obstruction in dogs (16) and patients (19) have been ascribed to the effect of large negative intrathoracic pressure (Pth) swings on ventricular interaction, leading to an inspiratory fall in systolic arterial pressure (Pa) by decreasing left ventricular stroke volume (LVSV). We found that this response is largely attenuated during inspiratory loading in the elderly (7, 20), but the underlying reasons remain unclear. We hypothesized that the decrease in ventricular compliance and diastolic performance in the elderly during spontaneous breathing (4, 21), as well as their vascular rigidity (15, 17), should play a role in airway obstruction, and that these complex cardiopulmonary relationships could be simulated by a mathematical model with the purpose of evaluating the putative age-related parameters involved. A model validated for the analysis of beat-by-beat fluctuations in Pa and respiratory activity appeared suitable and was available for public use (6, 12, 13).

METHODS

Data from 20 asymptomatic subjects, divided into a younger group (Y; n = 10, mean age 25.1 yr), and an older, sedentary group without evidence of cardiac disease (O; n = 10, mean age 65.5 yr), from an earlier work (7) were analyzed. The institutional review board approved the study protocol, and all subjects gave informed consent.

Systemic Pa was measured from a radial artery catheter, and Pth was measured by a standard esophageal balloon technique, as detailed previously (20). Subjects were seated upright and wore noseclips while breathing through a mouthpiece connected to a valve that separated inspiration from expiration. After a baseline period of quiet breathing, a graded inspiratory load was applied in steps (3–5 min) until a stable Pth around ~50 mmHg was reached.

Peak inspiratory fall in systolic Pa (as the end-expiratory minus the lowest systolic Pa during inspiration) and corresponding changes in Pth between expiration and inspiration were averaged from five consecutive respiratory cycles for each subject in the Y and O groups at each level of increasing inspiratory load.

Cardiopulmonary simulations were performed in MATLAB version R2009a software (The Math Works, Natick, MA) using an open-source, validated forward model (6, 11–13) capable of generating acceptable human pulsatile hemodynamic waveforms, cardiac output, and venous return curves and beat-by-beat variability over short time periods and stable experimental conditions.

The block diagram of the model is shown in Fig. 1 from Mukkamala (11), where charge is analogous to blood volume (ml), current to blood flow rate (ml/s), and voltage to pressure (mmHg). The model consists of six compartments representing the left (LV) and right (RV) ventricles, systemic arteries and veins, and pulmonary arteries and veins. Each compartment consists of a linear or nonlinear resistance, a linear and nonlinear time-varying compliance, and associated un-stressed volume (a box encompassing a circuit element denotes a nonlinear element). The systemic venous resistance is represented by a Starling resistor (with chamber pressure set to atmospheric pressure), while the pulmonary arterial resistance is represented by an infinite number of parallel Starling resistors (with chamber pressure equal to alveolar pressure). The compliances of the ventricular pressure-volume relationships vary periodically over time as a function of the heart rate (but not as a function of Pth) and are responsible for driving the flow of blood. The reference pressure for the ventricular and pulmonary compartments is set to Pth.

The model of ventilatory mechanics, depicted in Fig. 6 of Mukkamala (11), incorporates the effects of instantaneous lung volume on Pth (t) and alveolar pressure (t). The resistor (Rair) represents the airway between the atmosphere and the lungs, and the capacitor represents the lung compartment.

Airway obstruction simulation data were obtained at each of 13-step increments in Rair, from a baseline (default) value of 0.0026 to 0.1626 mmHg·s·ml⁻¹, resulting in a Pth from ~5.36- to ~52.38-mmHg range. Simulated curves of RV and LV pressures and volumes, Pth, and comparisons of Pa and Pth were automatically generated for the entire Rair range.

Preliminary simulation of the Pa-Pth relationship to determine the effect of parameter adjustment showed a linear output of the model over a wide range of Pth and parameter values. By using the default parameters (Table 1), the function correlated well with the reference Y group linear experimental values at Pth below ~25 mmHg (Fig. 1).

Matching the output for higher, nonlinear Pth values was attempted on the assumption of an increased intrathoracic vascular elastance at high Rair (11, 12) and implemented by inserting an additional capacitance. The Cnew capacitance added to the original model is a model element of the intrathoracic aorta in parallel with arterial capacitance (Ca) and is simply a corrective term for Ca, i.e., total capacitance at the arterial pressure node is Ca + Cnew. To simulate more rigidity at higher pressure, Cnew was modified as a negative term to have the
same dynamic profile as Pth (independent of heart rate) and loops through a vector of $R_{air}$ values at each simulation step. To obtain the profile, Pth was normalized and multiplied by a gain that is to be optimized to match the nonlinear Y experimental data (reference values) past the breakpoint of Pth. Nonlinear optimization was accomplished using the `fminsearch` MATLAB routine, where $C_{new}$ was inversely correlated with $R_{air}$.

The model required a substantial combined modification (obtained by successive approximations) of most of the default parameters (with the exception of the RV end-systolic compliance, Table 1) to fit the O group Pa-Pth data with a linear output. The nonlinear optimization using $C_{new}$ was not applied for the O group where $C_{new} = 0$.

Baroreflex activation appeared to have no significant effect on the simulations for both groups and remained off.

RESULTS

Heart rate, respiratory rate, and tidal volume for the two groups were not significantly different between baseline and inspiratory load.

![Fig. 1. Inspiratory fall in systolic arterial pressure (Pa) against corresponding change in intrathoracic pressure (Pth) are shown for the younger (Y) and older (O) groups. Superimposed data from Ref. 20 follow a similar trend. Simulated relationships using the model default parameters (sim Y linear) and the optimized (see text) nonlinear output (sim Y optimized) fit well with the Y data. The direct decline in the Pa with Pth was markedly reduced in the O group compared with the Y group. The same dependency was simulated by parameter adjustment (sim O).](http://ajpheart.physiology.org/)

![Fig. 2. Simulation of the inspiratory fall in left ventricular (LV) ejection pressure (PLV; as peak at expiration minus peak at inspiration) against Pth. The relationships showed a slope close to the identity line for the Y group (solid circles) and nearly one-third lower for the O group (solid triangles). Experimental values of Pa (X’s) were coincident with the simulation of the PLV decline in both groups (fewer Pa data points than in Fig. 1 were selected).](http://ajpheart.physiology.org/)

![Fig. 3. Simulation of peak transmural PLV (PLV_{tm}) at inspiration (PLV_{tm ins}) and at expiration (PLV_{tm exp}) as a function of Pth. Small differences between PLV_{tm ins} (large solid circles) and PLV_{tm exp} (small solid circles) at a given level of Pth in the linear range of the Y group indicate low impedance in PLV, as opposed to a higher impedance in the nonlinear segment (difference between large and small open circles). This effect was more pronounced in the O group (difference between large and small triangles). PLV_{tm ins Y} and PLV_{tm ins O}, PLV_{tm ins} in the Y and O groups, respectively; PLV_{tm exp Y} and PLV_{tm exp O}, PLV_{tm exp} in the Y and O groups, respectively; PLV_{tm ins Y opt} and PLV_{tm exp Y opt}, optimized PLV_{tm ins Y} and PLV_{tm exp Y}, respectively.](http://ajpheart.physiology.org/)
The inspiratory fall in peak PLV (peak end-expiration minus peak inspiration) (Fig. 2) was strongly correlated with the Pa-Pth relationship in the O group and Y group, both in the linear and nonlinear ranges, adding support to the realistic performance of the computational model with parameter modification.

The nearly equal decrease in peak PLV with Pth over the linear simulation in the Y group suggests that the transmural PLV (PLV_{tm}, as PLV minus Pth) at inspiration (PLV_{tm ins Y} in Fig. 3) and at expiration (PLV_{tm exp Y}) should be very similar.

In contrast, in the Y curvilinear section (i.e., less decline, higher PLV), the PLV_{tm ins Y} (open circles in Fig. 3) was increasingly higher due to the reduced fall in PLV, whereas the PLV_{tm exp Y} remained close to the linear values. This difference reflects an increased afterload on inspiration at Pth greater than −25 mmHg.

This effect was exaggerated in the O group with a significantly lower inspiratory fall in PLV over the entire Pth range (Fig. 2) and a larger PLV_{tm} difference (~38%) between inspiration and expiration compared with the difference in the nonlinear segment of the Y group (Fig. 3).

The relationships of the inspiratory decline in LVSV as a function of PLV and PLV_{tm} are shown in Fig. 4. The decrease in LVSV over the full linear range of Pth was comparable in both groups (Y group 5% and O group 7%). However, LVSV in the Y group showed a larger and steeper decrease (17%) in the nonlinear region, where PLV plateaued and the PLV_{tm} abruptly increased.

**DISCUSSION**

This study shows a novel age-dependent pattern in the inspiratory fall in Pa during airway obstruction that can be understood in terms of varying compliances and afterload in a cardiopulmonary model simulating increased inspiratory load (up to −52-mmHg Pth) on spontaneous breathing. Limited approaches simulating isolated deep inspirations (<40 mmHg Pth) were described in previous cardiopulmonary models (Table 2) without a correlation to actual Pa variability in human subjects.

In both studies by Amoore et al. (2, 3), the simulation consisted of a sustained inspiratory effort for about 10 heartbeats that caused a rapid transient in ventricular volumes, followed by a slower late change after 3 beats. Although they only measured isolated inspiratory efforts, their RV- and LV-simulated volume changes were comparable to those described in the present Y group by using beat-by-beat analysis at varying levels of R_{air}.

These findings are in keeping with the accepted notion that decreased Pth reduces absolute PLV and thus reduces LVSV.

**Table 2. Comparative simulations of decreasing Pth**

<table>
<thead>
<tr>
<th>Pth, mmHg</th>
<th>RVEDV</th>
<th>LVEDV</th>
<th>LVESV</th>
<th>LVSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoore (Ref. 2)</td>
<td>−12</td>
<td>+52 transient, +16 late</td>
<td>−3.6 transient, +25 late</td>
<td>+1.0</td>
</tr>
<tr>
<td>Amoore and Santamore (Ref. 3)*</td>
<td>−14</td>
<td>+54 transient, +25 late</td>
<td>−3.0 transient, +30 late</td>
<td>+4.3</td>
</tr>
<tr>
<td>Amoore and Santamore (Ref. 3)†</td>
<td>−25</td>
<td>+85</td>
<td>−5</td>
<td>−17</td>
</tr>
<tr>
<td>Present study‡</td>
<td>−24</td>
<td>+21.7</td>
<td>−6.6</td>
<td>+5</td>
</tr>
</tbody>
</table>

Values are %change from peak. Pth, intrathoracic pressure; RVEDV, right ventricular end-diastolic volume; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume. *Values taken from Fig. 4 and Table 4. †Estimated from Fig. 6; no values for LVESV > −14-mmHg Pth were reported. ‡Young group; steady-state values at each level of airway resistance.
by increasing LV afterload [LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) late increase during sustained inspirations]. LVSV is further reduced through ventricular interdependence by increasing diastolic and systolic LV elastances (transient LVEDV decrease). The magnitude of the LVSV decrease was linearly related to Pth (<20 mmHg) (2, 3) and was confirmed with the present data (Figs. 1 and 2).

As the depth of inspiration is increased (more negative Pth), the augmented RVEDV is progressively restricted as a result of pericardial and septal constraining effects, with lesser impact on the initial decrease in LVEDV (Table 2). Following this reduced diastolic ventricular interdependence, the afterload becomes the dominant mechanism (5, 8, 14). This could explain why the steep LVSV decline found in the nonlinear region of the Y group is compatible with increased arterial stiffness, as suggested by the large transmural pressure changes (Figs. 3 and 4). Conversely, in the linear Y group simulation, PLV decreased by an amount similar to that by which Pth is decreased during inspiration (Fig. 2), rendering the LV transmural pressure shown in Fig. 3 (peak PLV minus negative Pth) quite similar at expiration (PLV exp Y) and inspiration (PLV ins Y).

The same finding of unchanged PLV ins reported during prolonged inspirations in dogs (14), although measured at a single low level of Pth (−11 mmHg), suggested an absence of afterload by the alternative explanation of a decline in effective LV intracavitary pressure (PLV ins Y) progressively increased (PLV ins Y) progressively increased (Fig. 3), causing a further inspiratory fall in LVSV (Fig. 4).

The linear relationships of the inspiratory fall in Pa obtained in the O group, as well as in the Y group <25-mmHg Pth (Fig. 2), denote a remarkable direct transmission of Pth to vascular and ventricular compartments during inspiratory loading, as we previously suggested (7, 20). In the elderly, a much lower Pa indicates a reduced transmission of Pth compatible with decreased vascular and LV compliance. In fact, simulated PLV ins values were higher and LVSV decline was lower in the O group than in the Y group (Figs. 1 and 2), implying an increased afterload and stiffness for the aging LV, even at low Pth, when it was subjected to equal swings of negative Pth as in the Y group. Increased arterial elastance (41%) and LV stiffness (34%) reported in the elderly (4) by echocardiography and mean wedge pressure (as a surrogate for LV end-diastolic pressure), a 32% prevalence of asymptomatic ventricular dysfunction for ages 55–64 yr (1), and altered diastolic dysfunction and increased vascular stiffness that may contribute to systolic dysfunction (10) are consistent with the O group parameter adjustment (Table 1). In addition, age-related arterial stiffening indexes may double those of subjects younger than 50 yr (17), and venous compliance was reduced by 45% in the elderly (15). Even in Y subjects, the observed curvilinear Pa at high Pth may include increased vascular elastance, as supported by the simulation with the added dynamic Ca.

Although the pressure relationships described in Figs. 3 and 4 were approximately linear, additional modeling of ventricular function by the linear stroke work-end diastolic volume approach (18) would have been limited by the lack of experimental estimates of ventricular dimensions. One may speculate that the experimental data could have been matched with different parameter choices; however, good fit simulations by the model linear output appeared restricted to their default parameters for the experimental Y data (<25-mmHg Pth) and to seven parameters modified by successive iterations within a narrow, clinically compatible range for the entire experimental O data.

In summary, a marked age-dependent attenuation of cardio-pulmonary interaction during airway obstruction induced by increasing inspiratory loading is described. Experimental findings of arterial blood pressure fluctuations and mathematical model simulations provide insight on a dominant role of LV afterload linearly related to Pth in the elderly, whereas, in younger subjects, this effect appears nonlinear (as a reduced Pa above −25 mmHg). The apparent perfusion preservation by less LVSV decline at high negative Pth with aging could be misleading and actually reflects diastolic dysfunction and increased LV transmural intracavitary pressure.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


