Model Study of Inspiratory Fall of Blood Pressure in Airway Obstruction

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Abstract: Inspiratory fall of systolic blood pressure (IFSBP) is used as an index to assess the respiratory influences on non-linear dynamics of heart rate variability. In an in-vivo situation it is particularly difficult to isolate individual effects of heart rate, vascular tone, pleural pressure variation, and ventricular interdependence. A computer model of the cardiopulmonary system was adapted to this problem, relating mechanisms such as baroreflex regulation of heart rate in response to respiratory oscillations. The model provided time-course simulations of hemodynamics by numerically integrating 28 nonlinear, time-varying differential equations. Two approaches for baroreflex regulation were tested, including a simple 1st-order relationship between R-R interval (RRI) and SBP and the autoregressive moving average (ARMA) model. Experimental data were obtained retrospectively from 22 patients with chronic airway obstruction before and during breathing through an external resistance. Magnitude and phase relations between arterial pressure and pleural pressure were evaluated. The computer model provided good fits to arterial pressure waveforms: correlation coefficients (r) ranging from 0.71 to 0.96 (mean±SD: 0.87±0.06) with a simple 1st-order RRI-SBP model. It was observed that the ARMA model did not further improve the goodness of fit. However, no dominant parameter was found for phase relations.

Key–Words: Baroreflex regulation, Cardiopulmonary system, Computational model, Pulsus paradoxus, Inspiratory fall of systolic blood pressure (IFSBP)

1 Introduction

Although it has been reported that the inspiratory fall of systolic blood pressure (IFSBP) can be affected by various factors including baroreflex sensitivity [1], left ventricular afterload [2], aging [3], intrathoracic pressure [4], interventricular septal coupling [5], obstructive sleep apnea [6], airway obstruction[7], and cardiac tamponade[8], it is particularly difficult to isolate individual effects in an in-vivo situation. It is well accepted that IFSBP is driven by the variation of pleural pressure due to respiration. However, the mechanisms for affecting the magnitude and phase of IFSBP are not well understood. Since a comprehensive computer model of the cardiopulmonary system based on the right-left heart interaction has been developed, it is used as a quantitative platform for studying various physiological mechanisms.

The purpose of this study was to develop a phenomenological model capable of simulating arterial pressure waveforms under various respiratory effects. As an approach to assess respiratory effects on arterial pressure, the magnitude and phase relations between arterial pressure and pleural pressure are derived. Preliminary evaluation of the model was based on clinical data obtained from patients during airway obstruction, which accentuated IFSBP to a certain extent.

2 Methods

Experimental data were obtained retrospectively from 22 patients with chronic airway obstruction during studies of inspiratory loading. To assess the aging effects, subjects were divided into two groups: 9 elderly (64 ± 3.6 yr) and 13 young (25.1 ± 5.2 yr) patients. No patient had clinical evidence of cardiac disease.

Patient data were originally recorded in hard-copy forms and scanned into a digital computer. For comparison with the model-generated waveforms, arterial and pleural pressure waveforms were traced with the use of a customized curve tracing application.

The model also included an optimization algorithm for fitting sinusoidal curves to measured pleural pressure and the systolic and diastolic envelopes of the arterial pressure (Fig. 1). Respiratory variation (RV) was calculated as the minimum inspiratory pleural pressure minus the maximum expiratory pleural pres-
Figure 1: Arterial and pleural pressures from a patient with airway obstruction (dotted) and fitting sinusoidal curves (solid). Systolic gain was defined by

\[ G_s = \frac{IFSAP}{RV} \]

where RV was the magnitude of respiratory variation.

Fluctuations in arterial pressure were adequately represented by IFSBP and IFDBP which stand for inspiratory fall of systolic and diastolic blood pressure, respectively. With the assumption that the frequency of systolic and diastolic envelopes of arterial pressure is the same as respiratory rate, magnitude and phase for each fitting sinusoidal waveforms were obtained. Then as the representation of the relation between arterial pressure and pleural pressure, the systolic gain \( G_s \) and the diastolic gain \( G_d \) are defined by the ratio of IFSBP and IFDBP over RV as following:

\[ G_s = \frac{IFSBP}{RV} \]

and

\[ G_d = \frac{IFDBP}{RV} \).

Similarly, the systolic phase difference \( P_s \) and the diastolic phase difference \( P_d \) are defined with reference to phase of pleural pressure waveform.

\[ P_s = \phi_s - \phi_p \]

\[ P_d = \phi_d - \phi_p \]

2.1 Data analysis

Statistical analysis of the obtained data such as \( G_s \), IFSBP was done using t-test, paired and unpaired as appropriate: paired for comparing parameters in the same group and unpaired for comparison between groups. Additionally, linear regression analysis were employed. \( P < 0.05 \) was considered statistically significant.

2.2 Effect of respiration

Pleural pressure represents the respiratory effect on hemodynamics and is assumed to vary over time according to an exponential charge-discharge waveform defined with baseline, amplitude, respiration period, inspiration period, inspiration time constant, and expiration time constant [21]. However, with this shape of waveform, even slight increase in amplitude was likely to result in numerical instability. In order to provide an accurate representation of the clinical hemodynamic data, we tried a new distorted square waveform for pleural pressure and defined eight parameters such as baseline, amplitude, respiration period, inspiration period, ascending/descending inspiration time constant, and ascending/descending expiration time constant. Fig. 2 illustrates an example of measured pleural pressure with matching computer generated (a) distorted square and (b) exponential waveforms.

2.3 Baroreflex regulation

As one of the homeostatic control, the mean arterial pressure is closely monitored and maintained at approximately 90 mmHg. An elevation in arterial pres-
ure increases the baroreceptor nerve activity which in turn increases/decreases parasympathetic/sympathetic nerve activity. These causes a decrease in heart rate leading to a decrease in cardiac output and thus restore the arterial pressure back to normal. Studies have pointed out that not only the immediate effect of SBP on RRI but also the delayed, buffered effect should be considered. Hence, in this model study, two approaches for baroreflex regulation were tested: 1) One is an autoregressive moving average (ARMA) model by Patton et al. which predicts the next RRI from the present SBP and as well as previous RRI and SBP [15].

\[
RRI(n) = - \sum_{k=1}^{p} \alpha(k) RRI(n-k) + \sum_{k=0}^{p} b(k) SBP(n-k)
\]

2) The other is a simple 1st-order model that predicts the next RRI from the present SBP according to the formula:

\[
RRI(n) = G_{baro}(SBP(n) - 120) + 0.855
\]

where \(G_{baro}\) is the baroreflex gain. This formula was based on an operating point at heart rate = 70 bpm and SBP = 120 mmHg [21]. \(G_{baro}\) was set at 0.0053 according to data reported by Burattini et al [2].

3 Results and Discussions

With an assumption that aging may affect the respiratory fluctuations in arterial pressure, total 22 patients were divided into two groups according to age. Statistic data such as age, IFSBP, RV, \(G_s\), and correlation coefficients in young and old group were shown in Table 1. The individuals in young group showed slightly higher IFSBP and IFDBP than the ones in elder group; however, the differences were not statistically significant according to unpaired t-tests. Several different approaches were attempted to estimate the baroreflex sensitivity. The time domain procedure is based on the spontaneous sequences of 3 or more consecutive heart beats in which both SBP and RRI increase (+/+ sequences) or decrease (-/- sequences). As the index of BRS, the slope of the linear regression line between SBP and RRI values was calculated when the correlation coefficient was 0.85 or greater. Hence, BRS is closely dependent on the number of measuring points. However, it was impossible to apply this method to our clinical data because no baroreflex sequence was found through total 22 data set. With the high breathing rate of 0.33±0.11 Hz for old and 0.41±0.14 Hz for young group, systolic blood pressure oscillations are too fast to produce enough baroreflex sequences.

As for the effects of breathing rate on the relationships between SBP fluctuations and RRI changes, a large number of studies validated that increases in the breathing rate are associated with reduction in systolic blood pressure oscillations. It is also known that the respiratory inter-relationships between SBP and RRI is poor in high frequency (eg. 0.3 Hz). Included in Table 1 BRS computed as the \(alpha\)-index for old and young subjects during obstructed breathing.

As an example of the \(t\)-test and linear regression analysis results, the regression equations for the relationship between IFSBP and RV are

Old: \(IFSBP = 0.9 \times RV + 19.6, r = 0.67\)

Young: \(IFSBP = 0.51 \times RV + 27.2, r = 0.25\)

And the regression equations for IFSBP and IFDBP are

Old: \(IFSBP = 0.7 \times IFDBP - 0.3, r = 0.99\)

Young: \(IFSBP = 0.5 \times IFDBP + 9.8, r = 0.47\)

While the correlation between IFSBP and IFDBP in elder group was very strong \((r = 0.99)\), it was weak in young group \((r = 0.47)\). In other words, in elder group, what affects the systolic blood pressure also affects the diastolic blood pressure. But, in young group, the systolic and diastolic changes are somewhat independent of each other.

In addition to IFSBP-IFDBP correlation, we also found a significant difference between old and young group in heart rate. It is well known that baroreceptors have a critical role in the maintenance of the relationship between heart rate and systolic blood pressure. As arterial pressure decreases, heart rate is increased by the sinoaortic baroreflex control. It seems likely that the elderly subjects failed to respond to changes in arterial blood pressure promptly. Ironically this stable heart rate made it possible to get strong correlation between clinical data and model generated data in old group. As for young subjects, even though we increased correlation by turning on baroreflex control, the correlation coefficient could not exceed 0.9 except one subject out of 13 young subjects.

All patients’ descriptive data such as IFSBP, IFDBP, and RV are derived from the fitted sinusoidal curves of systolic and diastolic envelopes of arterial pressure and pleural pressure. Thus they are based on an assumption that systolic and diastolic blood pressure follow the respiratory fluctuations with a regular pattern. But, instead systolic peaks or diastolic valleys are characteristically variable because the respiratory fluctuations are different for each breath. The lower \(G_s\) for the older group is in keeping with the observed larger variability of systolic and diastolic blood pressure in young group.
The result of the sensitivity analysis is summarized in Table 2, in which only those model parameters with the magnitude gain or the phase gain ≥ 0.05 are listed. Model parameters with all gains < 0.05 are considered insensitive and are excluded from Table 2. Parameter values for control are shown beside each parameter label. As for the intrathoracic pressure, baseline is set to -3.7 mmHg and pressure amplitude is -20 mmHg. Respiration period and inspiration period are set to 5 seconds and 2 seconds, respectively. Inertance (L) and viscoelastance (Ω) values in the model are generally insensitive, with all gains < 0.05. Elastance (E) defined by volume constant (Φ) and the zero-volume elastance(E0) are generally insensitive and thus not shown in Table 2. On the contrary, time-varying elastances (e) defining contractility of the heart are relatively sensitive. Especially time-varying elastances for left heart show very strong sensitivities. Each time-varying elastance is characterized by a baseline and an amplitude component. A parameter which affects the systolic gain positively also affects the diastolic gain positively. It is noticeable that elastance amplitude and baseline for left ventricle (E1va, E1vb) are compensating each other. In other words, whereas 10% increase of E1va increases both IFSBP and IFDBP, 10% increase of E1vb decreases both of them.

By assuming pleural pressure an eight-parameter distorted square waveform instead of a six-parameter exponential charge-discharge waveform, it was possible to decrease the amplitude pressure as low as -70 mmHg (for Young #5, RV=88 mmHg) without suffering from numerical problems. Also the sensitivity analysis results listed in Table 2 indicated that both waveforms were compatible. However, neither a distorted square waveform nor an exponential waveform is sufficient to follow the clinical pleural pressure. Since the respiration period of patient is not the same for each breath, we may need to characterize the pleural pressure by far more sophisticated equation with nonlinear time-varying parameters.

Fig. 3 illustrates a typical case of computer simulation of the arterial pressure waveform in comparison with the measured waveform. Similarity represented by the correlation coefficient (r) is 0.85. Fig. 4 shows another example. It is notable that without including any baroreflex regulatory mechanism in this case, the resulting fit to arterial pressure waveform was poor (Fig. 4(a), r = 0.50). By including the simple baroreflex regulation of RRI the goodness of fit was drastically improved (Fig. 4(b), r = 0.85). The baroreflex gain was maintained constant (Gbaro = 0.0053) except for four cases in young group. For these four cases Gbaro was slightly increased to obtain better fits to the arterial pressure waveforms. The ARMA model for baroreflex regulation yielded comparable results, but didn’t further improve the correlation coefficients. With the simple baroreflex regulation the correlation coefficient (r) between the model-generated and measured arterial pressures was 0.87 ± 0.06, ranging from 0.71 to 0.96, n = 22. As summarized in Table 1, the correlation coefficient for elder group was significantly higher than that for young group.

### 4 Conclusions

Without the presence of severe autonomic derangement, baroreflex regulation of heart rate played a significant role in cardiopulmonary interaction during airway obstruction and was a crucial component in our computer model. For our modelling purposes the incorporation of baroreflex regulation based on a simple

**Table 1: Statistics of patient data (mean±sd)**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Age</th>
<th>IFSAP</th>
<th>PPV</th>
<th>G_s</th>
<th>Correlation (r)*</th>
<th>BRS_o**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td>13</td>
<td>25±5</td>
<td>31±10</td>
<td>42.9±19.8</td>
<td>0.82±0.33</td>
<td>0.84±0.06</td>
<td>0.086±0.031</td>
</tr>
<tr>
<td>Old</td>
<td>9</td>
<td>64±4</td>
<td>29±12</td>
<td>46.8±16.9</td>
<td>0.64±0.21</td>
<td>0.91±0.03</td>
<td>0.081±0.018</td>
</tr>
</tbody>
</table>

* correlation between clinical data and model generated data.
** gain of transfer function [ms/mmHg].

![Figure 3: Measured and model-generated arterial and pleural pressures; correlation coefficient r = 0.85.](image-url)
Table 2: Sensitivity analysis in terms of gain

<table>
<thead>
<tr>
<th>Model parameter</th>
<th>Sensitivity gain</th>
<th>$P_{pl}$ : exponential</th>
<th>$P_{pl}$ : distorted square</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$G_s$</td>
<td>$G_d$</td>
<td>$P_s$</td>
</tr>
<tr>
<td>$\Phi_{puc}$</td>
<td>60 ml</td>
<td>0.06</td>
<td>0.12</td>
</tr>
<tr>
<td>$\Phi_\alpha$</td>
<td>70 ml</td>
<td>-0.41</td>
<td>-0.05</td>
</tr>
<tr>
<td>$R_{vr}$</td>
<td>0.005 mmHg/ml</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>$R_{puc}$</td>
<td>0.04 mmHg/ml</td>
<td>0.12</td>
<td>0.1</td>
</tr>
<tr>
<td>$R_{aa}$</td>
<td>0.04 mmHg/ml</td>
<td>-0.06</td>
<td>-0.06</td>
</tr>
<tr>
<td>$R_s$</td>
<td>1.2 mmHg/ml</td>
<td>0.27</td>
<td>0.18</td>
</tr>
<tr>
<td>$E_{raa}$</td>
<td>0.04 mmHg/ml</td>
<td>-0.05</td>
<td>-0.06</td>
</tr>
<tr>
<td>$E_{rab}$</td>
<td>0.06 mmHg/ml</td>
<td>-0.08</td>
<td>-0.18</td>
</tr>
<tr>
<td>$E_{rvb}$</td>
<td>0.04 mmHg/ml</td>
<td>-0.09</td>
<td>-0.36</td>
</tr>
<tr>
<td>$E_{a0}$</td>
<td>0.05 mmHg/ml</td>
<td>0.24</td>
<td>0.19</td>
</tr>
<tr>
<td>$E_{r0}$</td>
<td>0.07 mmHg/ml</td>
<td>0.06</td>
<td>0.08</td>
</tr>
<tr>
<td>$E_{lab}$</td>
<td>0.09 mmHg/ml</td>
<td>0.3</td>
<td>0.28</td>
</tr>
<tr>
<td>$E_{rva}$</td>
<td>6.0 mmHg/ml</td>
<td>0.48</td>
<td>0.42</td>
</tr>
<tr>
<td>$E_{rsv}$</td>
<td>0.07 mmHg/ml</td>
<td>-0.65</td>
<td>-0.4</td>
</tr>
<tr>
<td>$P_{vr}$</td>
<td>5.0 mmHg</td>
<td>-0.1</td>
<td>-0.1</td>
</tr>
<tr>
<td>$P_{fv}$</td>
<td>-3.7 mmHg</td>
<td>0.18</td>
<td>0.13</td>
</tr>
<tr>
<td>$K_{pc}$</td>
<td>1.0 mmHg</td>
<td>-0.06</td>
<td>-0.06</td>
</tr>
<tr>
<td>$V_{p0b}$</td>
<td>380 ml</td>
<td>-0.12</td>
<td>-0.53</td>
</tr>
</tbody>
</table>

See [21] for glossary.

linear RRI-SBP relation was sufficient; it was not necessary to use a more sophisticated ARMA model for RRI predictions. Even though arterial blood pressure is regulated in changes in heart rate as well as stroke volume and total peripheral resistance, only the effects of arterial baroreflex in heart rate was considered for this study. It was not necessary to include baroreflex regulation of peripheral resistance (vascular tone) to improve IFSBP predictions. Between young patients and elder patients examined in this study there were no statistically significant differences in IFSBP and systolic gain. However, the correlation coefficient for fitting arterial pressure for elder group was significantly higher than that for young group. This suggested that the autonomic function of the young group might contain additional components with dynamics and complexity beyond the simple baroreflex formula implemented in the present model. Even though phase synchronization between the cardiac and the respiratory system is a well-accepted phenomenon, no clear model parameter was observed in this study. The phenomenological model developed in this study will benefit further investigations on mechanisms of cardiovascular–respiratory interactions relevant to systolic blood pressure.

References:


[3] Davies, L. C., D. P. Francis, P. Ponikowski, M. F. Piepoli, and A. J. Coats. Relation of heart rate and blood pressure turbulence following premature ventricular complexes to baroreflex...


