Heart rate control and mechanical cardiopulmonary coupling to assess central volume: a systems analysis

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Barbieri, Riccardo, John K. Triedman, and J. Philip Saul. Heart rate control and mechanical cardiopulmonary coupling to assess central volume: a systems analysis. Am J Physiol Regul Integr Comp Physiol 283: R1210-R1220, 2002.—Small negative changes of central volume reduce cardiac output without significant alterations of arterial blood pressure (ABP), suggesting an adequate regulatory response. Furthermore, evidence has arisen supporting a Bainbridge reflex (tachycardia with hypervolemia) in humans. To investigate these phenomena, multivariate autoregressive techniques were used to evaluate the beat-to-beat interactions between respiration, R-R interval, and ABP at six levels of decreased and increased central volume. With reductions of central volume below control, baroreflex and respiratory sinus arrhythmia gains were reduced, while with increases of volume above control, gains increased for the first two levels but decreased again at the highest volume level, suggesting the presence of a Bainbridge reflex in healthy human subjects. The mechanical influence of respiration on central venous pressure (CVP) had an unexpected shift in phase at the point of mild central hypervolemia, with the expected negative relation at lower volumes (inspiration lowers CVP) but a positive relation at higher volumes (inspiration raises CVP). We conclude that multivariate techniques can quantify the relations between a variety of respiratory and hemodynamic parameters, allowing for the in vivo assessment of complex cardiorespiratory interactions during manipulations of central volume. The results identify the presence of a Bainbridge reflex in humans and suggest that short-term cardiovascular control is optimized at mild hypervolemia.

baroreflex; cardiopulmonary reflex; hypovolemia; hypervolemia; respiration; blood pressure

MODERATE CHANGES of central venous volume, such as those that occur with changes in posture, may have dramatic effects on cardiac output without significant alterations of arterial pressure (10, 11). This simple observation demonstrates the potent ability of the two primary mechanisms responsible for short-term arterial pressure regulation: arterial and cardiopulmonary baroreflexes to maintain arterial blood pressure (ABP) in a fairly narrow range during a wide variety of hemodynamic stressors. Although it appears that this regulation is facilitated by constant adaptation and interaction of these two reflexes, the specific dynamics of these processes remain a subject of considerable debate. On the basis of the observation that small reductions of central volume induced by low levels of lower body negative pressure (LBNP) do not lead to significant reductions of arterial pressure (1, 10), a number of investigators have concluded that unloading of cardiopulmonary receptors in the atria and ventricles is the primary stimulus for reflex increases in sympathetic activation to muscle vascular beds, subsequent vasoconstriction, and maintenance of arterial pressure, despite reduced cardiac output (22). However, more recently, two studies have brought this hypothesis into question. Jacobsen et al. (9) first demonstrated that elimination of any decrease in arterial pressure with phenylephrine during LBNP markedly reduces the muscle sympathetic response. Taylor et al. (23) then demonstrated that despite the maintenance of arterial pressure during low levels of LBNP, systolic ascending aortic area as a measure of aortic baroreceptor input actually decreased. Both of these studies suggest that arterial baroreflexes do play an important role in maintaining arterial pressure during reductions of central volume but that the combination of cardiopulmonary and baroreflex control is simply potent enough to prevent reductions of arterial pressure. Furthermore, there is considerable evidence that arterial and cardiopulmonary baroreflexes interact, such that cardiopulmonary receptor unloading via reductions in central volume may lead to enhancement of carotid arterial baroreflex gain (18).

Heart rate control has been a less emphasized, but potentially important, component of the reflex response to changes in central volume. As with arterial pressure, low levels of LBNP produce minimal if any change in mean heart rate (10), an observation previously used to support the argument that arterial baroreflexes played no role in the response. However, a number of investigators, beginning with Bainbridge (3, 27), have demon-
strated reflex tachycardia with volume loading and reflex bradycardia with volume reduction in dogs, changes opposite those expected with an arterial baroreflex response. Such observations introduce the possibility that the lack of a change in mean heart rate during nonhypotensive LBNP is due to offsetting reflex effects on heart rate via the cardiopulmonary and arterial baroreflexes. Several recent findings support such a hypothesis. First, although the presence of the Bainbridge reflex has been controversial in humans (3), one report has clearly demonstrated reflex tachycardia with volume loading in humans (17). Furthermore, Triedman et al. (25) found that mild hypovolemia from a 10% blood donation significantly changed arterial baroreflex control of heart rate without changing either mean heart rate or arterial pressure, consistent with the findings of others during low levels of LBNP (8).

In this study, both unloading and loading of cardiopulmonary receptors have been employed to assess the influence of central volume on short-term control of heart rate and arterial pressure. Because of their ability to identify interactions between cardiovascular variables, autoregressive (AR) multivariate techniques (4) are used to investigate the relations between respiration, R-R interval, and ABP.

METHODS

Experimental protocol. The study protocol was approved by the institutional human studies committee, and written informed consent was obtained from all participants. A total of 13 healthy human subjects between the ages of 20 and 25 yr (median 23 yr), weight range 57–86 kg (median 65.5 kg), underwent the protocol.

Surface electrocardiogram (ECG), instantaneous lung volume [respiration (Resp)], central venous pressure (CVP), and ABP were monitored during 8-min segments in a variety of conditions. Instantaneous lung volume was recorded with a Respirtrace two-belt impedance plethysmograph (Noninvasive Monitoring Systems, Ardsley, NY) and calibrated by having subjects inflate and deflate an 800-ml bag. A central venous line was inserted via the left median cubital or cephalic vein, positioned in the superior vena cava, and flushed continuously with heparinized saline. CVP was transduced with a Statham strain-gauge transducer, which was calibrated with a water manometer and positioned at the level of the right atrium. ABP was measured with a noninvasive finger photoplethysmograph (Finapres, Ohmeda, Englewood, CO) applied to the right third digit. Data were recorded after the subjects were comfortable and cardiovascular variables were observed to be stable. Room temperature was maintained at 24°C.

Respiratory intervals were set for each subject with an auditory cue (beep). Subjects were accustomed to these cues for several minutes at a constant respiratory interval of 4 s (0.25 Hz, 15 breaths/min). For each experimental period of 8 min, the cues occurred with intervals between 1 and 15 s, randomly chosen from a Poisson distribution, with a mean interval of 4 s, or 15 breaths/min. The random-interval breathing technique broadens the frequency spectrum of the respiratory signal in a manner approximating filtered white noise. The technique and its use in physiological frequency-domain studies have been described previously (7). LBNP was applied by use of a Plexiglas chamber that accommodated the hips and lower extremities of the subject. This device allowed for rapid application of negative pressures down to –50 cmH2O. Cardiopulmonary receptors were first deactivated with small, incremental applications of LBNP (–5, –15, –30 mmHg), then control conditions were restored, and finally cardiopulmonary receptors were activated by passive leg raising (20° and 60°) and a 500-ml infusion of normal saline (NS). Data were acquired for a minimum of 8 min of random breathing in each condition.

Data acquisition and analysis. Signals were recorded on a Hewlett-Packard 3968 eight-track FM magnetic tape recorder. Simultaneous analog-to-digital conversion was performed at 360 Hz using specialized software on an 80386-based computer. Data were transferred to a workstation (SPARC 2, Sun Microsystems, Mountain View, CA) for off-line analysis. R-wave positions were detected digitally, and R-R intervals were converted into a smoothed instantaneous R-R interval time series constructed at 3.0 Hz by use of an algorithm described previously (6). CVP and Resp signals were digitally filtered at 1.5 Hz and decimated to 3.0 Hz. The ABP signal was also filtered at 1.5 Hz and decimated to 3.0 Hz to provide a mean ABP signal. Systolic (SBP) and diastolic blood pressure (DBP) values were detected from the unfiltered arterial pressure signal, and a third-order splining and filtering algorithm was used to construct 3-Hz time series of SBP and DBP. The result was synchronized 3.0-Hz time series of all the signals of interest. All signals were visually inspected for artifact. Time series of ~6 min (341 s, or 1,024 points) of R-R interval, Resp, CVP, SBP, and DBP were selected from each 8-min study period.

Bivariate AR spectral estimation. A bivariate AR model of order p can be described by the following equation

$$X(n) = - \sum_{k=1}^{p} A(k)X(n-k) + W(n)$$

where $$x_1(n)$$ and $$x_2(n)$$ are the output signals, $$w_1(n)$$ and $$w_2(n)$$ are white noises, and $$a_1(k)$$ and $$a_2(k)$$ are the AR coefficients. The p matrices of coefficients $$A(k)$$ were calculated by solving the extended Yule-Walker equations (13). Information about the whiteness of the input noise for each identification, and about the optimum orders, according to the Akaike criteria (2), allows for determination of the best order to choose for a proper identification of the spectral characteristics of the two signals and their interaction. Each transfer block described in Fig. 1 can then be identified by properly choosing the output signals $$x_1(n)$$ and $$x_2(n)$$ among Resp, R-R, SBP or DBP, and CVP. Relations between the output biological signals can be attributed to specific physiological mechanisms, indicated by the transfer boxes in Fig. 1. Each transfer function, represented by the boxes, can be identified using bivariate AR spectral estimation.

Parameter identification. Mean values for each experimental condition were calculated. The variability of each signal was calculated as the integrated power spectral density from 0 to 0.5 Hz. For each signal, the spectral parameters were extracted using a division into a low-frequency (LF) interval (0.04–0.15 Hz) and a high-frequency (HF) interval (0.15–0.5 Hz) (19). LF and HF coherent powers between each pair of signals were computed using the cross-spectrum normalized by the two autospectral power densities. For the baroreflex relations, SBP was used to identify the feedback response,
similarly to most other studies of the heart rate baroreflex (16, 26), while DBP was used to identify the feedforward response because of the clear effects of a change in R-R interval on DBP. Gain and phase values were also extracted at the two frequencies where the coherence between each pair of signals reached its maximum inside each of the frequency bands (LF and HF). Indexes were considered reliable for coherence values over 0.5. Data and some of the analyses from a single subject during one control epoch are shown in Fig. 2. The time domain signals (Fig. 2, Aa–Ae) clearly demonstrate the random interval nature of the breathing pattern and its irregular effects on the variability of each of the other signals displayed. The autospectras of R-R, SBP, and Resp are shown along with their AR components in Fig. 2, Ba–Bc. Despite the random nature of the respiratory cues, preferential peaks can be seen in the respiratory spectrum at about 0.08, 0.15, and 0.25 Hz, which are reflected in the spectra of both R-R and SBP. The coherence, gain, and phase spectra for the transfer relations between Resp and R-R (respiratory sinus arrhythmia), and SBP and R-R (baroreflex feedback), are shown in Fig. 2, Ca and Cb, respectively. Of note, the coherence spectra demonstrate peaks at the same frequencies as the autospectras in Fig. 2B, presumably related to the stronger respiratory signal input at those frequencies. All signals are highlighted at the points where coherence is >0.5, where the transfer relations were used to yield reliable estimates of gain and phase in the LF and HF regions. Phase values are defined between –360 and 0 degrees to evidence the physiological delay between each pair of variables, which will be addressed in RESULTS and DISCUSSION.

Statistics. The parameters identified by the multivariate procedure were averaged among the 13 subjects for each of the seven epochs. Parameters identified for the two control epochs were averaged together to give a single value for each index. The statistical analysis was performed using a $t$-test (paired 2 sample for the means). All epochs were considered for the statistical test: the results for the control epoch were compared first with each of the three volume reduction (LBNP) epochs, and then with each of the three volume loading epochs. A $P$ value of <0.05 was considered significant. Because the average data revealed what appeared to be a maximum in many of the gain parameters during volume loading, statistical comparison was also performed between the last two volume loading epochs, where the trend of some of the parameters appeared to change.

RESULTS

Most of the identified parameters are summarized in Tables 1 and 2, while some are shown separately in Figs. 3–7, as presented below. The $x$-axis of each graph represents the seven experimental epochs. LBNP epochs are shown on the left of the control epoch, and volume loading epochs on the right. The values are connected with solid lines, to highlight any trends due to the induced physiological changes. Each epoch value has vertical bars, which represent the SE of the mean. Asterisks mark the values statistically different from the combined control epoch, while the statistical difference between the last two volume loading epochs is marked with diamonds over the connecting line between the two points.

Mean values (Table 1, Fig. 3). The changes of CVP generally reflect the effects of the volume unloading and loading procedures. As expected, CVP decreases with each increase of LBNP, while it increases consistently with the 20° leg raise and the NS infusion, but minimally with the 60° leg raising (Fig. 3A). Mean R-R interval decreases (tachycardia) with decreases in CVP during LBNP, with significant changes by −15 mmHg LBNP. Similarly, there is initially a bradycardia (increased mean R-R) with volume loading at 20° and 60° leg raising; however, a tachycardia (reduced R-R) was observed at the highest level of volume induced with the NS infusion (Fig. 3B). Although the changes were not significantly different from control, R-R was significantly lower after NS than at 60° leg raise, when only those two epochs were considered. The observed relative tachycardia with volume loading is consistent with a Bainbridge reflex in this study (3, 17).

Mean arterial pressure, represented by ABP, was constant during LBNP, supporting the notion that mild unloading of cardiopulmonary receptors leads to minimal changes in arterial pressure (Fig. 3C). However, during volume loading, ABP values increased significantly with each change in loading, potentially invoking the dynamics of the arterial baroreflex loop (Fig. 3C).

Variance (Fig. 4). Although there were few significant changes in either total variance or variance in the two frequency bands LF and HF for any of the parameters measured, the variance for a number of parameters demonstrated trends that are consistent with changes in both the parameter means (Fig. 3) and transfer gains (Figs. 5 and 6). The total LF and HF variances of the respiratory signal were nearly constant for all the epochs, confirming the efficiency of the random breathing control technique.
in maintaining a constant respiratory stimulus over a variety of conditions and in both of the relevant frequency bands (Fig. 4A). The variance of CVP increased during volume unloading and decreased during volume loading, changes that appear most obvious in the HF band, and reached significance at maximum volume loading (Fig. 4B). R-R interval total variance changes had a similar pattern to that observed for R-R mean, with a maximum
peak at 60° leg raising, which seemed to be due completely to changes in the HF band (Fig. 4C). Furthermore, as with R-R mean, there was a significant reduction in R-R variance between 60° leg raising and maximum volume loading. SBP and DBP total and HF variance (Fig. 4D, DBP not shown) were nearly constant during volume unloading; however, LF variance appeared to increase slightly. Alternatively, total and LF variance for SBP decreased with volume loading, while HF variance remained nearly constant. Of note, although in general the changes in total R-R variance are in the opposite direction of those in total SBP variance, that was not the case for the last volume loading epoch, indicating that the decrease in R-R variance is not merely attributable to a change in SBP variability.

**Coherence.** Coherences were calculated for all the possible interactions between R-R, SBP (or DBP), Resp, and CVP. In Table 2, values are shown in the standard format for each signal pair (LBNP values on the left, and volume loading values on the right of the control results). For the effects of respiration on R-R interval [respiratory sinus arrhythmia (RSA)] and CVP (Resp-R-R and Resp-CVP), coherence values were generally higher in the HF than in the LF range. However, for those involving the baroreflex relations (SBP-R-R and R-R-DBP), LF coherence was generally higher than HF. The highest coherence values were found for the mechanical effect of respiration on central filling pressure (Resp-CVP), where coherence was close to 1 (mean 0.93) for all epochs in the HF range and averaged 0.78 in the LF range. These values reflect the close relation between Resp and CVP shown for the time domain signals in Fig. 2, Aa and Ab. High coherence values were also found for the baroreflex relations (SBP-R-R and R-R-DBP) and for the RSA (Resp-R-R). Importantly, for both the baroreflex and RSA at both

**Table 1. CVP, R-R interval, SBP and DBP averaged among all subjects for each experimental epoch.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0</th>
<th>-15</th>
<th>-5</th>
<th>Control</th>
<th>Leg+</th>
<th>Leg++</th>
<th>500 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP, mmHg</td>
<td>0.56 ± 1.1*</td>
<td>1.58 ± 0.7*</td>
<td>2.78 ± 0.6*</td>
<td>4.55 ± 0.8</td>
<td>5.61 ± 1.2</td>
<td>5.53 ± 1.2</td>
<td>5.53 ± 1.2</td>
</tr>
<tr>
<td>R-R, ms</td>
<td>840 ± 30*</td>
<td>884 ± 32*</td>
<td>921 ± 31</td>
<td>948 ± 25</td>
<td>993 ± 26*</td>
<td>997 ± 29*</td>
<td>927 ± 25†</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>104 ± 1.9</td>
<td>106 ± 1.4</td>
<td>106 ± 1.7</td>
<td>107 ± 1.3</td>
<td>111 ± 1.1*</td>
<td>113 ± 1.2*</td>
<td>115 ± 1.4*</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>61 ± 2.6</td>
<td>61 ± 1.9</td>
<td>59 ± 1.9</td>
<td>59 ± 2.8</td>
<td>62 ± 2.6*</td>
<td>66 ± 2.9*</td>
<td>69 ± 3.5*</td>
</tr>
</tbody>
</table>

Values are means ± SE. *Values statistically different from combined control epoch (Control). †Significantly different from leg++ volume loading epoch.

**Table 2. Summary of gain and coherence identified by bivariate AR estimation from each pair of signals for both the LF and HF ranges, averaged among all subjects for each experimental epoch.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0</th>
<th>-15</th>
<th>-5</th>
<th>Control</th>
<th>Leg+</th>
<th>Leg++</th>
<th>500 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSA gain LF</td>
<td>103 ± 18*</td>
<td>117 ± 15*</td>
<td>126 ± 23</td>
<td>174 ± 30</td>
<td>188 ± 33</td>
<td>171 ± 29</td>
<td>144 ± 37</td>
</tr>
<tr>
<td>RSA gain HF</td>
<td>73 ± 11*</td>
<td>96 ± 14*</td>
<td>128 ± 22</td>
<td>139 ± 27</td>
<td>169 ± 33</td>
<td>188 ± 11</td>
<td>137 ± 35†</td>
</tr>
<tr>
<td>Coherence LF</td>
<td>2.0 ± 0.06</td>
<td>0.53 ± 0.06</td>
<td>0.53 ± 0.08</td>
<td>0.55 ± 0.06</td>
<td>0.55 ± 0.06</td>
<td>0.72 ± 0.04</td>
<td>0.66 ± 0.04</td>
</tr>
<tr>
<td>Coherence HF</td>
<td>2.1 ± 0.04</td>
<td>0.82 ± 0.03</td>
<td>0.82 ± 0.02</td>
<td>0.79 ± 0.03</td>
<td>0.75 ± 0.07</td>
<td>0.79 ± 0.04</td>
<td>0.79 ± 0.04</td>
</tr>
<tr>
<td>Resp-CVP, mmHg/l</td>
<td>8.5 ± 1.6</td>
<td>9.0 ± 2.1</td>
<td>9.3 ± 2.9</td>
<td>7.3 ± 1.2</td>
<td>6.6 ± 1.2</td>
<td>5.1 ± 1.7</td>
<td>5.1 ± 1.6</td>
</tr>
<tr>
<td>Coherence LF</td>
<td>4.3 ± 0.07</td>
<td>3.6 ± 0.5</td>
<td>3.5 ± 0.6</td>
<td>3.6 ± 0.5</td>
<td>3.5 ± 0.6</td>
<td>3.4 ± 0.7</td>
<td>3.4 ± 0.9</td>
</tr>
<tr>
<td>Coherence HF</td>
<td>4.1 ± 0.05</td>
<td>0.56 ± 0.06</td>
<td>0.49 ± 0.07</td>
<td>0.59 ± 0.05</td>
<td>0.62 ± 0.07</td>
<td>0.59 ± 0.08</td>
<td>0.53 ± 0.08</td>
</tr>
<tr>
<td>Resp-CVP, mmHg/l</td>
<td>0.46 ± 0.04</td>
<td>0.54 ± 0.04</td>
<td>0.52 ± 0.04</td>
<td>0.55 ± 0.04</td>
<td>0.62 ± 0.02</td>
<td>0.59 ± 0.03</td>
<td>0.52 ± 0.07</td>
</tr>
<tr>
<td>Coherence LF</td>
<td>4.8 ± 0.07</td>
<td>6.3 ± 1.8*</td>
<td>6.2 ± 2.8</td>
<td>3.2 ± 0.9</td>
<td>2.3 ± 0.7</td>
<td>2.4 ± 0.6</td>
<td>2.3 ± 0.6*</td>
</tr>
<tr>
<td>Coherence HF</td>
<td>9.4 ± 2.2*</td>
<td>9.2 ± 2.2</td>
<td>6.8 ± 1.8</td>
<td>5.2 ± 1.2</td>
<td>3.2 ± 0.8</td>
<td>3.4 ± 0.8</td>
<td>3.3 ± 0.8</td>
</tr>
<tr>
<td>Coherence LF</td>
<td>0.88 ± 0.05*</td>
<td>0.88 ± 0.06</td>
<td>0.88 ± 0.04</td>
<td>0.77 ± 0.05</td>
<td>0.70 ± 0.09</td>
<td>0.67 ± 0.07</td>
<td>0.69 ± 0.07</td>
</tr>
<tr>
<td>Coherence HF</td>
<td>0.94 ± 0.03</td>
<td>0.92 ± 0.05</td>
<td>0.96 ± 0.02</td>
<td>0.92 ± 0.02</td>
<td>0.94 ± 0.01</td>
<td>0.90 ± 0.03</td>
<td>0.90 ± 0.04</td>
</tr>
<tr>
<td>SBP-R-R, ms/mmHg</td>
<td>11.4 ± 1.5*</td>
<td>17.1 ± 2.4</td>
<td>16.7 ± 2.9</td>
<td>21.7 ± 4.1</td>
<td>26.3 ± 3.7</td>
<td>31.0 ± 5.1*</td>
<td>27.6 ± 5.8</td>
</tr>
<tr>
<td>α-Gain LF</td>
<td>10.1 ± 1.6*</td>
<td>14.8 ± 2.5*</td>
<td>18.4 ± 2.6</td>
<td>23.8 ± 4.1</td>
<td>32.3 ± 5.4</td>
<td>31.2 ± 6.7</td>
<td>22.4 ± 4.6</td>
</tr>
<tr>
<td>α-Gain HF</td>
<td>0.62 ± 0.06</td>
<td>0.74 ± 0.03</td>
<td>0.72 ± 0.05</td>
<td>0.70 ± 0.07</td>
<td>0.78 ± 0.04</td>
<td>0.76 ± 0.05</td>
<td>0.64 ± 0.07</td>
</tr>
<tr>
<td>Coherence LF</td>
<td>0.60 ± 0.06</td>
<td>0.60 ± 0.06</td>
<td>0.64 ± 0.05</td>
<td>0.68 ± 0.04</td>
<td>0.73 ± 0.04</td>
<td>0.71 ± 0.04</td>
<td>0.61 ± 0.07</td>
</tr>
<tr>
<td>Coherence HF</td>
<td>0.80 ± 0.06</td>
<td>0.60 ± 0.06</td>
<td>0.64 ± 0.05</td>
<td>0.68 ± 0.04</td>
<td>0.74 ± 0.04</td>
<td>0.71 ± 0.04</td>
<td>0.62 ± 0.07</td>
</tr>
</tbody>
</table>

Values are means ± SE; coherence low-frequency (LF) and coherence high-frequency (HF) values are unitless. AR, autoregressive; Resp, respiration; Mech, mechanical: α-gain, α-baroreceptor gain; β-gain, β-feedback forward gain. *Values statistically different from combined control epoch. †Statistically different from leg++ volume loading epoch.
gain did occur between 60° leg raise and the NS infusion ($P < 0.02$). The mechanical influence of respiration on SBP was virtually constant, regardless of volume state, with the possible exception of a slight increase of gain at −30 mmHg LBNP (Table 2). The negative 90° phase at all epochs is consistent with that found previously (20) and appears to reflect the fact that the mechanical influence of respiration on intrathoracic pressure is related to the rate of change of lung volume (derivative), or flow (28).

**Baroreflex (Table 2, Fig. 6).** Again for demonstration purposes, only a single frequency range is shown, but for the baroreflex relations, the more traditional LF band is used (5). As noted for the RSA identification, the phase values obtained for the baroreflex relations seem reasonable for the nature of the physiological interactions between heart rate and arterial pressure. The feedback path from SBP to R-R ($\alpha$-Baro in Fig. 6) has a phase just below 0°, indicating that R-R interval increases (heart rate decreases) when SBP increases with a very short delay, all consistent with a vagally mediated response. Alternatively, the feedforward path from R-R to DBP ($\beta$-FF) has a phase around 90°, consistent with a 180° shift at 0 Hz (decreased R-R increases DBP) and a 2- to 3-s time delay for propagating a change in heart rate into a change in arterial pressure. Importantly, the $\alpha$-baroreflex feedback gain revealed the same characteristic trend shown by the R-R monovariate parameters and by the RSA gain, with the peak for baroreflex control of heart rate located at the same point of mild hypervolemia from the 60° leg raise as seen in the other parameters. The feedforward gain increased significantly at the two highest levels of hypovolemia ($P < 0.01$) and decreased significantly at the highest level of hypervolemia ($P < 0.01$).

**Resp-CVP.** The mechanical influence of respiration on central filling pressures had an unusual and somewhat unexpected finding. The gain increased slightly during the hypovolemia induced by LBNP and decreased about the same amount during volume loading. However, the phase underwent a dramatic nearly 180° shift at the first level of hypervolemia and remained significantly different from control at all levels of volume loading (Fig. 7). These observations may best be visualized by examining the time domain respiratory and CVP signals from one subject (Fig. 8). CVP clearly decreases with inspiration at −30 and −5 mmHg LBNP, has a somewhat biphasic response at control, and increases with inspiration during central volume expansion, beginning with the 20° leg raise.

**DISCUSSION**

There are three important new findings in this study. First, and most important, the data demonstrate that short-term cardiovascular control (RSA and baroreflex feedback) appears to be optimized at mild hypervolemia, suggesting that even awake supine normovolemic conditions can represent a state of very mild...
cardiovascular stress to normal human subjects. Second, both the time and frequency domain data strongly support the presence of a Bainbridge reflex (hypervolemia-induced tachycardia) at moderately elevated levels of central volume, presumably present, as Bainbridge suggested (3), to reduce cardiac preload under volume loading conditions. Third, an unexpected effect of volume loading was identified, in which the normal effect of respiration on CVP is reversed, serving as an indicator of intrathoracic volume status. The results from this study also confirm prior observations that mild to moderate levels of hypovolemia do not cause significant reductions in arterial pressure (10), explained in part in this study by a mild tachycardia and increased feedforward gain from heart rate to arterial pressure.

Optimization of heart rate control at mild hypervolemia. Multiple studies have demonstrated that mild hypovolemia induced by low levels of LBNP does not lead to significant reductions of arterial pressure (1, 9, 10); however, all of the precise mechanisms underlying this observation have never been fully elucidated. Some investigators have concluded that the unloading of cardiopulmonary receptors in the atria and ventricles leads to a reflex increase in sympathetic outflow to muscle vascular beds, subsequent vasoconstriction, and maintenance of arterial pressure, despite reduced cardiac output (22). However, other studies have brought this hypothesis into question, suggesting that arterial baroreflex mechanisms play the largest role (9). This study has used a different approach to quantify the cardiovascular response to mild to moderate levels of both hypo- and hypervolemia, employing the frequency response to small fluctuations of heart rate and arterial pressure induced by random respiratory activity to assess the response of the various control systems involved. Our findings demonstrate that indeed the gain and phase characteristics of multiple control systems do change with shifts in central volume and are consistent with some previous findings demonstrating a change in vagal heart rate control during low levels of LBNP (8) or nonhypotensive hemorrhage (25).

In this study, the two systems most responsible for controlling short-term fluctuations of heart rate, the arterial baroreflex and the RSA, both appeared to be optimized (point of maximum gain) in a state of mild hypervolemia. These findings are supported by a peak in R-R variance and a maximum for the mean R-R interval (lowest heart rate) at the same point, suggesting that indeed the cardiovascular system is in a condition of minimized stress. The fact that both the heart rate arterial baroreflex and RSA gains continually decline with progressive hypovolemia while arterial pressure is maintained suggests that neither of these control elements is fully responsible for the maintenance of pressure. Because central volume was not directly

Fig. 4. Total variance (left), LF variance (middle), and HF variance (right) of Resp (A), CVP (B), R-R interval (C), and SBP (D): averages for the group. Bars indicate SEs on the averaged values. *Epochs that significantly differ (P < 0.05) from the control epoch. •Significant difference between the leg++ and the 500-ml epoch.
perturbed on a beat-to-beat basis using a technique such as random LBNP (24), and muscle sympathetic outflow was not directly measured, the data from this study cannot be used to comment directly on either arterial baroreflex or cardiopulmonary reflex control of peripheral arterial resistance as the mechanism. However, we did observe increases in the feedforward gain from heart rate to arterial pressure (R-R-DBP), the “other half” of the arterial baroreflex. These changes indicate that in the volume-reduced state, the same change in heart rate is able to produce a larger change in arterial pressure and supports the notion that the elevation in mean heart rate helps prevent a fall in arterial pressure. The mechanism by which this feedforward gain might be increased might be related to the reduction in thoracic aortic size previously documented by Taylor et al. (23) during similar volume reductions. With arterial capacitance reduced, the
same change in cardiac output will lead to a larger change in pressure. Although we report on the feedforward gain to DBP, the findings were similar for SBP with a slightly longer phase lag. Regardless of which blood pressure parameter is used, the data from this study clearly address more directly the role of heart rate control and its optimization at mild hypervolemia than the precise mechanism of blood pressure maintenance during hypovolemia. Furthermore, it should be noted that the magnitude of the feedforward effect appears to be species and circumstance dependent, with a smaller effect noted by some in species such as rabbits (14), but a clear effect noted by others in the same species (26).

Bainbridge reflex in humans. The phenomenon of hypervolemia-induced tachycardia was first described by Bainbridge in 1915 (3) after observing heart rate elevations in anesthetized dogs during very large rapid infusions of volume to the left atrium, which markedly increased left atrial pressure. Bainbridge hypothesized that the reflex served the purpose of increasing cardiac output in response to increased venous return to the heart, reducing the elevation of cardiac preload. Although Bainbridge himself did not describe a bradycardia component to the reflex during lowering of atrial pressure, the basis of the Bainbridge reflex in animals was eventually described as the full cardiopulmonary reflex (15), parallel activation and deactivation of both sympathetic and parasympathetic efferent activity with hypo- and hypervolemia, respectively. Thus, al-

Fig. 7. Gain and phase calculated for the group in LF for the influence of Resp on CVP. *Epochs that significantly differ (P < 0.05) from the control epoch.

Fig. 8. Comparison between Resp (A) and CVP (B) during volume reduction (−30 and −5 mmHg) and volume loading (leg+ and 500 ml): 150-s segments extracted from recordings of a single complete experimental procedure.
though the cardiac sympathetic component of the cardiopulmonary reflex will generally be in the same direction as the cardiac component of the arterial baroreflex response (increased sympathetic outflow during hypovolemia rather than reduced), the cardiac parasympathetic or vagal component will generally be in the opposite direction (enhanced vagal outflow during hypovolemia). Given all of these complexities, it is not surprising that there has been a failure to consistently observe a clear Bainbridge reflex in humans. In fact, on the hypovolemia side, the heart rate response to mild reductions in central venous volume in humans has varied across the many studies in the literature from mild tachycardia as we observed in this study, to no change in heart rate to mild bradycardia (9, 18).

There have been relatively few studies of the heart rate response to hypervolemia in humans; however, recently Pawelczyk and Levine (17) found that tachycardia could indeed be induced with hypervolemic expansion in humans. These data are in agreement with our findings on mean R-R interval, but in addition, the data from this study go further to identify reductions in heart rate arterial baroreflex and RSA gain that parallel the reduction in R-R interval (tachycardia). Furthermore, we observed a significant drop in HF power for R-R interval, indicating a reduction in vagal modulation of heart rate, consistent with Bainbridge’s original hypothesis (3). These changes and the observation that HF power for R-R interval declines during LBNP-induced hypovolemia suggest that in humans, vagally mediated arterial baroreflex control of heart rate dominates during most mild central volume changes, consistent with other findings (9). However, with significant increases in volume, “Bainbridge” takes over by reducing mean and beat-to-beat vagal activity.

Respiratory modulation of CVP: phase changes with mild hypervolemia. Perhaps the most unique and certainly the most unexpected observation of this study is the dramatic nonlinear shift in the phase relation between respiratory activity and CVP with even the mildest level of hypervolemia (see Figs. 7 and 8 at leg±). Virtually every physiology text describes the well-known reduction in intrathoracic pressure during inspiration (28), which subsequently reduces intravascular pressure within the thorax and increases venous return during inspiration, leading to increased right ventricular output and a widening of the split in the second heart sound. The data from this study are consistent with such a scenario during control conditions and hypovolemia (Fig. 8, control and −5 and −30 mmHg) but demonstrate the opposite effects during hypervolemia, elevation of CVP during inspiration (Fig. 8, leg+ and 500 ml), presumably reducing any inspiratory-related increases in venous return. Although the methodology used in the study does not allow us to specifically address the underlying mechanism of this phenomenon, there are a few clues in the data. Because there was no notable change in CVP between the first two levels of hypervolemia (Fig. 3, leg+ and leg++), one can speculate that most of the blood pooled in the leg veins was emptied into the splanchnic and thoracic veins during the first leg elevation, representing a relatively large shift in volume. After that point, with the splanchnic bed full and with primarily diaphragmatic breathing in the supine position, inspiration probably led to compression of the abdominal veins, which with the legs raised forced blood into the thorax. Apparently, this effect overcame any reductions in pressure due to decreased intrathoracic pressure. The precise effect on total venous return to the heart is less clear, because blood in the superior systemic thoracic veins would actually be forced out of the thorax by the elevated pressure, rather than drawn into the thorax by negative pressure, but more blood would be forced into the thorax through the inferior thoracic systemic veins by positive pressure from the abdomen. Regardless of the mechanism underlying it, this sudden shift in phase between respiration and CVP represents a sensitive marker of central volume status, which may have clinical utility in the identification of optimum volume status.

Clinical utility of the findings. The three primary observations in this study can all be combined to derive a clinical algorithm for determining optimal volume status in critically ill patients. The simplest metric in this study to utilize in a clinical setting is the respiratory-CVP phase shift, which can be observed without any special tools on a standard cardiac monitor. A patient whose volume status is unclear could be volume loaded until the patient is at or near the point of a 0°, in-sync, relation, with periodic checks by slight elevations of the lower extremities. Because R-R interval is always available and arterial pressure usually available, a more sophisticated monitoring system could also continuously measure R-R interval, R-R interval HF power, RSA gain, and arterial baroreflex gain, as previously described (4). Optimized clinical status will theoretically be present at the maximum point for each of these variables, which occurs very near the Resp-CVP phase shift. Finally, any sign of activation of the Bainbridge reflex, as indicated by a decrease in one of these variables during volume loading, should be taken as a sign of volume overload.

Clearly, the above scenarios make a number of assumptions that would have to be tested in clinical trials before their routine use. Perhaps the most important assumption is that the abnormal heart and vasculature will respond similarly to that in the subjects presented here who have presumably normal physiology. Nonetheless, the possibility of having such sensitive clinical volume measures is intriguing.

Limitations. As noted previously, the data in this study cannot be used to fully explain the mechanisms by which mean arterial pressure is maintained during mild hypovolemia. In particular, without measurement of efferent sympathetic activity or systemic vascular resistance, the full role of the arterial and cardiopulmonary reflexes cannot be elucidated. Despite the clear observation of the phase shift between Resp and CVP, neither the precise mechanism underlying it nor the precise effects on venous return can be identified from the data collected here. Furthermore, despite using a
causal technique that attempts to separate out baroreflex effects from other effects on heart rate, random interval breathing introduces RSA in the LF range where the baroreflex normally predominates, potentially confounding the identification of the baroreflex. Finally, because no clinical studies have been performed to test the abilities of the described parameters to measure volume status, at this time the clinical utility of the findings is purely theoretical.

Conclusions. Systems analysis techniques can provide unique insights into cardiovascular regulation. In this study, the relations between respiration, arterial pressure, and CVP were used to investigate the physiological effects of mild to moderate reductions and elevations of central volume. Furthermore, random interval breathing was used to broaden the frequency content of the relations being studied. The data demonstrated first that heart rate control appeared to be maximized in a state of mild central hypervolemia, to a point where increases in volume lead to reductions in heart rate control gain, and tachycardia. These findings also confirmed the presence of a Bainbridge reflex in humans. Finally, an unexpected nonlinear phase shift in the mechanical coupling between respiration and CVP was identified during mild hypervolemia, near the point of maximum heart rate control. Together, the heart rate control and respiratory-CVP findings may potentially serve as sensitive markers of central volume status in critically ill patients.

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