Blood Pressure Modulation by Central Venous Pressure and Respiration
Buffering Effects of the Heart Rate Reflexes

John K. Triedman, MD; J. Philip Saul, MD

Background  Despite constant fluctuations in cardiac preload caused by the effects of respiration and changes in posture on venous return to the heart, arterial blood pressure remains remarkably constant. The effects of instantaneous lung volume (ILV) and variations of central venous pressure (CVP) on blood pressure (BP) were studied by use of frequency domain techniques to quantify the contribution of heart rate (HR) reflexes to attenuation of the effects of changes in right ventricular preload on arterial pressure.

Methods and Results  Random independent variation of ILV, then CVP (obtained using lower-body negative pressure), was performed in eight humans in the supine position. HR, ILV, CVP, and systolic (SBP) and diastolic (DBP) BP were recorded during control periods and after complete blockade obtained by use of 0.04 mg/kg atropine and 0.2 mg/kg propanolol. A frequency-domain analysis was performed on pairwise relations by the cross-spectral technique. During autonomic blockade, fluctuations in CVP were induced up to 0.14 Hz but caused corresponding changes in arterial pressure only up to 0.08 Hz (P<.02), indicating a mechanical damping effect of the heart and pulmonary vasculature. Fluctuations of BP were also delayed from CVP by 1.55 to 2.10 seconds. At frequencies <0.1 Hz, relations of CVP to all indices of BP increased with blockade (CVP-SBP, 0.9±0.5 versus 2.7±0.8 mm Hg/mm Hg, P<.01; CVP-DBP, 1.3±0.4 versus 4.3±1.4 mm Hg/mm Hg, P<.01; CVP-pulse pressure [PP], 1.0±0.1 versus 1.9±0.8 mm Hg/mm Hg, P<.05). Higher-frequency fluctuations of arterial BP were a relatively pure manifestation of respiratory activity. At frequencies from 0.15 to 0.35 Hz, the relation of ILV to SBP was unchanged with blockade, whereas relations of ILV to DBP and PP decreased (ILV-DBP, 6.1±3.5 versus 3.3±2.2 mm Hg/L, P<.02; ILV-PP, 7.0±4.3 versus 2.7±2.2 mm Hg/L, P<.01). An associated change in phase of these relations suggested that neurally mediated changes in HR may offset mechanical effects caused by respiration.

Conclusions  Both slow changes of BP (<0.08 Hz) induced by variations of CVP and more rapid changes induced by ILV are actively buffered by heart rate reflexes. During blockade, the mechanical properties of interposed cardiopulmonary structures limit CVP-induced fluctuations of BP. These findings have implications for BP regulation in pathological conditions associated with impairment of HR control. (Circulation. 1994;89:169-179.)

Key Words  • blood pressure • heart rate • Fourier analysis

Central venous return to the heart varies constantly, predominantly in response to changes in intrathoracic pressure and posture. In the isolated heart, Starling's law predicts increases in stroke volume that are nearly linearly related to filling pressures over a broad range. However, cardiac output and arterial blood pressure are relatively insensitive to changes in central venous pressure (CVP). Volume loading of experimental animals in the autonomically intact state causes changes in stroke volume that are largely compensated for by heart rate (HR) changes, resulting in an attenuated effect on total cardiac output.

These observations appear to apply only in the setting of intact autonomic cardiovascular regulation. The elimination of autonomic responses to afferent information obtained from arterial baroreceptors and chemoreceptors results in a marked increase in the variability of arterial blood pressure and in the response of mean arterial blood pressure to changes in CVP; Herndon and Sagawa noted changes in cardiac stroke volume of as much as 50% in response to changes in venous filling pressures of 1 cm H2O. In humans, sensitivity to volume loading is markedly augmented by ganglionic blockade, with both cardiac output and arterial blood pressure increased after transfusion. Deficiencies of rapid HR modulation have been observed in a variety of cardiovascular pathological conditions, including arterial hypertension and congestive heart failure, and after ischemic events and have been correlated with an increased risk of sudden death after myocardial infarction.

In this study, the hypothesis was tested that autonomic HR control attenuates fluctuations of arterial pressure caused by variations in venous return to the heart in autonomically intact humans. To estimate the importance of this regulatory effect, a frequency-domain approach was used to quantify the relations between respiration, CVP, and indices of arterial blood pressure both in the autonomically intact state and during pharmacologically induced total cardiac autonomic blockade. By inducing random fluctuations of venous return and respiratory activity that were independent of one another, it was possible to examine and...
distinguish the buffering effects of the HR reflexes on both pure low-frequency fluctuations of CVP and the higher-frequency effects associated with respiration and changes of intrathoracic pressure. Additionally, elimination of the HR reflexes, which would otherwise damp the response of arterial blood pressure to these induced fluctuations, allowed quantification of the hydraulic properties of the cardiopulmonary circulation.

Methods

Subject Group

The experimental group consisted of eight healthy young adult volunteers. Studies were performed in the morning, 1 to 2 hours after a light breakfast. No subject was taking medication or had smoked or consumed caffeinated beverages on the day of the study. Three of the subjects were women and five men, with a median age of 23 years (range, 20 to 25 years) and a median weight of 65.5 kg (range, 57.0 to 86.0 kg).

Experimental Protocol

The study protocol was approved by the institutional human studies committee, and written informed consent was obtained from all participants. Lower-body negative pressure (LBNP) was applied by use of a plexiglass chamber that accommodated the hips and lower extremities of the subjects. This device allowed for rapid application of negative pressures down to \(-50\) cm H\(_2\)O. Room temperature was maintained at \(75^\circ\)F.

Surface ECG, instantaneous lung volume (ILV), CVP, arterial blood pressure, and LBNP chamber pressure were monitored. ILV was recorded with a Respitrace two-belt impedance plethysmograph (Noninvasive Monitoring Systems, Ardsdale, NY) and calibrated by having subjects inhale and deflate an 800-mL bag. A central venous line was placed via the left median cubital or cephalic vein, positioned in the superior vena cava, and flushed continuously with heparinized saline. CVP and LBNP were transduced with Statham strain-gauge transducers, which were calibrated with a water manometer and positioned at the level of the right atrium. Arterial blood pressure was measured with a noninvasive volumeclamp device (Finapres, Ohmeda, Englewood, Colo) applied to the right third digit.

Data were recorded after the subjects were comfortable and cardiovascular variables were observed to be stable. 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 3.3 seconds (0.3 Hz, 18 breaths per minute). For the first experimental period of 8 minutes, the cues occurred with intervals between 1 and 15 seconds, randomly chosen from a Poisson distribution, with a mean interval of 4 seconds, or 15 breaths per minute. For the second period of 8 minutes, respiratory cues were again set at a constant 3.3-second interval, and LBNP was varied between 0 and \(-40\) cm H\(_2\)O with the same sequence of intervals used to control respiration in the first period. Tidal volume was not controlled. 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.\(^{15,16}\) In this study, application of LBNP at random intervals was similarly used to increase the spectral range of the CVP signal. Because respiration was independently controlled during random LBNP and because the induced changes in CVP were uniformly lower than the respiratory frequency of 0.3 Hz, the effects of ILV and random LBNP could be discriminated in the frequency domain (Fig 1).

Total cardiac autonomic blockade was obtained with propranolol (0.2 mg/kg IV) and atropine (0.04 mg/kg IV).\(^{17-19}\) Instruments were recalibrated, and the protocol outlined above was repeated. Recordings were completed within 20 minutes of the administration of the two drugs.

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 (DT2827, Data Translation, Marlboro, Mass) on an 80386-based computer (Deskpro, Compaq, Houston, Tex). R-wave positions were detected digitally, and RR intervals were converted into a smooth instantaneous HR time series constructed at 3 Hz by use of an algorithm described previously.\(^{20}\) CVP, LBNP, and ILV signals were digitally filtered at 1.5 Hz and decimated to 3 Hz. Systolic (SBP) and diastolic (DBP) blood pressures were identified in real time with an R-wave–triggered algorithm, and values were splined and sampled at 3 Hz so that all the constructed time series were synchronous. Pulse pressure (PP) was obtained by subtracting DBP from SBP.

Data were transferred to a workstation (SPARC 4, Sun Microsystems, Mountain View, Calif) for off-line analysis. All signals were visually inspected for artifact. Time series of approximately 6 minutes (341 seconds, or 1024 points) of HR, ILV, CVP, LBNP, SBP, DBP, and PP were selected from each
TABLE 1. Hemodynamic Variables Before and After Autonomic Blockade

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Autonomic Blockade</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random-Interval breathing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>57.1±9.0</td>
<td>95.4±15.3</td>
<td>.001</td>
</tr>
<tr>
<td>Lung volume variance, L²</td>
<td>0.06±0.03</td>
<td>0.07±0.09</td>
<td>.452</td>
</tr>
<tr>
<td>Central venous pressure, mm Hg</td>
<td>7.17±2.09</td>
<td>3.88±1.78</td>
<td>.013</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>110.0±3.2</td>
<td>118.4±5.6</td>
<td>.007</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>59.2±6.2</td>
<td>76.5±8.3</td>
<td>.001</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>50.9±6.8</td>
<td>41.8±7.1</td>
<td>.073</td>
</tr>
<tr>
<td>Random lower-body negative pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>57.6±9.6</td>
<td>95.0±13.9</td>
<td>.001</td>
</tr>
<tr>
<td>Lung volume variance, L²</td>
<td>0.08±0.11</td>
<td>0.07±0.07</td>
<td>.793</td>
</tr>
<tr>
<td>Central venous pressure, mm Hg</td>
<td>5.36±1.68</td>
<td>2.41±1.21</td>
<td>.018</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>108.9±6.3</td>
<td>117.4±3.2</td>
<td>.014</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>58.2±9.5</td>
<td>75.9±7.3</td>
<td>.004</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>50.6±7.7</td>
<td>39.3±5.6</td>
<td>.041</td>
</tr>
</tbody>
</table>

bpm indicates beats per minute. Data are presented as mean±SD. P values were determined by Wilcoxon test, from control to autonomic blockade conditions.

8-minute study period of random breathing or random LBNP for analysis. Mean values for each experimental condition were calculated. The variability of each signal was calculated as the integrated power spectral density from 0 to 0.35 Hz.

**Frequency-Domain Analyses**

Physiological signals have classically been represented and interpreted in the time domain, reflecting the manner in which they are acquired. Such signals are easily converted from the time domain to the frequency domain by Fourier techniques. With these techniques, the total variance of a signal can be broken down into its oscillatory components at individual frequencies.

The transfer function of two signals defines their relative power (gain) and timing (phase) over a range of frequencies of physiological interest and provides a statistical measure of reliability of the relation between the two signals, called coherence. This technique has been simply but effectively used to study respiratory sinus arrhythmia by plotting the gain and phase relations of respiratory activity to HR over a number of discrete frequencies. Use of random-interval techniques allows efficient collection of data over a broader and more continuous frequency spectrum. These principles can be extended to any physiologically coupled input and output signals, whether the coupling is mechanical or neural.

The following transfer relations were calculated by the cross-spectral technique (see "Appendix A"): ILV-HR, ILV-SBP, ILV-DBP, ILV-PP, "ILV-CVP, CVP-HR, CVP-SBP, CVP-DBP, CVP-PP, LBNP-CVP, and LBNP-ILV. The coherence estimate, which varies from 0 to 1, does not have direct physiological significance but serves as a statistical measure of the reliability of the transfer function estimate and of the linearity of the input/output relation. In this study, coherence was used to weight individual values of transfer magnitude and transfer phase in the calculation of group-averaged and band-averaged transfer functions by a previously described technique (also see "Appendix B"). A pilot study had shown that random application of LBNP was generally able to induce fluctuations of CVP up to 0.15 Hz. From this information, frequency bands were selected to allow us to examine the mechanical effects of CVP and ILV on blood pressure with minimal interference from the other (Fig 1). In this study, the relations between CVP and indices of blood pressure were studied in the frequency band 0 to 0.1 Hz, and the relations between ILV and indices of blood pressure were studied between 0.15 and 0.35 Hz.

Pure time delays between input and output signals were determined by identification of linear sections of the phase function and calculation of their slopes. For calculation of pure time delays between CVP and indices of blood pressure and between respiration and DBP, these calculations assumed a phase of 0° at 0 Hz, which would be consistent with a direct relation between the input and output signals (ie, increase in CVP causing an increase in blood pressure).

Transfer functions for the relations between LBNP and CVP and between CVP and SBP and DBP were modeled as low-pass filters after examination of the gain and phase functions suggested that they showed both a phase shift of 90° and an associated drop in gain. Corner frequency was estimated as the frequency at which the gain was 3 dB lower than the maximum gain (approximately 71% of maximum gain).

**Statistical Techniques**

The mean values of HR, CVP, SBP, DBP, and PP and the variance of HR, SBP, DBP, PP, and ILV were not assumed to be normally distributed, and comparisons were made between the experimental periods with the Wilcoxon signed-rank test. Transfer function gains were calculated as band averages as described above, and resultant values as well as values obtained for corner frequencies were compared by the Wilcoxon test. A value of P<.05 was considered statistically significant.

**Results**

**Effect of Autonomic Blockade on HR Control, Respiration, CVP, and Blood Pressure**

Autonomic blockade caused increases in mean HR and mean SBP and DBP as well as a nonsignificant decrease in PP. Variance of ILV, an estimate of average tidal volume, was unchanged, and mean CVP decreased with autonomic blockade (Table 1). During the random LBNP protocol, applied LBNP varied between 0 and approximately −30 mm Hg; mean values of applied LBNP over the 8-minute recording periods ranged from −5.2 to −7.3 mm Hg.

HR variability fell significantly with autonomic blockade (Table 2). Most residual HR variability was found
at frequencies <0.15 Hz; the power of the HR signal between 0.15 and 0.35 Hz fell to <2% of control values with autonomic blockade during both random-interval breathing and random LBNP (HR variability control versus autonomic blockade: with random-interval breathing, 5.84 versus 0.09 beats per minute squared, \( P < .002 \); with random LBNP, 5.63 versus 0.08 beats per minute squared, \( P < .001 \)). The effects of autonomic blockade on variability of indices of blood pressure varied with the protocol and are presented in Table 2.

### Low-Pass Filter Characteristics of Heart and Lungs During Autonomic Blockade

SBP and DBP time series from a single study involving random LBNP with and without autonomic blockade are presented with corresponding CVP and ILV time series in Fig 2. High-frequency respiratory oscillations in the CVP time series are superimposed on larger low-frequency changes caused by LBNP. The frequency-domain analysis of these relations is also presented, with plots of the mean gain, phase, and coherence of the relations of CVP to SBP and DBP in the control and blockade conditions. In the frequency domain, the low-frequency relations of CVP to indices of SBP and DBP demonstrated a frequency-dependent decrease in gain coupled with a phase shift, a pattern similar to that of a low-pass filter with a time delay. To quantify the ability of the autonomically blockaded heart to transmit changes in CVP to changes in SBP and DBP, we modeled the cardiopulmonary unit as a single-pole low-pass filter with a delay.

Application of random LBNP resulted in significant transmission of signal power to CVP, with 75% to 80% of CVP variance occurring at frequencies <0.20 Hz as assessed by the CVP power spectrum. In the autonomically intact control state, low-frequency variations in CVP were not associated with significant variability of indices of arterial blood pressure, and corner frequencies could not be calculated. Fig 3 shows the estimation of corner frequencies during autonomic blockade for the transfer functions that depict the mechanical effects of LBNP on CVP and of CVP on DBP. Mean corner frequency (frequency with 71% maximum signal transmission) of the LBNP on CVP relation was 0.13±0.05 Hz, and the relations of CVP to both SBP and DBP had mean corner frequencies of 0.08±0.01 Hz, significantly lower than the corresponding corner frequencies of the relation of LBNP to CVP (\( P < .02 \)). Thus, despite modulation of CVP to a frequency of 0.13 Hz by random application of LBNP, the arterial blood pressure response was damped to fluctuations >0.08 Hz during autonomic blockade.

The slopes of phase relations were calculated to quantify time delays from CVP to indices of blood pressure. Slopes of the relations of CVP to SBP and DBP were calculated from linear segments of phase functions in the frequency range 0 to 0.1 Hz. A change in CVP was reflected in SBP and DBP after a delay of 1.55 seconds (systolic) and 2.10 seconds (diastolic).

We interpreted these findings as demonstration of a mechanical damping effect of the heart and the pulmonary and thoracic vasculature on changes in CVP. The time delay noted between CVP events and changes in SBP and DBP reflects the fact that some of these changes are actually mediated by movement of blood through the pulmonary vasculature and not merely by propagation of pressure waves or ventricular interdependence. The fall in gain and phase roll-off above 0.08 Hz and the very small effect of CVP changes on blood pressure at 0.30 Hz (the respiratory frequency) indicate that little or no transmission of pressure effects was occurring at these higher frequencies, again supporting the notion that the observed effects are due to transmission of blood volume through the lungs.

### Relations of CVP to Indices of Blood Pressure

Referring again to Fig 2, an increase of the effect of low-frequency CVP variation on fluctuation of SBP and DBP can be easily appreciated after autonomic blockade in the time domain. Examination of the frequency-domain analysis during the control condition reveals low coherence values, indicating that there was little consistent relation between CVP and arterial pressure, despite the lower-frequency variation in CVP induced by LBNP, as depicted in Fig 1. The localized peak of high coherence at 0.3 Hz represents the effects of respiration.

| TABLE 2. Heart Rate and Blood Pressure Variability Before and After Autonomic Blockade |
|---------------------------------|-----------------|-----------------|----------|
| **Random-Interval breathing**   | **Control**     | **Autonomic Blockade** | **P**   |
| Heart rate, bpm²                | 18.0±12.1       | 0.9±0.7         | .002    |
| Systolic blood pressure, mm Hg² | 5.3±7.7         | 3.5±2.2         | .866    |
| Diastolic blood pressure, mm Hg²| 9.1±3.8         | 5.9±2.0         | .056    |
| Pulse pressure, mm Hg²          | 6.1±2.5         | 2.9±0.7         | .035    |

<table>
<thead>
<tr>
<th><strong>Random lower-body negative pressure</strong></th>
<th><strong>Control</strong></th>
<th><strong>Autonomic Blockade</strong></th>
<th><strong>P</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm²</td>
<td>17.5±10.5</td>
<td>3.4±5.2</td>
<td>.003</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg²</td>
<td>9.5±13.4</td>
<td>12.2±3.6</td>
<td>.024</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg²</td>
<td>9.4±3.6</td>
<td>28.0±14.4</td>
<td>.002</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg²</td>
<td>7.7±6.7</td>
<td>8.7±5.3</td>
<td>.726</td>
</tr>
</tbody>
</table>

bpm indicates beats per minute.

Variability is calculated as the integrated power spectral density over the range 0 to 0.35 Hz. Data are presented as mean±SD. \( P \) values were determined by Wilcoxon test, from control to autonomic blockade conditions.
In comparison with the control condition, autonomic blockade caused a significant increase in mean coherence between CVP and indices of blood pressure in the frequency range <0.10 Hz. Increased gains of the relations from CVP to SBP (0.9±0.5 mm Hg/mm Hg control versus 2.6±0.8 mm Hg/mm Hg blockade, \( P=.010 \)), DBP (1.3±0.4 mm Hg/mm Hg control versus 4.3±1.4 mm Hg/mm Hg blockade, \( P=.010 \)), and PP (1.0±0.3 mm Hg/mm Hg control versus 1.9±0.8 mm Hg/mm Hg blockade, \( P=.030 \)) were noted below 0.10 Hz with autonomic blockade (Fig 4). These data indicate that the effects of CVP on indices of blood pressure were significantly greater during autonomic blockade than in the control state.

### Relations of Respiratory Activity to Indices of Blood Pressure

SBP and DBP time series from a single study are presented with corresponding HR and ILV time series in Fig 5. The average gains of these relations for the study group over the frequency range 0.15 to 0.35 Hz are presented in Fig 6. In contrast to the low-frequency effect of CVP on blood pressure, which increased with autonomic blockade, the magnitude of both SBP and DBP variation at higher frequencies decreased with autonomic blockade. Fig 7 depicts the effect of autonomic blockade on respiration, DBP, and HR. In the autonomically intact state, respiratory sinus arrhythmia drove well-correlated changes in HR, which were rapidly followed by corresponding increases in DBP. During autonomic blockade, HR was unrelated to respiratory activity, and the pure mechanical relation between respiration and DBP showed a small decrease with
Inspiration rather than a large increase, reflecting the mechanical effects of intrathoracic pressure on arterial pressure.

This shift in the relation of ILV to DBP is demonstrated in the frequency-domain analysis (Fig 5). In the frequency range in which a significant respiratory effect on SBP and DBP was evident (>0.15 Hz), the relation of ILV to SBP was largely unaffected by autonomic blockade. The mean gain of the relation remained constant (3.4±1.6 mm Hg/mm Hg control versus 3.2±2.2 mm Hg/L blockade, P=.933), and mean phase was approximately −180° before and after blockade, consistent with the observation that SBP fell with inspiration. In contrast, the magnitude of the relation of ILV to DBP fell significantly with autonomic blockade (6.1±3.5 mm Hg/L control versus 3.3±2.2 mm Hg/L blockade, P=.014), and its phase shifted from approximately −90° to −180°, making it more or less indistinguishable from the relation of ILV to SBP.

The combined effect of these changes is reflected in the frequency response of PP to ILV (Fig 8). Because autonomic blockade shifted the effect of ILV on SBP and DBP from being 90° or more offset in phase to being nearly identical, the magnitude of PP changes with ILV became much smaller (7.0±4.3 mm Hg/L control versus 2.7±2.2 mm Hg/L blockade, P=.010), and its phase changed from approximately 180° before blockade (PP decreased with inspiration) to 0° (PP increased with inspiration). These data indicate that the effects of neurally mediated respiratory changes in HR tended to offset the underlying mechanical effects of respiration on blood pressure.

**Discussion**

The purpose of this experiment was to quantify the buffering effect of autonomically mediated HR variation on short-term fluctuations of blood pressure caused by induced changes in CVP and respiratory activity. Two techniques were used to vary right ventricular preload: random variation of voluntary respiratory activity, which caused fluctuations of venous return related to changes in intrathoracic and intra-abdominal pressures, and random variation of nonhypotensive LBNP, which caused variations of venous return and CVP largely unrelated to intrathoracic events. To further discriminate the effects of these differing stimuli, relations between respiration and venous and arterial blood pressure data were analyzed in selected regions of the frequency domain. This allowed us to discretely characterize the pure mechanical effects of CVP and respiration on blood pressure and to determine the importance of neurally mediated HR control in buffering the induced changes. The primary findings of this study are (1) a mechanical damping effect of the heart and thoracic vessels that limited the transmission of variations in CVP to arterial pressure to frequencies below approximately 0.1 Hz, (2) a potent effect of autonomically mediated HR control to attenuate fluctuations in arterial pressure caused by changes in CVP occurring below these frequencies, and (3) at higher frequencies, associated solely with respiratory activity, relations of
HR and blood pressure that tended to offset the mechanical effects of respiration on blood pressure.

**Effects of CVP on Blood Pressure: Mechanical Damping**

By limiting the frequency of respiratory activity during random LBNP application to a frequency range higher than the induced variability of the CVP, a relatively pure effect of CVP on blood pressure variables could be studied in the frequency range of 0 to approximately 0.20 Hz. Under conditions of autonomic blockade, oscillations of CVP induced by LBNP caused significantly greater arterial blood pressure fluctuations than during control conditions. However, this mechanical effect of CVP on blood pressure was limited by the interposition of the cardiopulmonary unit. CVP oscillations >0.08 Hz were not effectively transmitted to the arterial pressure, and a time delay was interposed between the two. Quantitatively, our data are similar to those described by Maloney et al., who observed a damping effect of an in vitro canine lung preparation, with a similar fall in transmitted pressure and flow variation above 0.1 Hz. This damping effect may be due to buffering of changes in venous return by variations in right ventricular diastolic and systolic function and/or properties of the pulmonary vasculature such as internal wave reflection, distribution of transit time, and the viscoelastic properties of the pulmonary vessels.

If right ventricular filling and/or pressure had had a direct effect on left ventricular function in this group of subjects, mediated by septal displacement in diastole, no upper limit on transmitted frequency should have been found, since this effect should have been transmitted instantaneously. Under the conditions in which these subjects were studied (supine, with moderately decreased CVP during autonomic blockade and nonhypotensive LBNP), no physiological effect of ventricular interdependence was observed. A model for the interaction of the cardiovascular system and intrathoracic pressure proposed by Beyar et al. demonstrated an effect of intrapericardial pressure on left ventricular end-diastolic volume but minimal effect attributable to interventricular interdependence. Gonzalez et al. noted that systolic right and left ventricular pressures varied inversely (ie, with a phase relation of 180°) during inspiration under conditions of experimentally elevated pericardial pressure in dogs but not at normal pericardial pressures. This literature demonstrates that although ventricular interdependence is an important phenomenon in the setting of increased intrapericardial pressures, data obtained at slightly subnormal filling pressures may show no direct effect of this type. This suggests that ventricular interdependence has a threshold for activity, but it does not allow us to determine whether the phenomenon is active at "normal" filling pressures.

**Effects of CVP on Blood Pressure: Attenuation by HR Control**

Lower-frequency oscillations of venous return induced by LBNP were transmitted to the arterial pres-
sure. In the control condition, the relations between CVP and indices of blood pressure were of low magnitude and had poor coherence over this low-frequency range. Institution of autonomic blockade caused the direct effect of low-frequency changes of CVP on SBP and, particularly, DBP to increase markedly. This finding indicates that in the control state, the effect of changes in right ventricular preload on blood pressure were well buffered by cardio regulatory mechanisms that were sensitive to the administration of atropine and propranolol, i.e., the HR reflexes. Although other compensatory vascular reflexes must have been activated by the induced changes in arterial pressure and CVP, the absence of autonomically mediated HR control was sufficient to permit marked increases in blood pressure variability.

The effect of CVP on DBP was augmented by autonomic blockade in excess of its effect on SBP. The explanation for this is not clear. If variations in SBP and DBP in this setting were caused entirely by changes in transport of blood across the pulmonary vascular bed, stroke volume and PP should have increased with increased CVP. It is possible that cyclic variations in vasomotor tone caused by an a-adrenergic response to changes in arterial and/or atrial pressures causing feedback in the 0.05 to 0.1 Hz range might have modified the mechanical response of arterial pressure to changes in CVP and caused a disproportionate increase in the gain of the relation of CVP to DBP.28
Mechanical Effects of Respiration on Venous Return and CVP

Respiratory activity has multiple complex effects on cardiac loading conditions. With inspiration and a decrease in intrathoracic pressure, a more favorable gradient is created for venous return to the heart. However, the effects of this gradient on actual venous return and resultant filling pressure are unpredictable. Transmural intracardiac pressures may be unrelated to measured CVP, and venous return at low intrathoracic pressures may be limited by caval collapse, which is dependent on mean CVP and both intrathoracic and abdominal pressures. Both hydraulic and geometric factors may increase left ventricular afterload, and changes in pulmonary vascular compliance may reduce left ventricular preload. Together, these influences conspire to create a significant fall in left ventricular stroke volume with inspiration. In the autonomically intact state, respiratory sinus arrhythmia and the HR baroreflexes also cause significant beat-to-beat changes in diastolic filling time and stroke volume.

The constraints of our experimental technique limited us to classifying these multiple interacting effects as either autonomically mediated (ie, sensitive to autonomic blockade) or mechanical. To remove the possible influence of changes in CVP induced by respiration from our analysis of the effect of respiration on blood pressure, we made use of our finding that CVP had a negligible effect on blood pressure above approximately 0.1 Hz and limited our analysis of the effect of respiration on blood pressure to the frequency range 0.15 to 0.35 Hz. This allowed us to exclude most of those effects that were mediated by changes in venous return and CVP. Thus, the observed effects of respiration on blood pressure presented here were mediated only by changes of intrathoracic pressure and HR control.

Effects of Respiration on Blood Pressure

If the effects of variations of venous return on arterial pressure were largely limited to low frequencies, as suggested above, other mechanisms than variation of CVP must mediate the effects of respiratory activity on SBP and DBP at higher frequencies. An immediate negative effect of inspiration was noted on both SBP and DBP during autonomic blockade and is presumed to be caused by the mechanical effects of decreased intrathoracic pressure on left ventricular loading and the thoracic arteries. Additionally, a positive effect of inspiration on DBP was noted in the autonomically intact state. This effect lagged behind the mechanical effect by a phase angle of 90°. Respiratory modulation of DBP both decreased in magnitude and changed its phase relation to respiration by 90° after autonomic blockade. The result of this change was that the large inspiratory decrease in PP changed to a small increase after autonomic blockade. These data indicate that under normal conditions, autonomically mediated changes in HR induced by respiration were the predominant modulators of DBP.

In contrast to changes in DBP, changes in SBP were insensitive to autonomic blockade and therefore predominantly mechanical in origin. Respiratory systolic variations in blood pressure led diastolic variations by a phase of 90° and were therefore probably mediated by the mechanical effects of intrathoracic pressure. Autonomic blockade eliminated the effect of respiration on HR and synchronized the phase of systolic and diastolic variation, indicating that in the absence of autonomic HR control, the same mechanical effects pertain to both indices of blood pressure. Although SBP and PP decreased with inspiration in the autonomically intact state, an increase in DBP will serve to offset these decreases and maintain mean arterial pressure. This suggests that a possible physiological role for respiratory sinus arrhythmia may be that of an open-loop baroreflex, stabilizing mean arterial blood pressure in the face of high-frequency fluctuations of intrathoracic pressure that are too rapid to be controlled effectively by the HR baroreflex.

Effect of Total Cardiac Autonomic Blockade

The doses of propranolol and atropine used to induce cardiac autonomic blockade have previously been
shown to completely block chronotropic and inotropic responses to vagal and sympathetic stimulation in humans for at least 20 minutes, as assessed by pharmacological techniques. Although a small amount of residual HR variability was noted in the subjects after blockade, it was noted primarily at low frequencies and may have been caused by either a small amount of residual sympathetic activity present during blockade and/or direct effect of mechanical deformation of the atria on the activity of the sinus node.

In addition to the expected effects of autonomic blockade (ie, increased HR and blood pressure), a decrease was noted in CVP. A similar decrease in left ventricular end-diastolic pressure and an increase in total cardiac output with total blockade in normal subjects was noted by Jose and Taylor and attributed by them to increased HR. Because end-diastolic pressure is related to CVP, shortening of diastolic time alone may be responsible for the decrease in CVP; passive circulatory mechanical effects associated with a transfer of blood volume from the venous to the arterial circulation may also have been operative.

Autonomic blockade is also likely to have had a significant effect on efferent α-adrenergic activity controlling systemic arteriolar and venous tone. These physiological parameters were not measured, nor can they be estimated from our data. Administration of propranolol results in increased systemic vascular resistance. Additionally, the observed decreases in CVP associated with nonhypotensive LBNP would have caused an unloading of cardiopulmonary baroreceptors, augmenting this effect. To an unknown extent, these effects on vascular tone may have been offset by the moderate elevation of arterial blood pressure seen during autonomic blockade. Because neurally mediated adjustments of systemic vascular tone may evolve in the frequency range of 0 to 0.05 Hz, changes in vascular tone could be in part responsible for modulating the response of blood pressure to changes in CVP. If this were the case, the effect of vascular reflexes to attenuate blood pressure changes during autonomic blockade would have caused us to underestimate the true importance of rapid HR control in attenuating blood pressure fluctuations.

Conclusions and Clinical Implications

These data show that, although fluctuations in venous return caused similar fluctuations in CVP, the heart and thoracic vasculature removed higher-frequency fluctuations by a mechanical damping effect. Lower-frequency fluctuations were transmitted to the left ventricle and caused the large variations in arterial pressure observed during autonomic blockade. In the autonomically intact state, however, these changes were efficiently buffered by the HR baroreflexes. Respiratory activity alone was responsible for high-frequency blood pressure fluctuations in this model. Such fluctuations could not be mediated by changes in CVP because of mechanical damping. Therefore, they must be due to a direct mechanical effect of respiration on blood pressure caused by changes in intrathoracic pressure. These mechanical effects of respiration on blood pressure were opposed by offsetting changes in HR caused by respiratory sinus arrhythmia.

Taken together, the findings of this study indicate that the autonomically mediated HR reflexes, including the HR baroreflexes and respiratory sinus arrhythmia, act in concert to attenuate both low- and high-frequency variations in arterial pressure caused by changes in intrathoracic pressure and venous return to the heart. This may have significant implications for the pathophysiology of blood pressure control in patients with abnormalities of HR control.

Appendix A

Calculation of Transfer Function Estimates

Transfer functions were calculated according to the cross-spectral technique:

\[ H(f) = S_x(f)/S_y(f) \]

where \( H(f) \) represents the complex transfer function and \( S_x \) and \( S_y \) represent the autospectrum and the cross-spectrum of the input and output signals, \( x \) and \( y \). Cross-spectral and autospectral estimates were computed by the Blackman-Tukey method, with a four-point (0.006-Hz) gaussian window for smoothing in the frequency domain. The real and imaginary components of \( H(f) \), \( H_r(f) \) and \( H_i(f) \), were used to compute the transfer magnitude, or gain \( |H(f)| \), transfer phase \( \theta(f) \), and coherence \( \text{Coh}_i(f) \) (Equations 2 through 4) of the relation between the input and output as a function of frequency.

\[ |H(f)| = [H_r(f)^2 + H_i(f)^2]^{1/2} \]

\[ \theta(f) = \tan^{-1}[H_i(f)/H_r(f)] \]

\[ \text{Coh}_i(f) = [S_x(f)/S_y(f)]^2 \text{Coh}_4(f) \]

Appendix B

Band-Average Transfer Magnitude Estimates

Measurement variance is associated with the transfer function computation at each frequency, as reflected by a coherence <1. In addition, a population variance is present secondary to differences between individuals. It has been previously shown that the measurement variance \( \tau_{\text{meas}}(f) \) associated with the \( i \)-th individual transfer magnitude estimate is

\[ \tau_{\text{meas}}(f) = K[H_i(f)]^2 \frac{1 - \text{Coh}_i(f)}{\text{Coh}_i(f)} \]

where \( H_i(f) \) and \( \text{Coh}_i(f) \) are the \( i \)-th individual transfer magnitude and squared coherence functions and \( K \) is a constant related to the degree of spectral smoothing. The population variance \( \rho_{\text{meas}}(f) \) is independent of this variable and is subsequently calculated by standard statistical techniques. The estimator variances \( \tau_{\text{meas}}(f) \) can be used as weights in calculating the band-average transfer magnitude estimate \( H(\text{band}) \)

\[ |H(\text{band})| = \frac{\sum_{i=1}^{N} [H_i(f)/\tau_{\text{meas}}(f)]}{\sum_{i=1}^{N} 1/\tau_{\text{meas}}(f)} \]

where \( N \) is the number of individual estimates in each frequency band of interest.

Acknowledgments

This work was supported by a Biomedical Engineering grant from the Whitaker Foundation. Dr. Friedman is supported in part by National Institutes of Health training grant 7301 and Physician-Investigator Fellowship 13-606-901 from the Mas-
saschusettes Affiliate of the American Heart Association. Dr Saul is supported by Clinical Investigator Award K08-HL02380-03 from the National Institutes of Health.

References


Blood pressure modulation by central venous pressure and respiration. Buffering effects of the heart rate reflexes.
J K Triedman and J P Saul

Circulation. 1994;89:169-179
doi: 10.1161/01.CIR.89.1.169

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/89/1/169

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/