Cardiorespiratory interactions during periodic breathing in awake chronic heart failure patients

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Cardiorespiratory interactions during periodic breathing in awake chronic heart failure patients. Am. J. Physiol. Heart Circ. Physiol. 278: H932–H941, 2000.—We applied spectral techniques to the analysis of cardiorespiratory signals (instantaneous lung volume (ILV), instantaneous tidal volume (ITV), arterial O2 saturation (SaO2) at the ear, heart rate (HR), systolic (SAP), and diastolic (DAP) arterial pressure) during nonapneic periodic breathing (PB) in 29 awake chronic heart failure (CHF) patients and estimated the timing relationships between respiratory and slow cardiovascular (<0.04 Hz) oscillations. Our aim was 1) to elucidate major mechanisms involved in cardiorespiratory interactions during PB and 2) to test the hypothesis of a central vasomotor origin of PB. All cardiovascular signals were characterized by a dominant (>84% of total power) oscillation at the frequency of PB (mean ± SE: 0.022 ± 0.0008 Hz), highly coherent (>0.89), and delayed with respect to ITV (ITV-HR, 2.4 ± 0.72 s; ITV-SAP, 6.7 ± 0.65 s; ITV-DAP, 3.2 ± 0.61 s; P < 0.01). SaO2 was highly coherent with (coherence function = 0.96 ± 0.009) and almost opposite in phase to ITV. These findings demonstrate the existence of a generalized cardiorespiratory rhythm led by the ventilatory oscillation and suggest that 1) the cyclic increase in inspiratory drive and cardiopulmonary reflexes and 2) mechanical effects of PB-induced changes in intrathoracic pressure are the more likely sources of the HR and blood pressure oscillations, respectively. The timing relationship between ITV and blood pressure signals excludes the possibility that PB represents the effect of a central vasomotor rhythm.

CHRONIC HEART FAILURE (CHF) patients often develop a periodic breathing (PB) pattern either during sleep (14, 27, 35) or while awake (10, 26, 33). The origin of this breathing abnormality is still being debated among investigators. Two main hypotheses have been proposed so far: the “central” hypothesis, which explains PB as the effect of a central vasomotor rhythm (2, 44), and the “instability” hypothesis, which explains PB as a self-sustaining oscillation due to the loss of stability in the closed-loop chemical control of ventilation (3, 18). Several investigators have observed that the cyclic rise and fall in ventilation, which characterizes PB (cycle length: 25–100 s), is accompanied by phase-linked oscillations of arterial blood gases, heart rate (HR), and arterial blood pressure (4, 7, 9, 11, 26, 33, 37), indicating that during PB a deep simultaneous involvement of the respiratory and cardiovascular systems does take place. Because of this peculiarity, PB constitutes a unique experimental model for investigating cardiorespiratory interactions at very low frequencies (VLF, <0.04 Hz) (28).

Basic physiological mechanisms that mediate the interaction between respiration and circulation have been extensively studied in both animals and human subjects (6, 22). Little is known, however, about the role they play in the peculiar context of PB in CHF patients. Previous attempts to analyze cardiorespiratory oscillations during PB have addressed only specific aspects of the relationship between respiratory and circulatory parameters (9, 26, 33, 37) or have been performed during sleep (11), an experimental condition that greatly complicates the interpretation of results because of the interaction between sleep state and ventilatory control (17).

In this study we performed a comprehensive time- and frequency-domain analysis of cardiorespiratory parameters during sustained episodes of PB in awake CHF patients and applied advanced digital signal processing techniques to extract relevant information from the data. Particular attention was paid to mutual relationships between respiratory and cardiovascular oscillations in terms of coherence and phase shift. Our aim was to use this information to identify major mechanisms that link the slow oscillation of ventilation and arterial O2 saturation (SaO2) during PB to the corresponding oscillation of HR and arterial blood pressure and to verify whether the timing relationship between ventilatory and blood pressure changes is compatible with the hypothesis of a central vasomotor origin of PB.

METHODS

Subjects

Subjects for the study were patients with dilated cardiomyopathy and moderate to severe heart failure consecutively admitted to the Heart Failure Unit of Montesano Medical Center for consideration for heart transplantation between mid-1996 and the end of 1997. Inclusion criteria were 1) stable clinical conditions (no changes in signs or symptoms in the 2 wk preceding the study); 2) sinus rhythm; 3) no treatment with β-blockers; and 4) no previous history of...
pulmonary or neurological disease, acute myocardial infarction, or cardiac surgery within the previous 6 mo. During routine assessment of autonomic function 51% of the patients exhibited a sustained PB pattern, which was of the Cheyne-Stokes type in 36% of them (see Definitions). Patients with Cheyne-Stokes were excluded because the accompanying recurrent apneas are most likely triggered by reductions of arterial PCO2 (PaCO2) below the apneic threshold (19), thus involving marked nonlinear relationships between ventilatory signals that cannot be properly analyzed by the linear techniques used in this study. We also excluded patients with poor signal quality (see Signal Analysis). This selection led to a final sample of 29 patients with PB, who were ~21% of those admitted to the study.

All subjects gave their informed consent to the study, which was approved by the local Ethical Committee.

Protocol and Signal Acquisition

After instrumentation and a 15-min period for signal stabilization, an 8-min supine resting recording of electrocardiogram (ECG) was taken, measurements were performed of instantaneous lung volume (ILV) by inductive plethysmography (Respitrace Plus, Non-Invasive Monitoring Systems, Miami Beach, FL), noninvasive measurements of arterial blood pressure were made by the volume-damp method (Finapres 2300, Ohmeda, Englewood, CO), and SaO2 was measured by a fast-response (processing delay: 1.5 s) pulse oximeter with an ear probe (Biox 3740, Ohmeda, Louisville, CO). Before each recording, the Finapres self-adjustment was switched off to avoid discontinuities in the acquired signals. All signals were sampled at 250 Hz and stored on a personal computer (PC) workstation. Calibration of lung volume measurement was performed by taking a simultaneous 30-s recording of the respiratory flow (model 47304A, Hewlett-Packard, Waltham, MA) at the beginning of each experimental session. Flow was digitally integrated, and the linear regression between this signal and the Respitrace signal was calculated to obtain the calibration factor.

Signal Analysis

The ILV and SaO2 signals were decimated down to 2 Hz. To obtain the heart period time series, each QRS complex was first detected by searching for the points of the low-pass filtered first derivative of the ECG signal, which exceeded an adaptive threshold. Fiducial points were then estimated with a time resolution of 1 ms by finding the nearest zero-crossing after linear interpolation between adjacent samples. Ectopic beats were linearly interpolated. Patients with a high rate (>5%) of ectopic events were discarded. Beat-to-beat systolic arterial pressure (SAP) values were obtained as the maximum of the pressure curve within each heart period. Corresponding diastolic arterial pressure (DAP) values were obtained as the minimum of the pressure curve between each QRS complex and the following systolic peak. R-R interval and pressure time series were interpolated by a cubic spline algorithm and resampled at 2 Hz. The heart period signal was transformed into the corresponding HR signal by inversion and multiplication by 60. From the ILV signal, we derived an instantaneous tidal volume (ITV) signal by first fitting the end-expiratory and end-inspiratory points with two cubic splines and then sampling the difference between the two curves at 2 Hz. Similarly, we obtained an instantaneous breath duration signal from the breath duration sequence.

The curves of ILV, ITV, SaO2, SAP, DAP, and HR were plotted together on the PC screen, and once it was ascertained that the breathing pattern of the patient had the required characteristics (nonapneic PB), a subrecord 180–300 s long with all signals free from artifacts, large transients, or marked changes in the fluctuating behavior of the signals was interactively selected (20). The latter are requirements for proper application of spectral analysis techniques (30). If even a single signal out of the six considered did not satisfy the previous requirements, the patient was excluded from analysis. Because we were interested in spectral components >0.01 Hz, our choice of the record length was the best trade-off between the stationarity requirement for spectral estimation and the need to have an adequate number of samples to obtain accurate spectral estimates (32). In all signals the analysis software measured automatically the peak and trough related to each PB cycle and averaged the results over all PB cycles in the selected segment. These average values are referred to as maximum and minimum, respectively, of the signal. To assess the change in breath duration between the hyperpneic and hypopneic phases of PB, the mean breath duration in an 8-s interval centered in the two phases of each PB cycle was computed. Results were then averaged over all PB cycles of the selected record. Linear dependence analysis via least-squares nonlinear fitting was applied to all signals to remove slow trends or oscillations slower than the components of interest, which would otherwise appear in the spectral density function as a broad component near 0 Hz (30).

Univariate spectral analysis was performed on all signals using the autoregressive approach (Burg algorithm) and was verified by the classic nonparametric approach of BlackmanTukey (Parzen window with a bandwidth of 0.015 Hz) (30). Following well-established standards for the analysis of cardiovascular variability signals (41), we divided the bandwidth of the signals into three frequency bands: the very low-frequency (VLF) band (0.01–0.04 Hz), the low-frequency (LF) band (0.04–0.15 Hz) and the high-frequency (HF) or respiratory band (0.15–0.45 Hz). This choice was adequate for the analysis of respiratory and cardiovascular oscillations associated with PB, because they are typically centered within the VLF band. The central frequency and power of spectral components within each band were automatically identified and estimated by the spectral decomposition algorithm of Johnsen and Andersen (15).

The relationship between different combinations of signals was assessed by means of bivariate spectral analysis, estimating the coherence function and phase spectrum. For univariate analysis, we used the autoregressive approach and verified the results with the Blackman-Tukey method. The coherence function is a measure of the strength of linear association between two time series at each frequency and is the exact analog of the standard r² statistic in linear regression analysis. Its square root is commonly referred to as “correlation coefficient in the frequency domain” (34). Phase spectra were plotted using the conventional “wrapped” format (i.e., representing phase shifts between −180° and 180°), but for computations the “unwrapped” format was used. By convention, the phase shift between two signals S1 and S2 was negative if S1 preceded S2.

Definitions

The following definitions were used throughout the study. PB was defined as a sustained oscillation of ventilation characterized by smooth, regularly recurring cycles of hyperventilation and hypopnea or apnea. Cheyne-Stokes breathing was defined as an extreme form of PB in which the hyperpneic phases are separated by frank periods of apnea (4, 7). The PB frequency was defined as the central frequency of the VLF component of the ITV signal in the VLF band. The respiratory
frequency was defined as the central frequency of the HF component of the ILV signal. When two or more neighboring spectral components were identified by the spectral decomposition algorithm in the HF band, the barycentric frequency was considered.

Phase and Time Delay Estimation

The phase shift between two signals at the frequency of PB was obtained as a point estimate of the phase spectrum at that frequency. The corresponding time delay was estimated using the relationship:

\[
\text{time delay} = \frac{\pi}{360 \times f_{\text{PB}}} \frac{\phi}{2}
\]

where \(\phi\) is the phase shift in degrees and \(f_{\text{PB}}\) is the PB frequency in Hz. This relationship exploits the quasi-periodic nature of cardiorespiratory signals during PB. Point estimates of the phase shift were accepted only if both spectral estimation methods provided consistent results and the corresponding coherence function was >0.5 and statistically significant at the 5% level.

To be considered for analysis, estimated time delays between the different combinations of signals in each patient had to satisfy a consistency check. For instance, given three signals, A, B, and C, the algebraic sum of the time delay between signals A and B and between signals B and C has to be equal to the time delay between signals A and C. The accuracy of phase shifts of blood pressure signals obtained noninvasively by the Finapres device has been verified in a previous study (31).

A Cardiorespiratory Control Model

To have a suitable conceptual framework for the analysis and interpretation of cardiorespiratory oscillations during PB, we developed a schematic model of the respiratory and cardiovascular control systems and of their mutual relationships, which is represented in Fig. 1. The top part of the model shows main elements of the chemical feedback control system of ventilation: the respiratory network in the central nervous system (the controller), respiratory muscles (the effectors), the lungs (the plant), arterial blood gas tensions (the controlled variables), the circulatory delays \(t_1\) and \(t_2\) between the lungs and peripheral chemoreceptors, including mixing effects in the heart and vasculature, and the aortic and carotid chemoreceptors (the feedback sensors). Furthermore, the model shows the two signals of the loop that were actually measured in this study: the ILV signal and the SaO2 signal, the latter being recorded after the circulatory delay between carotid bodies and the ear. Central chemoreceptors have been omitted because, due to their slow dynamics (previous studies in humans estimated the time constant of central chemoreceptors to be \(\approx 110\) s), their response at the typical PB frequencies (i.e., \(\approx 0.02\) Hz) should be markedly attenuated (18, 19).

In the bottom part of Fig. 1, major elements of cardiovascular regulation are schematized. Systemic arterial blood pres-
pressure (measured as SAP and DAP) is the controlled variable, the cardiovascular network in the central nervous system is the controller, and sympathetic and vagal efferents are the driving signals for the sinoatrial node and arterial smooth muscles (the effectors). The heart and vasculature represent the controlled system, and the feedback sensors are constituted by baroreceptors. The effect of sympathetic efferents on heart contractility and venous return has been omitted.

Major links between the two control systems have been represented in the model by a gray area of synaptic interactions, within the central nervous system, between respiratory and cardiovascular neurons, and by the direct mechanical coupling between respiration and circulation mediated by intrathoracic pressure changes. The latter affect arterial blood pressure through modulation of left ventricular (LV) stroke volume and efferent reflexes from cardiac and pulmonary vascular receptors. These receptors together with chemoreceptors, lung stretch receptors, and arterial baroreceptors have projections to a common area of the central nervous system, mainly identified in the nucleus tractus solitarii (40). The complex synaptic interactions that take place within this area probably constitute the major anatomic basis of cardiorespiratory interactions and central integration.

Statistical Analysis

Data are presented as means ± SE. Skewed data are represented as medians with interquartile range. Within-group comparisons were performed by the t-test for dependent samples or by the Wilcoxon matched-pairs test when appropriate. Correlation between data was assessed by the Pearson correlation coefficient. The significance level was set at 0.05. When multiple comparisons were performed, the Bonferroni correction was applied to control for the multiplicity effect.

RESULTS

Clinical and demographic characteristics of the subjects of the study are given in Table 1. Recordings of ILV, ITV, SaO₂, HR, SAP, and DAP signals from one representative subject are shown in Fig. 2 (left). The ILV signal exhibits the typical cyclic modulation of breath amplitude characteristic of PB. As a consequence, the ITV signal appears as a rhythmic waveform resembling a distorted sinusoid and oscillating around 0.027 Hz (VLF band). The respiratory frequency is fairly stable around 0.29 Hz during the different phases of PB, implying that minute ventilation will closely mimic ITV changes. Note that the ILV signal shows an oscillation of the end-expiratory lung volume synchronous with breath amplitude changes. The SaO₂ signal at the ear oscillates at the same frequency of the ITV, changing proportionally in the opposite direction with a little delay.

In the overall group the respiratory frequency was 0.34 ± 0.02 Hz. Maximum and minimum tidal volumes were 0.5 ± 0.05 and 0.12 ± 0.02 liter, respectively. Mean breath duration was 3.1 ± 0.1 s in the hyperpneic phase and 2.9 ± 0.1 s in the hypopneic phase (P = 0.01). Although statistically significant, this change is actually very small (<7%). Average SaO₂ was 93.4 ± 0.4%, with a maximum-to-minimum change of 2.2 ± 0.3%. A more or less pronounced oscillation of the end-expiratory lung volume synchronous with the oscillation of breath amplitude was observed in 90% of the patients.

Mean HR, SAP, and DAP were 72 ± 2.4 beats/min, 100 ± 2.4 mmHg, and 57 ± 1.5 mmHg, respectively. Changes between the hyperpneic and the hypopneic phase (maximum to minimum) were 5.2 ± 0.6 beats/min, 10.7 ± 0.7 mmHg, and 6.6 ± 0.4 mmHg, respectively. The correlation between the peak-to-peak change in HR (maximum to minimum) and the corresponding change in SAP and DAP across patients was 0.08 (P = 0.68) and 0.2 (P = 0.29), respectively.

A dominant oscillation at the same frequency of slow changes in respiration can be seen in the time series of HR, SAP, and DAP (Fig. 2, left). Of note, these oscillations lag behind the ITV oscillation. A higher frequency component related to phasic respiratory activity can be observed in all cardiovascular signals.

The autorspectra of all signals are shown in Fig. 2 (right). The ILV signal is characterized by two major oscillatory components (peaks), one at the frequency of PB (VLF band) and the other at the frequency of phasic respiratory activity (HF band). The spectrum of the other signals is dominated by a well-defined, narrow band peak within the VLF band. A spectral component at the same frequency of phasic respiratory activity can also be noted in the blood pressure signals, whereas in the HR signal this spectral contribution is so small that it is not detectable in the power spectrum plot. The central frequency (Hz) of the VLF component in the overall group was 0.022 ± 0.0009, 0.022 ± 0.0008, 0.021 ± 0.0008, 0.021 ± 0.0008, 0.021 ± 0.0008, 0.021 ± 0.0007, and 0.021 ± 0.0007 for ILV, ITV, SaO₂, HR, SAP, and DAP, respectively (P > 0.11 for all pairwise comparisons). By computing the reciprocal of the PB frequency, we found that the corresponding length of the PB cycle was 40.3 ± 1.7 s.

Descriptive statistics for the spectral powers of ILV, HR, SAP, and DAP in the VLF and HF band are reported in absolute units and as percentage values of the total power in Table 2. The slow oscillatory component of the ILV signal accounts for about one-half the overall signal variance, whereas in all cardiovascular signals it accounts for more than 83%.

In all patients the coherence between ILV and ITV at the PB frequency approached 1 and the corresponding phase

<table>
<thead>
<tr>
<th>Table 1. Clinical characteristics of patients of study</th>
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<tr>
<td>Age, yr</td>
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<tr>
<td>Male-to-female ratio</td>
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<tr>
<td>NYHA class</td>
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<tr>
<td>Etiology, %</td>
</tr>
<tr>
<td>Ischemic</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
<tr>
<td>LVEF, %</td>
</tr>
<tr>
<td>CI, l·min⁻¹·m⁻²</td>
</tr>
<tr>
<td>Therapy, %</td>
</tr>
<tr>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>Diuretics</td>
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<tr>
<td>Nitrates</td>
</tr>
<tr>
<td>Digoxin</td>
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<tr>
<td>Other vasodilators</td>
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<tr>
<td>Amiodarone</td>
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</tbody>
</table>

Values are means ± SE; n = 29 patients. NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CI, cardiac index; ACE, angiotensin-converting enzyme.
shift was centered near zero degrees (first row of Table 3), suggesting a very close linear association and synchronicity between the VLF component of lung volume and the corresponding oscillation of tidal volume.

The coherence and transfer phase functions between ITV and SaO2, HR, SAP, and DAP for the subject in Fig. 2 are shown in Fig. 3. Here the frequency axis is bounded at 0.1 Hz to provide finer details around the VLF peak. The coherence of ITV-SaO2 shows a clear peak at the frequency of PB. The corresponding phase shift is −227° ("wrapping" must be taken into account). A high coherence value (>0.95) can be noted in the other panels of Fig. 3 between ITV and all cardiovascular signals. Phase spectra clearly show that
the VLF oscillation of ITV leads the corresponding oscillation of HR, SAP, and DAP (223°, 253°, and 240°, respectively, corresponding to 2.4, 5.5, and 4.1 s).

Descriptive statistics for the overall group are given in Table 3. The phase shifts between the oscillation of tidal volume and the oscillation of HR, DAP, and SAP are all significantly different from zero (the significance level for each test according to the Bonferroni method was 0.05/5 = 0.01). In four subjects the HR oscillation anticipated the ITV oscillation by 3.8, 5.7, 2, and 0.8 s, respectively. In three subjects, the DAP oscillation anticipated the ITV oscillation by 4.2, 3.1, and 1 s, respectively. The SAP always followed the tidal volume signal.

The overall timing relationships between the cardiorespiratory oscillations observed during PB are schematized graphically in Fig. 4. These oscillations have been represented as pure sinusoids having a period of 50 s (0.02 Hz) and normalized amplitude. The ITV signal is the leading signal, and the delays of the other signals (in brackets) are the average values given in Table 3. The SaO2 signal is drawn apart for better clarity. Considering that this signal represents a delayed version of what is actually sensed by carotid chemoreceptors, due to the carotid-to-ear circulatory delay (Fig. 1), it is noteworthy that it oscillates almost out of phase with respect to the tidal volume oscillation.

**DISCUSSION**

In this study we applied time- and frequency-domain techniques to the analysis of respiratory and cardiovascular oscillations during nonapneic PB in CHF patients. We found that the HR, SAP, and DAP signals were characterized by a dominant oscillatory component at the frequency of PB, which was highly coherent and delayed with respect to the oscillation of ventilation. We also found that cyclic changes of SaO2 mea-

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**Table 2. Absolute and percentage powers in VLF and HF bands**

<table>
<thead>
<tr>
<th></th>
<th>VLF</th>
<th>HF</th>
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<tbody>
<tr>
<td>ILV</td>
<td>0.012 (0.02)</td>
<td>0.015 (0.01)</td>
</tr>
<tr>
<td>%</td>
<td>48 (20)</td>
<td>46 (23)</td>
</tr>
<tr>
<td>HR</td>
<td>2.6 (4.4)*</td>
<td>0.26 (0.3)</td>
</tr>
<tr>
<td>%</td>
<td>85 (18)*</td>
<td>5 (7)</td>
</tr>
<tr>
<td>SAP</td>
<td>13.7 (10)*</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>%</td>
<td>86 (18)*</td>
<td>5 (15)</td>
</tr>
<tr>
<td>DAP</td>
<td>4.3 (6)*</td>
<td>0.6 (0.4)</td>
</tr>
<tr>
<td>%</td>
<td>84 (12)*</td>
<td>10 (6)</td>
</tr>
</tbody>
</table>

Values are medians (interquartile range) because most variables have a skewed distribution. ILV, instantaneous lung volume; HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; VLF, very low frequency (0.01–0.04 Hz); HF, high frequency (0.15–0.45 Hz). *P < 0.001 compared with HF band.

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**Table 3. Coherence and phase shift at the periodic breathing frequency between ventilatory signals and between instantaneous tidal volume and cardiovascular signals**

<table>
<thead>
<tr>
<th>Coherence</th>
<th>Phase Shift, °</th>
<th>Delay, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILV-ITV</td>
<td>0.96 ± 0.0093</td>
<td>−2.3 ± 2.6†</td>
</tr>
<tr>
<td>ITV-SaO2</td>
<td>0.96 ± 0.0093</td>
<td>−205.9 ± 3.2</td>
</tr>
<tr>
<td>ITV-HR</td>
<td>0.91 ± 0.0130</td>
<td>−17.2 ± 5.0*</td>
</tr>
<tr>
<td>ITV-SAP</td>
<td>0.89 ± 0.0167</td>
<td>−50.4 ± 4.6*</td>
</tr>
<tr>
<td>ITV-DAP</td>
<td>0.89 ± 0.0130</td>
<td>−25.3 ± 4.8*</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SE. ITV, instantaneous tidal volume; SaO2, O2 saturation at the ear. The phase shift and the delay between ITV and SaO2 have been corrected for the intrinsic delay (1.5 s) of ear oximeter. *P = 0.002 in testing the hypothesis of a phase shift = 0; P < 0.001 compared with the phase shift ITV-SAP; P = 0.09 compared with the phase shift ITV-DAP. †P > 0.4 in testing the hypothesis of a phase shift = 0. *P < 0.001 in testing the hypothesis of a phase shift = 0. Superimposable significance probabilities were obtained for corresponding time delays.
reported by other investigators, is almost totally due to the modulation of tidal volume (1, 10). Spectral analysis revealed that the lung volume signal is mainly composed of two quasi-periodic oscillatory components of nearly equal power, one at the frequency of phasic respiratory activity and the other at the frequency of PB, in the middle of the VLF band, a finding in agreement with a previous analytical study (28). We found high coherence and synchrony between the VLF component of lung volume and the oscillation of tidal volume; therefore, the two signals can be used interchangeably in analyzing the link between ventilation and cardiovascular signals at the PB frequency. We chose the ITV signal by virtue of its better visual effectiveness in evidencing ventilatory oscillations and its higher signal-to-noise ratio compared with ILV. Our study does not answer the question of whether the link between ventilation and circulation in the VLF band takes place via a demodulation of the lung volume (i.e., via tidal volume) or via the lung volume itself. Nevertheless, it demonstrates that, contrary to previous suggestions (38), a demodulation is not necessary to explain this link.

The overall phase shift between the slow oscillation of ITV and the corresponding oscillation of SaO2 at the ear, after correction for the intrinsic shift of the oximeter, was −206°. This phase shift takes into account the pure convective transport of the blood from the lungs to the ear plus the lung washout time and mixing effects in the heart and vasculature (18). Assuming the carotid-to-ear phase shift (see Fig. 1) to be about 10% of the overall shift between the lungs and the ear, the lung-to-carotid bodies phase shift should be about −185°, indicating that O2 saturation changes at carotid chemoreceptors were almost opposite in phase with respect to tidal volume changes. This relationship is consistent with the instability hypothesis of PB (3, 18). Although not measured in this study, it is known that during PB PaCO2 oscillates opposite in phase to the SaO2 oscillation (9, 13). It is therefore sensible to assume that during PB peripheral chemoreceptors are stimulated by a simultaneous cyclic increase of PaCO2 and decrease of SaO2. Their relative importance in evoking cardiovascular responses, however, is still not clear (22).

It might be argued that the changes in blood CO2 during PB would also stimulate central chemoreceptors and evoke cardiovascular reflexes. However, on one hand, these receptors respond too slowly to follow CO2 fluctuations during PB (18, 19, 45); on the other hand, a clear understanding about the integrative role of central chemosensitive structures in the overall control of circulation and respiration is still lacking (24).

Cardiorespiratory Interactions

Heart rate. Looking at the schematic plot of Fig. 4A, it can be seen that the cyclic increase of tidal volume during PB is followed by an increase of HR after an average delay of 2.4 s. Because the increase of the former is almost simultaneous with the decrease of SaO2 at carotid chemoreceptors (Fig. 4B), and taking into account that a contemporary increase of PaCO2 is

Ventilatory Oscillations

Changes in breath duration between the hypopneic and hyperpneic phase of PB were negligible, indicating that the fluctuation of minute ventilation during PB, as measured at the ear, near carotid chemoreceptors, were almost opposite in phase to concomitant changes in tidal volume. These findings provide definitive confirmation of the existence of a generalized cardiorespiratory rhythm during PB and clearly indicate that PB cannot be the effect of a primary vasomotor rhythm. Because several concurrent mechanisms may contribute to link ventilatory to cardiovascular changes, the knowledge of the timing relationships between these changes allows identification of those mechanisms that are most likely to be dominant and exclusion of those that are not compatible with experimental findings. It is worth emphasizing that our study was performed in awake patients who had a mild-to-moderate form of PB. This has two important implications. On one hand, our findings widen the current knowledge of the PB phenomenon, because historically most studies have focused on its extreme manifestation of central apneas during sleep (7, 14, 27, 35, 42). On the other hand, they allow a more precise identification of the underlying physiopathological mechanisms, because they are not affected by the confounding effect of large system nonlinearities in ventilatory regulation and sleep-induced physiological changes (11, 17).

Cardiorespiratory Interactions

Heart rate. Looking at the schematic plot of Fig. 4A, it can be seen that the cyclic increase of tidal volume during PB is followed by an increase of HR after an average delay of 2.4 s. Because the increase of the former is almost simultaneous with the decrease of SaO2 at carotid chemoreceptors (Fig. 4B), and taking into account that a contemporary increase of PaCO2 is
expected to take place (9, 13), the behavior of HR appears as the typical tachycardic response to stimulation of carotid chemoreceptors (6, 22). Although the reductions of $\text{Sa}_O_2$, observed in our patients during PB were small and the mean $\text{Sa}_O_2$ only slightly reduced, hypoxic chemosensitivity is known to be enhanced in CHF patients, likely due to increased catecholamine levels and/or ischemic hypoxia at peripheral chemoreceptors (5). It is also possible that the noninvasive measurement of $\text{Sa}_O_2$ underestimated the magnitude of periodic desaturations, as recently shown in a comparison with intra-arterial measurements (11). Classic physiology explains the tachycardia that follows carotid chemoreceptor stimulation as the effect of increased central inspiratory drive and lung stretch receptor discharge brought about by the reflex hyperventilation. These mechanisms are believed to oppose and prevail over a primary reflex bradycardia mediated by the vagus (6, 22). Recently, however, evidence has been provided that pulmonary stretch receptors are not essential to mediate the reflex tachycardia, although they may contribute to its potentiation (25, 39). Hence, also taking into account that CHF patients in this study exhibited limited lung volume excursions during the hyperpneic phases of PB, it seems unlikely that lung stretch receptors played a major role in the generation of the VLF oscillation of HR.

Besides carotid chemoreceptors, aortic chemoreceptors also should be stimulated cyclically by the oscillating arterial blood gas tensions during PB. In animal experiments, stimulation of aortic chemoreceptors evoked tachycardia, but sometimes bradycardia (22), whereas in humans a cardioacceleration effect has been hypothesized (8, 39). Because during PB these receptors are stimulated before carotid chemoreceptors (i.e., before the hyperventilation phase takes place; see Figs. 1 and 4), a reflex tachycardic response might explain why we found the HR oscillation to anticipate the ITV before the hyperventilation phase takes place; see Figs. 1 and 4), a reflex tachycardic response might explain why we found the HR oscillation to anticipate the ITV (Fig. 4A) and hence the decrease in the negativity of the ITV (4A) and hence the increase in the negativity of the ITV oscillation of HR.

Cardiopulmonary receptors in the atra and pulmonary veins with sympathetic afferent fibers are known to elicit excitatory effects on HR when stretched by an increase in volume load (6, 21). It is thus conceivable that during PB the cyclic increase in systemic venous return brought about by the decrease in intrathoracic pressure during the hyperpneic phases elicits a cyclic reflex increase of HR. The magnitude of this reflex is likely to be enhanced in CHF patients compared with normal individuals as recently demonstrated in a canine model (36). Therefore, excluding the fact that slow changes of HR during PB represent a baroreceptor-mediated reflex to the VLF oscillation of blood pressure, as HR leads blood pressure (Fig. 4), central effects caused by the cyclic increase in inspiratory drive and reflex effects caused by mechanical stimulation of cardiac and pulmonary vascular receptors remain the most probable major determinants of these changes.

Arterial blood pressure. We found that DAP and SAP signals increased after the increase in tidal volume with an average delay of 3.2 and 6.7 s, respectively. Hence, blood pressure fluctuations during PB appear to be the effect of ventilatory changes rather than their cause. This finding excludes the possibility that PB originates from a fluctuation of vasomotor tone driven by a central rhythm, as previously suggested by other investigators (2, 44). In fact, if this hypothesis were true, we would have found that the pressure oscillation preceded the respiratory oscillation.

Slow changes in lung volume during PB cause corresponding changes in intrathoracic pressure, and these, in turn, are likely to contribute to the VLF oscillation of blood pressure (Fig. 1) by modulating LV stroke volume. Indeed, available data on lung-heart hemodynamics show that cyclic changes in both the pulmonary and cardiac circulation do occur during PB in CHF (9, 12, 23). The effect of a negative intrathoracic pressure on LV stroke volume depends on the complex interplay between three main alterations it brings about on LV hemodynamics: increase in afterload, reduction in end-diastolic volume due to ventricular interdependence, and increase in end-diastolic volume due to increased systemic venous return delayed through the pulmonary circuit (16, 29). Because we found that blood pressure increased following the increase in tidal volume (and hence the increase in the negativity of the ITV oscillation of HR), our data suggest that the increase in venous return, which contributes to raise LV ejection, prevailed over the increase in afterload and ventricular interdependence, which cause an opposite effect.

Carotid chemoreceptor stimulation is known to reflexly induce changes in systemic vascular resistance. Although the primary reflex is vasoconstriction, this is counteracted or overridden by pulmonary stretch receptor reflexes elicited by the concurrent hyperventilation, eventually causing a reduction in total peripheral resistance (6, 22). During PB, however, the timing of blood pressure signals with respect to ITV (Fig. 4A) excludes the possibility that blood pressure changes represent the effect of a dominant vasodilator reflex for, in this case, the blood pressure should decrease and not increase after the hyperventilation phases. An increase in sympathetic outflow to smooth muscles due to increased central inspiratory drive is also expected to accompany the hyperventilation phases (22). Recently, however, Van de Borne and co-workers (43) measured muscle sympathetic nerve activity in a group of CHF patients during PB and found that the maximum increase in sympathetic activity preceded the beginning of the hyperventilation phases. These results suggest that neither the cyclic stimulation of carotid chemoreceptors nor the cyclic increase in central respiratory drive was responsible for the oscillation of blood pressure.

Stimulation of aortic chemoreceptors in dogs elicits a vasoconstrictor response comparable in magnitude to that of carotid chemoreceptors without the adverse effect of contemporary hyperventilation (6, 22). Although no data are available on human subjects, we cannot exclude the possibility that the cyclic stimula-
tion of these receptors during PB contributed to the oscillation of blood pressure, explaining the anticipation of the DAP with respect to the ITV in some subjects. This interpretation, however, is purely conjectural.

Cyclic changes of HR during PB are almost simultaneous with DAP changes and lead SAP changes; hence, a mechanical link between HR and arterial blood pressure might be hypothesized. To verify this hypothesis, we assessed the relationship between HR and blood pressure peak-to-peak excursions across subjects and found that they were uncorrelated. Moreover, we observed marked VLF oscillations of SAP and DAP in cardiac transplant patients with a PB pattern despite the absence of variation in HR (unpublished data).

Therefore, we were led to conclude that slow HR changes during PB hardly contributed to the VLF fluctuation of arterial blood pressure.

In conclusion, this study provides definitive evidence that during PB a common VLF oscillation ~0.02 Hz is shared by the respiratory and cardiovascular systems and constitutes the source of almost all the variability in cardiovascular parameters. The analysis of timing relationships between signals revealed that the cyclic change in ventilation is out of phase with respect to the O_2 saturation oscillation at carotid chemoreceptors and leads the oscillation of HR, DAP, and SAP. The latter finding excludes the possibility that PB represents the primary pulmonary ventilation peak-to-peak excursions across subjects and found that they were uncorrelated. Moreover, we observed marked VLF oscillations of SAP and DAP in cardiac transplant patients with a PB pattern despite the absence of variation in HR (unpublished data). Therefore, we were led to conclude that slow HR changes during PB hardly contributed to the VLF fluctuation of arterial blood pressure.

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