Periodic breathing in heart failure patients: testing the hypothesis of instability of the chemoreflex loop

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Pinna, G. D., R. Maestri, A. Mortara, M. T. La Rovere, F. Fanfulla, and P. Sleight. Periodic breathing in heart failure patients: testing the hypothesis of instability of the chemoreflex loop. J Appl Physiol 89: 2147–2157, 2000.—In this study, we applied time- and frequency-domain signal processing techniques to the analysis of respiratory and arterial O2 saturation (SaO2) oscillations during nonapneic periodic breathing (PB) in 37 supine awake chronic heart failure patients. O2 was administered to eight of them at 3 l/min. Instantaneous tidal volume and instantaneous minute ventilation (IMV) signals were obtained from the lung volume signal. The main objectives were to verify 1) whether the timing relationship between IMV and SaO2 was consistent with modeling predictions derived from the instability hypothesis of PB and 2) whether O2 administration, by decreasing loop gain and increasing O2 stores, would have increased system stability reducing or abolishing the ventilatory oscillation. PB was centered around 0.021 Hz, whereas respiratory rate was centered around 0.33 Hz and was almost stable between hyperventilation and hypopnea. The average phase shift between IMV and SaO2 at the PB frequency was 205° (95% confidence interval 198–212°). In 12 of 37 patients in whom we measured the pure circulatory delay, the predicted lung-to-ear delay was 28.8 ± 5.2 s and the corresponding observed delay was 30.9 ± 8.8 s (P = 0.13). In seven of eight patients, O2 administration abolished PB (in the eighth patient, SaO2 did not increase). These results show a remarkable consistency between theoretical expectations derived from the instability hypothesis and experimental observations and clearly indicate that a condition of loss of stability in the chemical feedback control of ventilation might play a determinant role in the genesis of PB in awake chronic heart failure patients.

respiratory control; spectral analysis; ventilatory oscillations; O2 administration; chemoreceptors

A CYCLIC BREATHING PATTERN characterized by a smooth rise and fall in ventilation with cycle lengths ranging from ~25 to 100 s (0.01–0.04 Hz) is frequently observed in chronic heart failure (CHF) patients and is commonly referred to as periodic breathing (PB) (15, 19, 29, 30, 33) or, usually when separated by apnea, Cheyne-Stokes respiration (6, 12). Often, the same patient may exhibit a continuum of different patterns of breathing, ranging from normal breathing (i.e., without cyclic modulation of ventilation) to mild PB up to cyclic periods of apnea. These patterns are also influenced by wakefulness or sleep, posture, and physical and mental activity.

Most studies on the phenomenon of PB in CHF patients have been performed during sleep (34). The prevalence of PB in awake CHF patients is, however, greater than usually believed. Awake recordings in controlled laboratory conditions showed a sustained PB pattern in 25–66% of patients with mild to moderate CHF (New York Heart Association class I to class III) (15, 29, 33).

The physiological mechanisms responsible for PB in CHF patients are still a matter of debate. Two major hypotheses, however, have received most attention in the last two decades. The “central” hypothesis explains PB as the manifestation of a central vasomotor rhythm that modulates ventilation either indirectly through modulation of blood flow or directly through central irradiation to respiratory centers (3, 17, 35). The “instability” hypothesis, on the contrary, explains PB as a self-sustaining oscillation due to the loss of stability in the closed-loop chemical control of ventilation (5, 6). This loss of stability is thought to be caused by the concurrent presence of slow circulation time between lungs and chemoreceptors, enhanced loop gain, and underdamping of CO2 and O2 body stores (34).

The instability hypothesis has gained wider acceptance than the central hypothesis mainly because of its sound theoretical basis, using mathematical models of the respiratory control system (4, 24, 26). These studies have shown that increased circulatory delay and loop gain brought about by the decreased cardiac output of CHF patients may lead to instability in their feedback control of ventilation. This implies that in some CHF patients there is a critical frequency (i.e., the PB frequency) at which a perturbation traveling around the

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Protocol and signal acquisition. After instrumentation and a 15-min period for signal stabilization, we made an 8-min supine resting recording of instantaneous lung volume (ILV) by inductive plethysmography (Respitrace Plus, Non-Invasive Monitoring Systems, Miami Beach, FL) and arterial O₂ saturation (SaO₂) by a fast-response (processing delay 1.5 s) pulse oximeter with an ear probe (Biox 3740, Ohmeda, Louisville, CO). Calibration of lung volume measurements was carried out by taking a simultaneous 30-s recording of the respiratory flow at the beginning of each experimental session via a Fleisch pneumotachograph (model 47304A, Hewlett Packard, Waltham, MA). Flow was digitally integrated and regressed on the Respitrace signal to obtain the calibration factor. At the end of the resting recording, 12 of the 37 patients underwent an apnea trial (see the description below), and nasal O₂ was administered to 8 patients at a rate of 3 l/min.

Signal analysis. An instantaneous tidal volume (ITV) signal was derived from ILV by a cubic spline interpolation of the end-expiratory and of the end-inspiratory points and then computing the difference (Fig. 1). A cubic spline was also used to interpolate the time series of breath duration, giving an instantaneous breath-duration signal. Dividing the ITV by instantaneous breath duration gave an instantaneous minute ventilation (IMV) signal (Fig. 1). To validate our method, we produced known minute ventilation signals by inflating and deflating a standard 1-liter syringe through a pneumotachograph, following a metronome set at 12 and 15 breaths/min. Flow was digitally integrated to obtain ILV, and the latter was then processed by our software to obtain IMV, giving, respectively, 12.02 and 15.03 l/min.

All signals were resampled at 2 Hz and plotted on a personal computer screen. A portion free from large transients or artifacts with a duration ranging from 180 to 300 s was interactively selected.

Peaks and troughs (max, min) of the ITV and SaO₂ signals were derived by special software. Mean breath duration in an 8-s interval centered in the two phases of each PB cycle (hyperpnea, hypopnea) was computed and averaged over all cycles.

Univariate spectral analysis was performed by using the autoregressive method (31), and the central frequency of main oscillatory components was automatically identified and estimated by a spectral decomposition algorithm (22).

Autoregressive bivariate spectral analysis was performed to assess the relationships between signals, and the coherence and transfer functions were estimated (28). 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 led 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.

The PB frequency (fPB) was defined as the central frequency of the spectral component of the IMV signal in the band 0.01–0.04 Hz. The lung volume modulation index (LVMI) was defined as the average depth of modulation of breath amplitude, that is

\[
LVMI = \frac{\sum_{i=1}^{L} (ITV_{\text{max}} - ITV_{\text{min}})/ITV_{\text{max}}}{L} \times 100
\]
where \( i = 1, 2 \ldots L \) are the PB cycles within the record analyzed. Hence, the LVMI ranges from 0% (constant breath amplitude) to 100% (PB with apnea). The peak-to-nadir O\(_2\) saturation was defined as the average peak-to-nadir change of SaO\(_2\) over the observed PB cycles, that is

\[
\text{SaO}_2\text{PN} = \frac{1}{L} \sum_{i=1}^{L} (\text{SaO}_2\text{max} - \text{SaO}_2\text{min})
\]

The respiratory frequency was defined as the frequency of the phasic activity of the ILV signal derived from spectral decomposition.

**Modeling assumptions.** A simplified model of the respiratory control system (Fig. 2), which emphasizes the critical delay elements of the loop, was used throughout the study as a reference for the analysis and interpretation of observed data. The main elements of the respiratory control loop are 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 delays between the lungs and carotid bodies and between the lungs and brain tissue (including the lag from the gas exchange process in the lungs, the pure time delay due to the convective transport process, mixing effects in the heart and arterial vasculature, and the time necessary for the entering blood to impose its CO\(_2\)-H\(^+\) status on the brain tissue), the delay between stimulation of carotid chemoreceptors and the reflex ventilation (peripheral chemoreflex delay), and the carotid and central chemoreceptors (the feedback sensors).

Aortic chemoreceptors have not been depicted because their contribution to the overall ventilatory response is much weaker than that of the other chemoreceptors (16). The model shows the two signals of the loop that were actually measured in this study, namely IMV and SaO\(_2\), the latter being recorded after the circulatory delay between carotid bodies and the ear. Major assumptions relative to this model were that 1) the dynamics of central chemoreceptors is much slower than that of carotid chemoreceptors, causing the ventilatory response at the frequency of PB to be mainly mediated by carotid chemoreceptors and 2) the oscillation of SaO\(_2\) during PB is accompanied by a concurrent oscillation of PaCO\(_2\) and the two are out of phase (i.e., 180° phase shift).

**Phase and time delay estimation.** The phase shift between two signals at the frequency of PB was obtained as the value of the phase spectrum at that frequency. The corresponding time delay was estimated by using the relationship

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

where \( \theta \) and \( \phi \) are the phase shift in degrees and radians, respectively, and \( f_{PB} \) and \( T_{PB} \) are the PB frequency (in Hz) and the PB wavelength (in s), respectively.

**Testing modeling predictions.** To test whether modeling predictions derived from the instability hypothesis were consistent with experimental observations, we focused on the phase shift of the PB oscillation around the peripheral chemoreflex loop (Fig. 2). If the hypothesis of instability is true, this shift has to satisfy the equation

\[
\varphi_{\text{Loop}} = \varphi_{\text{LC}} + \varphi_{\text{PR}} = \pi
\]
where $\phi_{LC}$ is the phase shift contribution from the lungs to the carotid body and $\phi_{PR}$ is the lag contribution between the blood gas oscillation at the carotid body and the oscillation in ventilation; that is, the peripheral chemoreflex phase shift. What we could actually measure in our experimental set up, however, was the overall phase shift $\varphi_{LE}$ from the lungs to the ear lobe, which can be easily derived from the analysis of the relationship between the IMV and SaO2 signals (Fig. 2). We can express this phase shift as

$$\varphi_{LE} = \varphi_{LC} + \varphi_{CE}$$

(5)

where $\varphi_{CE}$ is the lag introduced by the carotid-to-ear path. Substituting $\varphi_{LC}$ from Eq. 5 into Eq. 4, we obtain

$$\varphi_{LE} = \pi + \varphi_{CR} - \varphi_{PR}$$

(6)

Passing now from phase shifts to corresponding time delays (with the same meanings to the subscripts) using the relationship in Eq. 3, Eq. 6 becomes

$$T_{LE} = \frac{T_{PR}}{2} + T_{CE} - T_{PR}$$

(7)

This equation tells us that, under the hypothesis that the PB oscillation derives from instability in the chemoreflex loop of ventilation, the overall delay of this oscillation around the loop (i.e., $T_{LE} - T_{CE} + T_{PR}$) has to equal half the PB wavelength. An estimate of $T_{CE}$ can be obtained by reasonably assuming that the carotid-to-ear delay is mostly due to the pure convective process of the blood (i.e., mixing effects are negligible) and, expressing it as a fraction of the pure delay $T_{LE}$ between the lungs and the ear, this fraction being approximately given by the ratio of carotid-to-ear distance to the lung-to-ear distance. Taking 6 cm and 40 cm as representative measurements of these distances (21), we have

$$T_{CE} \equiv \frac{6}{40} \times T_{LE} = 0.15 \times T_{LE}$$

(8)

Hence Eq. 7 becomes

$$T_{LE} = \frac{T_{PR}}{2} + 0.15 \times T_{LE} - T_{PR}$$

(9)

which allows us to predict $T_{LE}$ having $T_{PB}$, $T_{LE}$, and $T_{PR}$. To this purpose, we estimated $T_{LE}$ in a subset of 12 patients by asking them to hold their breath as long as possible at the end of expiration and then to inspire abruptly with the highest possible vigor. In this way, we created a step change in ventilation that was followed by a step increase of SaO2 at the ear. The distance between the two steps (Fig. 3), averaged over two consecutive trials, was taken as the desired estimate. A rough estimate of $T_{PR}$ was obtained from time constants of the dynamics of the ventilatory response to hypoxia and of mixing effects in the heart and arteries measured by previous investigators (10, 25). Although these time constants were derived from healthy subjects, the estimated $T_{PR}$ should not be different from that of CHF patients (see details of this estimation procedure in the APPENDIX).

Statistical analysis. Data are presented as means ± SD. Pairwise comparisons were performed by the t-test for dependent samples. The significance level was set at 0.05.

RESULTS

Ventilatory oscillations during PB. The demographic and clinical characteristics of the subjects of the study are given in Table 1. In the O2 subgroup, hemodynamic indexes were well representative of the overall group [left ventricular ejection fraction = 22 ± 8%, cardiac index = 1.8 ± 0.5 (l·min⁻¹·m⁻²)]. A typical recording of ILV, ITV, IMV, and SaO2 signals during PB is shown in Fig. 4, left. The ITV signal appears as a smooth quasi-periodic waveform. Note also that the ILV signal shows an oscillation of the end-expiratory lung volume synchronous with breath amplitude changes. The respiratory frequency is fairly stable during the different phases of PB. As a consequence, the IMV signal is very similar to the ITV signal. An oscillation at the same frequency of the IMV signal characterizes the behavior of O2 saturation at the ear. In Fig. 4, right, the corresponding power spectral density function of all signals is plotted. The spectrum of the ILV signal is characterized by two well-defined peaks, one at the frequency of
PB and the other at the frequency of phasic respiratory activity, whereas the spectrum of the other signals is dominated by a peak around 0.02 Hz.

The respiratory frequency was $0.33 \pm 0.06$ Hz (20 ± 4 breaths per minute). Mean breath duration was $3.1 \pm 0.4$ s in the hyperpneic phase and $2.9 \pm 0.5$ s in the hypopneic phase ($P = 0.001$). Although statistically significant, this change is actually very small (<7%). Major parameters describing ventilation and SaO$_2$ fluctuations during PB are given in Table 2. To appreciate the representativeness of the O$_2$ subgroup relative to the overall group of the study, data from these patients are reported in the second row of the same table.

The central frequency of the spectral component associated with PB was $0.021 \pm 0.004$ Hz for ILV, $0.021 \pm 0.005$ Hz for ITV, $0.021 \pm 0.004$ Hz for IMV (PB frequency), and $0.021 \pm 0.004$ Hz for SaO$_2$. By computing the reciprocal of the PB frequency, we found that the corresponding length of the PB cycle was $49.8 \pm 8$ s.

We observed a rather pronounced oscillation of the end-expiratory lung volume synchronous with the oscillation of breath amplitude in 89% of the patients. By simultaneously recording ventilatory activity in a subsample of subjects by use of the Fleisch pneumotachograph (see METHODS), we found that this end-expiratory volume oscillation was independent of the technique used for recording ventilatory activity.

A coherence approaching unity and a near-zero phase shift at the PB frequency were found both between ILV and ITV ($0.96 \pm 0.04$, $-2 \pm 11^\circ$, not significant) and between ITV and IMV ($0.98 \pm 0.02$, $-1 \pm 9^\circ$, not significant), thus indicating that during PB there is a very close linear association and synchronicity between the slow component of lung volume and the corresponding oscillation of tidal volume, and between the oscillation of tidal volume and the corresponding oscillation of minute ventilation.

Table 1. Demographic and clinical characteristics of the patients

| Age, yr | 54.4 ± 7 |
| Male/female | 35/2 |
| NYHA class | 2.3 ± 0.6 |
| Etiology, % | 66 |
| Ischemic | 66 |
| Idiopathic | 34 |
| LVEF, % | 25 ± 7 |
| CI, l·min$^{-1}$·m$^{-2}$ | 2.0 ± 0.5 |

Values are means ± SD; $n = 37$. NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CI, cardiac index.
The coherence between IMV and SaO2 at the PB frequency was very high (0.95 ± 0.05). The phase shift between the two signals (which, as explained in METHODS, is an estimate of the phase shift around the ventilatory control loop plus the carotid-to-ear lag minus the phase shift due to the peripheral chemoreflex dynamics) exceeded 180° by 25°, with a 95% confidence interval comprised between 18° and 32°. The corresponding lung-to-ear delay was 28.3 ± 5.5 s.

Comparing predicted and observed delays. In the subgroup of 12 patients who underwent the end-expiratory apnea trial, the PB wavelength was 56.2 ± 9.5 s, corresponding to a PB frequency of 0.019 ± 0.003 Hz. The lung-to-ear delay was 30.9 ± 8.8 s, with a pure time delay contribution of 13.9 ± 3.7 s. By Eq. 8, the resulting estimate of the carotid-to-ear delay was 2.1 ± 0.6 s. The estimate of the delay TPR between the blood gas oscillation at the carotid body and the oscillation in ventilation was 1.4 ± 0.1 s. Inserting estimated values into Eq. 9, we obtained a predicted lung-to-ear delay of 28.8 ± 5.2 s (P = 0.13 for the comparison with observed values).

O2 administration. The effect of O2 administration in the patients of the O2 subgroup, to reduce or minimize the chemoreceptor drive, was the abolition of PB in 7 of 8 CHF patients. A representative example of successful O2 administration is given in Fig. 5. In these subjects, the mean SaO2 passed from 93.4% (basal condition) to 95.9% (P = 0.03) during O2 administration. It is noteworthy that the only patient in which PB was not abolished showed a very small increase in SaO2 (0.7%), suggesting that probably he did not breathe O2 properly.

<table>
<thead>
<tr>
<th></th>
<th>Average IMV, l/min</th>
<th>Average SaO2, %</th>
<th>ITvmax, liters</th>
<th>LVMI, %</th>
<th>SaO2PN, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 37)</td>
<td>6.7 ± 3</td>
<td>93.2 ± 1.9</td>
<td>0.57 ± 0.2</td>
<td>75 ± 15</td>
<td>2.2 ± 1.5</td>
</tr>
<tr>
<td>O2 subgroup (n = 8)</td>
<td>7.2 ± 4</td>
<td>93.4 ± 1.5</td>
<td>0.60 ± 0.2</td>
<td>72 ± 20</td>
<td>2.2 ± 1.3</td>
</tr>
</tbody>
</table>

Values are means ± SD. O2 subgroup, the subgroup of patients who were subjected to O2 administration after the basal recording; IMV, instantaneous minute volume. ITvmax, average maximum tidal volume over all periodic breathing cycles; LVMI, lung volume modulation index (see text for definition); SaO2PN, average peak-to-nadir O2 saturation.
DISCUSSION

Simultaneous recordings of ventilatory activity and \( \text{SaO}_2 \) at the ear during episodes of nonapneic PB in awake CHF patients have been analyzed in this study through time- and frequency-domain signal processing techniques, and the phase shift of the oscillation traveling around the peripheral chemoreflex loop has been estimated to be compared with the predicted value derived from the instability hypothesis. Given that one of the leading factors of instability of a feedback control system is increased loop gain, \( \text{O}_2 \) was administered to a subset of the patients to assess whether reducing the gain would have eliminated the ventilatory oscillation. The results of the study were remarkably consistent with theoretical expectations formulated on the basis of the instability hypothesis.

Adequacy of modeling assumptions and measurement techniques. A large body of experimental data has accumulated to support the notion that central chemoreceptors are characterized by a much slower dynamics than peripheral chemoreceptors. Previous studies in humans have shown that the time constant for the ventilatory response of central chemoreceptors is around one order of magnitude greater than that of peripheral chemoreceptors (11, 36). We expect this ratio to be even greater in CHF patients because of their reduced cerebral blood flow. Therefore, the response of central chemoreceptors at frequencies \( \sim 0.02 \) Hz (i.e., the typical PB frequency) will be markedly attenuated and the phase shift will be well below \(-180^\circ\). Because the overall response of the ventilatory controller can be modeled as the vectorial summation of the central and peripheral contributions (24), a dominant role of carotid body chemoreceptors in the mediation of PB seems well justified. Indeed, in a simulated study using a brain tissue washout time constant of 80 s, Khoo and co-workers (24) showed that the central contribution to the overall loop gain of the respiratory control system is much smaller than the peripheral contribution. We confirmed these results in our own simulations. The critical role of peripheral chemoreceptors in the development of PB in cats has been demonstrated previously (7).

Although intuitive, experimental evidence that \( \text{SaO}_2 \) and \( \text{Paco}_2 \) oscillate out of phase during PB has been provided in previous studies (13, 18).

We derived the peripheral chemoreflex delay from the time constants of the overall ventilatory response and of mixing effects in the heart and arteries obtained by other investigators in healthy subjects (10, 25).

Fig. 5. Representative tracings of ILV and \( \text{SaO}_2 \) from one patient of the \( \text{O}_2 \) subgroup before (basal condition) and during \( \text{O}_2 \) administration. Notice the complete abolition of periodic breathing and the marked increase of \( \text{SaO}_2 \) after the therapeutic intervention.
Although these time constants are expected to be markedly different in CHF patients because of enlarged left heart volumes, impaired hemodynamic function, and congested lungs, the lag associated with the response of peripheral chemoreceptors should not be. However, it is prudent to recognize that several simplifications were introduced in the overall computing procedure. Taking into account the difficulty of executing complex or invasive measurements in such severely diseased patients, we should regard our measurements as approximate estimates of the true peripheral chemoreflex delay, albeit the best presently possible.

The measurement of SaO₂ through pulse oximetry deserves some final comments. Although this is a widely accepted technique (accuracy ranges from 2% to 6% when compared with intra-arterial determinations; Ref. 9), measurements may be underestimated in the case of perfusion abnormalities. Franklin and co-workers (17) compared invasively measured SaO₂ during Cheyne-Stokes breathing with that obtained by the same pulse oximeter as the one employed in our study and found that periodic desaturations were less severe when measured by the latter. Hence, we cannot exclude that the peak-to-nadir changes in O₂ saturation measured in this study were somewhat lower than their actual values in arterial blood.

New descriptors of respiratory oscillations during PB. Using digital signal processing techniques, we derived from the original lung volume signal two new signals describing, in a continuous manner, changes over time of tidal volume and minute ventilation. The major advantage offered by these signals was that they could be resampled at the same frequency as that of the other respiratory signals, thus allowing the application of bivariate spectral analysis to obtain measurements of phase shifts from phase spectra. Using this approach, we found a high coherence between the low-frequency (0.01–0.04 Hz) component of the lung volume signal and the oscillation of tidal volume, and between the latter and the corresponding oscillation of minute ventilation, thus making these three signals virtually interchangeable in describing the cyclic oscillation of ventilatory activity during PB. In particular, the very close linear relationship and synchronicity between ITV and IMV and the very small (<7%) change in breath duration between the hyperpneic and hypopneic ventilation phases clearly indicate that the oscillation of minute ventilation during PB is almost totally due to the variation of tidal volume, with very little contribution from changes in respiratory rate. These findings are consistent with results from other investigators obtained in different experimental conditions (2, 15).

A marked wandering of the ventilatory baseline synchronous with the oscillation of tidal volume was observed in most subjects of the study. This oscillation has rarely been observed by other investigators and probably represents a purely mechanical phenomenon, arising from the fact that the duration of expiration is insufficient to permit complete exhalation when tidal volume increases during the hyperpneic phases of PB.

PB and the instability hypothesis. We found that the phase shift between minute ventilation and ear O₂ saturation at the PB frequency was significantly >180°, a result consistent with Eq. 6 derived from the instability hypothesis, provided that the carotid-to-ear lag is greater than the peripheral chemoreflex lag. Indeed, this is what we found in the apnea trial group. This finding is likely due to the fact that the carotid-to-ear delay arises from the slow blood transport process, which is expected to be further slowed down in CHF patients, whereas the peripheral chemoreflex delay is mainly due to the neural dynamics of the chemoreflex. We also found that the predicted measurement of the lung-to-ear delay, as given by Eq. 7, was very close to observed values, the difference being on average ∼7% of the expected value. Hence, these results indicate a remarkable consistency between theoretical expectations from the instability hypothesis and experimental observations. An example of how this concept is confirmed by empirical observations is given in Fig. 6, showing the transition phase between stable and oscillating ventilatory behavior. It can be noticed that a transient perturbation characterized by a sudden decrease in ventilation causes a delayed and pronounced decrease in O₂ saturation at the ear. This is almost simultaneous with the increase in ventilation, suggesting a causal relationship. The increase in ventilation in turn causes a delayed increase in SaO₂, accompanied by an opposite change in ventilation, and so on.

Our results, however, do not exclude the possibility that a central rhythm may play a role in the genesis of PB. Indeed, it seems realistic to hypothesize that the closed-loop control of ventilation of CHF patients can be often in a condition of “relative stability” (4). This is a state of the system characterized by an open-loop gain <1 at the critical frequency at which the phase shift of the loop is 180°. In this condition, the corresponding closed-loop gain shows a pronounced peak at the so-called resonant frequency. The closer the open-loop gain is to 1, the stronger the magnification and the narrower the bandwidth at the resonant frequency. This condition seems highly likely in CHF patients, because the reduced cardiac output brings about a concurrent increase of both the gain and the phase shift of the loop (4, 24). Moreover, hypoxic chemosensitivity is known to be enhanced in CHF patients, likely as a result of increased catecholamine levels and/or ischemic hypoxia at peripheral chemoreceptors (8, 14). Hence, if there is even a feeble central rhythm in the range 0.01–0.04 Hz and its frequency coincides with the resonant frequency of the loop, a full-blown oscillation will occur. If the gain increases further up to or over 1, the system becomes unstable and the oscillation tends to get larger and larger until the nonlinear characteristics of the loop intervene. Two major criticisms, however, can be addressed to this hypothesis. First, the frequency of PB is not the same among different populations of subjects or different physio-
logical conditions. Healthy subjects at high altitude, for instance, develop PB at a higher frequency than CHF patients, which would imply a different central rhythm. This discrepancy seems rather hard to explain. Second, the sudden appearance of PB after a transient perturbation, such as in the example of Fig. 6, is also difficult to understand in terms of an underlying central rhythm, because it would imply either that this rhythm starts abruptly or that a sudden change in the control loop parameters (e.g., the gain) takes place.

The estimate of the pure convective transport delay between the lungs and the ear was $\sim 14$ s, a result very close to the average circulatory delay of $12.4$ s measured by Ahmed and co-workers (1) from the hypoxic ventilatory response of CHF patients with nocturnal Cheyne-Stokes breathing. In our subjects, this delay accounted for about half the overall lung-to-ear delay, indicating that the time constants related to the gas exchange process in the lungs and to mixing effects in the heart and vasculature play a critical role in the setting of the PB phenomenon.

The effect of O$_2$ administration on respiration in CHF patients with Cheyne-Stokes respiration has been previously studied mainly during sleep (20, 34). Results from these investigations clearly show that supplemental O$_2$ reduces Cheyne-Stokes respiration, reduces the number of apneas, consolidates sleep, and reduces cyclic O$_2$ desaturations and the associated sleep hypoxemia. Differently, in our study, O$_2$ was administered to awake patients with nonapneic PB. In this condition, changes in central ventilatory drive induced by sleep-waking transitions (17, 23) are avoided, as are marked system nonlinearities associated with periodic reductions of $P_{aCO_2}$ below the apneic threshold (27). Our experimental setting for O$_2$ administration should therefore be appropriate to test the instability hypothesis according to the proposed model. Our experiments do show that elevating the mean level of O$_2$ saturation in the blood and hence reducing loop gain and increasing O$_2$ stores abolishes PB in almost all patients. This finding, again, is consistent with the instability hypothesis. Similar results have been recently reported by Ponikowski and co-workers (33) in a group of awake CHF patients with a mixed composition of apneic and nonapneic PB.

In conclusion, PB is a complex phenomenon that appears in different pathological conditions as well as in healthy subjects under different physiological states. It is thus conceivable that several, perhaps concurrent, mechanisms might contribute to its development. One of the most frequently claimed mecha-

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Fig. 6. Onset of periodic breathing in a chronic heart failure patient. A transient sudden decrease in ventilation causes a delayed and pronounced decrease in $SaO_2$. This is almost simultaneous with the increase in ventilation (ILV), suggesting a causal relationship. The increase in ventilation, in turn, causes a delayed increase in $SaO_2$, accompanied by an opposite change in ventilation, and so on.
nisms is instability in the chemical feedback control of ventilation. We tested this hypothesis in the specific context of awake CHF patients with nonapneic PB. This allowed a more precise identification of the underlying pathophysiological mechanisms, because they are not confounded by large system nonlinearities in ventilatory regulation and sleep-induced physiological changes. Two major aspects were specifically considered: the magnitude of the phase shift and related time delay between minute ventilation and O₂ saturation at the ear and the changes induced in the breathing pattern by O₂ administration. Experimental observations were consistent with stated expectations. Although these findings do not represent a conclusive proof in favor of the instability hypothesis, they clearly indicate that a condition of loss of stability in the chemical feedback control of ventilation, due to increased circulatory delay and loop gain, might play a determinant role in the genesis of PB in awake CHF patients. The analysis of cardiovascular oscillations during PB further supports this concept (32).

Our data highlight the critical role played by both the gas exchange process in the lungs and mixing effects in the heart and arterial vessels in the development of a long lung-to-carotid delay and, possibly, enhanced loop gain in CHF patients.

**APPENDIX**

To estimate \( T_{PR} \), it is convenient to express it as (see Eq. 3)

\[
T_{PR} = \frac{\varphi_{PR}}{2\pi \times f_{PR}} - \frac{\varphi_{VR} - \varphi_{H} - \varphi_{V}}{2\pi \times f_{PR}} - \tan^{-1}(2\pi f_{PR}\tau_{VR}) - \tan^{-1}(2\pi f_{PR}\tau_{H}) - \tan^{-1}(2\pi f_{PR}\tau_{V})
\]

\[
= \frac{\tan^{-1}(2\pi f_{PR}\tau_{VR})}{2\pi \times f_{PR}} - \frac{\tan^{-1}(2\pi f_{PR}\tau_{H}) - \tan^{-1}(2\pi f_{PR}\tau_{V})}{2\pi \times f_{PR}}
\]

where \( \varphi_{VR} \) is the phase shift of the PB oscillation around the ventilatory loop due to the cascade effects of mixing effects in the heart (\( \varphi_{H} \)) and arteries (\( \varphi_{V} \)) and of the peripheral chemoreflex response (\( \varphi_{PR} \)). We attributed 4.9 s to \( \tau_{VR} \), which is the median time constant for the dynamics of the ventilatory response to hypoxia found by Clement et al. in humans by combining data from different shapes of the hypoxic input (10). The median was preferred to the mean value due to the marked skewness of results. Conversely, we attributed 1 s and 2 s to the time constants for the heart (\( \tau_{H} \)) and arteries (\( \tau_{V} \)), respectively, as found by Lange et al. (25) using a dye-dilution technique in catheterized humans.

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**REFERENCES**


