Dynamic ventilatory response to CO\textsubscript{2} in congestive heart failure patients with and without central sleep apnea

ZBIGNIEW L. TOPOR, LINDA JOHANNSON, JERZY KASPRZYK, and JOHN E. REMMERS

Center for Biomedical Engineering, University of Kentucky, Lexington, Kentucky 40506; Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada T2N 4N1; and Institute of Automatic Control, Silesian Technical University, 44-101 Gliwice, Poland

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Nonobstructive (i.e., central) sleep apnea is a major cause of sleep-disordered breathing in patients with stable congestive heart failure (CHF). Although central sleep apnea (CSA) is prevalent in this population, occurring in 40–50% of patients, its pathogenesis is poorly understood. Dynamic loop gain and delay of the chemoreflex response to CO\textsubscript{2} was measured during wakefulness in CHF patients with and without CSA by use of a pseudorandom binary CO\textsubscript{2} stimulus method. Use of a hyperoxic background minimized responses derived from peripheral chemoreceptors. The closed-loop and open-loop gain, estimated from the impulse response, was three times greater in patients with nocturnal CSA (n = 9) than in non-CSA patients (n = 9). Loop dynamics, estimated by the 95% response duration time, did not differ between the two groups of patients. We speculate that an increase in dynamic gain of the central chemoreflex response to CO\textsubscript{2} contributes to the genesis of CSA in patients with CHF.

Central chemosensitivity; pseudorandom binary stimulation; impulse response; dynamic loop gain; carbon dioxide

Central or nonobstructive sleep apnea is a common form of sleep-disordered breathing in patients with heart failure or cerebral vascular disease. Javaheri (13) and later Javaheri et al. (15) estimated that up to 40% of patients with heart failure display this type of breathing during sleep. Central sleep apnea (CSA) often takes the form of Cheyne-Stokes respiration in which pulmonary ventilation waxes and wanes with a period of \~{}50 s. The pathogenesis of CSA is still a matter of debate (2, 23, 27, 36). Two major hypotheses have been proposed: 1) the “chemoreflex instability” hypothesis, which explains CSA as a self-sustaining oscillation due to the loss of stability in the closed-loop chemoreflex control of ventilation (11, 24, 26, 27), and 2) the “central” hypothesis, which explains CSA as the manifestation of an intrinsic oscillation originating in the central nervous system that periodically modulates ventilation either indirectly through a modulation of heart rate and blood pressure or directly through neuronal activation of respiratory centers (3, 7, 10, 35).

In the chemoreflex instability hypothesis, the oscillation may result either from a prolonged delay in the feedback loop (i.e., increased lung-to-chemoreceptor circulation time) or from an increase in the gain of the control system. The former may be caused by reduced cardiac output, increased cardiac chamber size, and increased circulating blood volume. The gain of the respiratory system is increased in heart failure, as evidenced by increased hypercapnic ventilatory response. Wilcox et al. (33) and Xie et al. (34) postulate that observed hypocapnia can be explained by an increase in ventilatory response to CO\textsubscript{2}. Javaheri (14), using a quasi-steady-state, open-loop method, found that ventilatory response to CO\textsubscript{2} was greater in heart failure patients with CSA than in those having no sleep-disordered breathing. The results presented recently by Pinna et al. (26) indicate that a condition of loss of stability in the closed-loop chemoreflex control of ventilation due to a long lung-to-carotid delay and, possibly, enhanced loop gain play a critical role in the genesis of CSA.

The present study further tests the chemoreflex instability notion by examining dynamic gain and delay of the chemoreflex response to CO\textsubscript{2} during wakefulness in heart failure patients with and without CSA. These aspects of the response to CO\textsubscript{2} were evaluated using the pseudorandom binary stimulus (PRBS) perturbation method, which involves single- or dual-breath presentation of increased CO\textsubscript{2} concentration in a pseudorandom sequence (12, 16, 19, 22). In the study reported here, we use a background of hyperoxia to suppress the peripheral chemoreceptors as a source of CO\textsubscript{2} chemosensitivity. Thus, we test the hypothesis that the dynamic gain or delay of the central chemoreflex loop is greater in congestive heart failure (CHF) patients with CSA than in those with no sleep-disordered breathing. Careful consideration should be given to the fact that a residual contribution from the peripheral chemoreceptors is probably still present in measured response to CO\textsubscript{2}.

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METHODS

All experiments involving human subjects were performed in the Alberta Lung Association Sleep Laboratory located at the Foothills Hospital in Calgary. The experimental protocol was approved by the Medical Bioethics Committee. Informed consent was obtained from all subjects.

Subjects. An initial population of male patients with stable CHF was screened by using home oximetry monitoring with an automatic analysis algorithm, which identified a 3% decrease in O₂ saturation as a respiratory disturbance (32). Based on the value of the respiratory disturbance index (RDI), the patients were separated into two groups: those with sleep apnea (RDI > 10) and those without sleep apnea (RDI < 10). Patients with sleep apnea underwent further polysomnographic study to confirm the diagnosis from the automated analysis of digital oximetry and to exclude cases of obstructive apnea. In this way, two groups of CHF patients were formed, one consisting of nine subjects with CSA during sleep and a second made up of nine subjects without CSA.

Patient characteristics are shown in Table 1. Differences in age and body mass index (BMI) between CSA and non-CSA patients were not statistically significant. A third group of seven healthy subjects was studied to provide comparison with published data (19). This group is characterized by mean age value of 30.9 ± 10.4 yr and mean value of BMI equal to 23.13 ± 2.29 kg/m².

Experimental methods. The experimental apparatus used to randomize inhaled gas mixture and collect data was similar to that used by Modarrezadeh and Bruce (21). Subjects breathed through a modified, low-dead space nose mask similar to that used by Modarrezadeh and Bruce (21). Subjects breathed through a modified, low-dead space nose mask similar to that used by Modarrezadeh and Bruce (21). Subjects breathed through a modified, low-dead space nose mask similar to that used by Modarrezadeh and Bruce (21). Subjects breathed through a modified, low-dead space nose mask similar to that used by Modarrezadeh and Bruce (21).

The experimental protocol consisted of breathing 100% O₂ for ~10 min before the inspired gas was switched between 100% O₂ and 95% O₂-5% CO₂ on a breath-by-breath basis according to a 63-breath long maximum length PRBS (9, 12, 19, 21, 22). Because inclusion of more experimental data enhances confidence in the derived parameters, we attempted to present each subject with eight repetitions of the basic sequence. Thus a master sequence 504 breaths long stored in the computer determined the number of successive inspirations containing 0 or 5% of CO₂. Sometimes, because of technical difficulties (i.e., failure of the balloon valves), we were able to present only a part of this master sequence before the experiment had to be terminated. The run was accepted as a successful if at least four 63-breath sequences were presented before termination. After a 30-min intermission, when subjects breathed room air, the entire sequence, including the 10-min period of O₂ breathing, was repeated. Thus a total of 8–16 PRBS sequences were presented to each subject over the two runs.

After each experimental run, the subjects were asked whether they were relaxed and comfortable during the study and whether they could sense when inhaled gas mixture contained increased level of CO₂. No one reported that they could taste the CO₂ mixture. Three subjects complained that others (12, 19, 21). During expiration, the inspiratory port of the nonrebreathing valve was connected through humidifiers to one of two rubber bags containing either 100% O₂ or 95% O₂-5% CO₂ by inflating and deflating balloon valves. Gas mixtures from compressed gas cylinders were continuously supplied to the bags, creating a small positive pressure (~2 cmH₂O), which ensured clearance of the valve dead space during expiration.

A battery of solenoid valves controlled by a computer was used to deflate or to inflate balloon valves by connecting them to the vacuum or pressurized air source. The noisy solenoid valves were located in an adjacent room so that the subject received no auditory cues regarding operation of the valves. On any particular inspiration, one valve was inflated and one was deflated, allowing the appropriate preselected gas mixture to be presented to the subject. The pressure inside the balloon valves was recorded for verification of their status during each breath. A Validyne DP-45 differential pressure transducer (Validyne, Northridge, CA) was used in combination with the low-resistance pneumotachograph to measure both inspiratory and expiratory airflow. The on-line program controlling the solenoid valves tracked the flow signal so that valve closing and opening could be confined to expiration. A Beckman LB-1 CO₂ analyzer (Beckman, Fullerton, CA) was used for a continuous measurement of CO₂ fraction with the sampling needle positioned at the airway opening. All measured signals were recorded on strip chart (Gould, Cleveland, OH) and digitized by an analog-to-digital converter at a sampling rate of 33 Hz. Digitized data was sent to an 80486 microcomputer for storage and further off-line analysis.

During the experimental runs, the subject lay supine listening to music through headphones. Before each run, the subject was reminded to breathe through the nose and was encouraged to relax but to remain awake with eyes open. By use of a remote video camera, the subject was monitored to verify wakefulness during the trial. To eliminate any voluntary effects on breathing, the true purpose of the study was concealed from the subject by falsely asserting that we were investigating the cardiovascular response to different gas mixtures. We placed three electrocardiogram electrodes on every subject before the experimental run, but no attempt was made to record from them. The true purpose of the study was disclosed to the subject at the end of the study.

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they did not feel comfortable during the experimental run, and we repeated their trials on a subsequent date. Two sham runs, in which the inspired mixture was pseudorandomly switched between two bags containing 100% O₂, were recorded for two subjects. Results from these runs were used to determine whether the measured ventilatory responses were due to the experimental procedures other than stimulation with alternating CO₂ levels. No significant increase in minute ventilation was observed in the sham tests.

Data analysis. All data analyses were performed by an investigator skilled in the application of the system-identification software and blinded to the results of the O₂ saturation screening.

The analog data were carefully inspected. Comparison of the CO₂ signal with balloon valve pressure and the PRBS sequence identified all the instances of valve malfunction. In all such cases, the original PRBS sequence was corrected to correspond to the actual valve status.

We used ABREATH 5.2 respiratory analysis program (RHT-InfoDat, Montreal, Quebec, Canada) to integrate the digitized airflow signal. The integrated signal yielded breath-by-breath values of inspiratory tidal volume (VT), inspiratory and expiratory times, total breath duration, breathing frequency, and inspiratory minute ventilation (VI). All calculated variables were then tabulated and visually inspected. This step allowed also for identification and removal of all events incorrectly identified as breaths. After all errors were discarded, the program calculated the means and standard deviations of all variables.

The digitized CO₂ signal produced breath-by-breath values of end-tidal partial pressure of CO₂ (PETCO₂). The corrected PRBS sequence was transformed into the sequence of breath-by-breath values of inspired fractional CO₂ concentration (FiCO₂), and every experimental run was represented by three temporally aligned signals consisting of breath-by-breath values of VI, PETCO₂, and FiCO₂. Khoo et al. (16) suggest that all these values should be resampled at the average breath duration for that particular run to compensate for the breath-to-breath variation in breath duration. On the other hand, Dhawale and Bruce (5) demonstrated that if the variation in breath duration is reasonably small (standard deviation < 20% of mean breath duration), then its effect on the accuracy of the PRBS method is negligible. Because this criterion was fulfilled in all experimental runs, we did not resample.

Extreme values, euphemistically referred to as “outliers,” were defined as values for which the absolute deviation from the mean exceeds two standard deviations. Because their source is usually stochastic in nature and external to the identification experiment, we eliminated these points before the analysis by the system identification software. In our experiments, the outliers commonly appeared to be spontaneous augmented breaths (or sighs) having a prolonged expiratory time and followed by a breath of reduced VT. Because the effect of a sigh spans two breaths, both the large and the small breaths should be considered during correction process. VI values for each breath and the following breath were replaced by the values calculated by linear interpolation involving two adjacent unaffected breaths. Figure 1 shows VI signal obtained for a normal subject before and after the correction process.

Because our goal was to measure the dynamic response of the ventilatory control system, all input and output signals were represented as variations from their respective mean values so that the measured responses reflected changes from the mean level of ventilation. The mean values for all measured signals were determined from the last 5 min of O₂ breathing period just before application of PRBS sequence.

According to the procedure introduced by Modarresszadeh et al. (22), we calculated two types of responses: 1) the VI response to a single-breath increase in FiCO₂ (reflecting the closed-loop dynamics of the respiratory CO₂ control system, including the ventilation feedback loop); and 2) the VI response to a single-breath increase in PETCO₂ (reflecting the open-loop response of the central ventilatory controller). To obtain these dynamic responses, we used the general system identification technique with transfer function estimation based on the prediction error method (PEM) (20, 28). The PEM models the output of the linear system y(n) (in our case VI) as the sum of the response of the system to a deterministic input u(n) (PETCO₂ or FiCO₂) and random noise e(n). Two general model structures described by the following equations were considered in our search for the best model.

**Box-Jenkins (B-J) structure**

\[
y(n) = q^{-nk} \frac{B(q)}{F(q)} u(n) + \frac{C(q)}{D(q)} e(n) \quad n = 1, 2, \ldots, N \quad (1)
\]

**Autoregressive with moving average and external input (ARMAX) structure**

\[
y(n) = q^{-nk} \frac{B(q)}{A(q)} u(n) + \frac{C(q)}{A(q)} e(n) \quad n = 1, 2, \ldots, N \quad (2)
\]

In both equations n is the breath number, nk is the pure time delay between u(n) and y(n), N is the total length of the data.
record used in the analysis, and A, B, C, D, and F are polynomials in the delay operator \( q^{-1} \) with the order \( na, nb, nc, nd, \) and \( nf, \) respectively. The general B-J structure can be described as \( M_{B,J}(nk; nb, nc, nd, nf) \). Similarly, the general ARMAX structure can be described as \( M_{ARMAX}(nk; na, nb, nc) \). Any particular B-J or ARMAX model is characterized by a specific absolute time delay and by specific orders of polynomials.

We employed the system identification software MULTI-EDIP (Uniprod, Gliwice, Poland) to obtain optimal values of the absolute time delay and orders of all polynomials for both general model structures. To obtain the optimal values for one session of data for each subject, for the open-loop and the closed-loop system our computer program started from the initial value of \( nk = 1 \) and incremented by one the order of one of three (ARMAX structure) or four (B-J structure) polynomials in a stepwise fashion until all of them reach the maximum value of six. In the next step, the value on \( nk \) was increased by one and again polynomials orders were varied. This step was repeated until \( nk \) reached the maximum allowable value of 11. The estimation of model parameters was performed for every possible model. The final selection of the optimal values and corresponding model parameters was based on the following criteria: 1) the Bayes information criterion, 2) the determination of the whiteness of the residuals and testing for lack of statistically significant correlation between the input signal and the residuals, and 3) the variance and statistical significance of all estimated parameters.

To compare the characteristics of the closed-loop and open-loop impulse response in control subjects, CHF patients with CSA, and CHF patients without CSA, we calculated the peak magnitude of the response as well as the time that it takes to complete 95% of the response (the time required for the response to decay from its peak value to 5% of the peak value). The peak magnitude of the response, referred to as magnitude of the response, was considered to be the estimate of the CO₂ responsiveness. The 95% duration time, referred to as delay, was used as an estimation of the delay time associated with central chemoreflex and includes circulatory transit delay from lungs to brain plus the “wash in” and “wash out” equilibration times of the central chemoreceptors in the brain.

Group data were presented as means ± SD. The independent t-test was used to compare groups. Statistical significance was taken at \( P < 0.05 \).

RESULTS

Low-order models (\( ni ≤ 3 \)) that minimized the Bayes information criterion and met the two additional criteria for acceptability presented above were found for all subjects. By these criteria, the ARMAX structure generated better results than B-J in all cases.

Closed-loop analysis. Figure 2 shows an example of the closed-loop Vi response to a single-breath 1% increase in \( FICO₂ \) during hyperoxia for one typical subject from each group. After one or two breaths of absolute delay, the response rises rapidly, reaching peak value within two breaths. This rapid rise is followed by a gradual decay 125–250 s long.

The most prevalent model for the closed-loop ventilatory response for normal subjects was \( M_{ARMAX}(nk; 2, 0, 1) \) with \( nk \) value ranging from 1 to 3. Mean values of the peak magnitude of the response and 95% duration time were 0.0656 ± 0.013 l/min and 334.7 ± 127.7 s, respectively. Lai and Bruce (19) reported that the typical model for normal subjects under hyperoxic conditions was \( M_{B,J}(2; 1, 2, 2, 2) \). The mean value of the amplitude of the response was 0.079 ± 0.034 l/min, and no duration time was calculated. On the basis of the graphic representation of a closed-loop ventilatory impulse response for two subjects shown in this paper, we estimate the value of this parameter to be on the order of 200 s.

A typical model determined for CHF patients without CSA was \( M_{ARMAX}(nk; 2, 0, 1) \) with \( nk \) value ranging from 1 to 4. The peak magnitude of the response and 95% duration time were 0.0612 ± 0.03 l/min and 358.71 ± 108.2 s, respectively. Models determined for CHF patients with CSA had higher orders than those determined for CHF patients without CSA, with \( nk \) value ranging from 1 to 3. In five of nine models, \( nb \) was >0. The values of both peak response parameters were 0.161 ± 0.04 l/min and 278.7 ± 66.9 s, respectively. Figure 3 illustrates means and standard deviations of the closed-loop impulse response peak value and 95% response duration time for all three groups of subjects. The peak magnitude of the response was 2.63 times higher for CHF patients with CSA compared with patients without CSA (\( P < 0.01 \)). The value of 95% duration time did not differ significantly between the two groups.

Open-loop analysis. The most prevalent model for the open-loop ventilatory response for our normal subjects was \( M_{ARMAX}(nk; 1, 0, 1) \) with \( nk \) value ranging from 1 to 3. Only in four subjects was a higher order model \( M_{ARMAX}(nk; 2, 0, 1) \) determined. Mean values of the peak magnitude of the response and 95% duration time were 0.0380 ± 0.011 l/min and 304.5 ± 93.2 s, respectively. Lai and Bruce (19) reported that the best model for open-loop response was \( M_{B,J}(2; 1, 2, 1, 1) \). Mean value of the peak magnitude of the response reported by these authors was 0.058 ± 0.037 l/min.

For CHF patients without CSA, the model \( M_{ARMAX}(nk; 2, 0, 1) \), with \( nk \) ranging from 1 to 3, was selected for six subjects; the remaining three models
were of the $\mathbf{M}_{\text{ARMAX}}(nk; 0, 1)$ order. For this group, mean values of amplitude and delay were $0.0281 \pm 0.0145$ and $318.5 \pm 51.15$ s, respectively. For CHF patients with CSA, all but one of the models were of $\mathbf{M}_{\text{ARMAX}}(nk; 0, 1)$ order, with $nk$ ranging in the value from 1 to 4. The mean values of both ventilatory response parameters were $0.088 \pm 0.023$ l/min and $206.4 \pm 94.0$ s. The peak magnitude of the response was 3.1 times higher for CHF patients with CSA compared with patients without CSA ($P < 0.01$). The value of 95% duration time did not differ significantly between the two groups.

Figure 4 illustrates means and standard deviations of the open-loop impulse response peak value and 95% response duration time for all three groups of subjects. The mean value of the peak magnitude of the open-loop ventilatory response was lower compared with the closed-loop mean value for all subjects groups.

**DISCUSSION**

The use of PRBS testing for quantifying ventilatory chemosensitivity has been explored in previous studies (12, 16, 19, 22), and the results of the present study for normal subjects agree with those reported previously (19). The present study compared the dynamic ventilatory response to a CO$_2$ pulse in CHF patients with and without CSA while awake. The results reveal that the amplitude of the response was greater in the former than the latter group but that the delay was not significantly different between the two groups. Because the studies were performed under hyperoxic conditions, we infer that the dynamic ventilatory response represents predominantly the behavior of the central chemoreflex loop, although a contribution from the peripheral chemoreceptors cannot be excluded.

We used an automated O$_2$ saturation algorithm for screening for CSA in patients having CHF. This algorithm has a 95% sensitivity for identifying obstructive respiratory disturbances (32). Its performance in central respiratory disturbances is unknown, and this introduces the possibility of misclassification of patients regarding whether or not they have CSA. Furthermore, patients having ventilatory instability and O$_2$ desaturation <3% would not have been identified by our screening method. However, current classification systems would not have identified these patients as having sleep-disordered breathing.

In his recent study, Javaheri (14) employed the Read rebreathing method to evaluate the hyperoxic hypercapnic ventilatory response in CHF patients with and without CSA. He reported that the ventilatory response to CO$_2$, which in this case represents steady-state chemoreflex gain was significantly increased in patients with CSA. Our test of the dynamic ventilatory response offers several advantages over the progres-
sive, quasi-steady-state test used by Javaheri. First, dynamic testing assesses the response dynamics as well as the magnitude of the response to a chemical stimulus to breathe. Second, testing of the dynamic control of the respiration allows for the assessment of the role of the different components of the system, such as controller, plant, and negative ventilatory feedback. Third, because arterial \( P_{CO_2} \) varies only slightly during a PRBS run, psychological and perceptual aspects of progressively increasing high levels of \( CO_2 \) are minimized. Finally, the dynamic response of the control system reflects the behavior of the system exposed to transient perturbation of chemical stimuli such as happens during minor “errors” or sustained ventilatory oscillations as in CSA.

Comparison of results from the group of normal subjects with data reported in the literature. The models and properties of the ventilatory response for hyperoxic normal subjects compare favorably with the experimental results reported by Lai and Bruce (19). Our values for peak magnitude and 95% duration, calculated for both closed- and open-loop responses, are compared with those from Lai and Bruce in Table 2.

Before employing the PEM method to calculate the closed-loop ventilatory response, Lai and Bruce (19) multiplied every element of the original input vector \( F_{ICO_2}(n) \) by the respective value of \( V_T \), \( V_T(n) \), creating a new input vector proportional to the volume of \( CO_2 \) inhaled in each breath. This operation was originally proposed by Modarreszadeh et al. (22) to correct for variations of the inhaled amount of \( CO_2 \) caused by variable \( V_T \). We did not follow this procedure and used the original perturbing signal \( F_{ICO_2}(n) \) throughout the analysis. As a consequence of this decision, the value of the amplitude of the closed-loop response reported by Lai and Bruce (19) is scaled differently than the value from our study. The literature values reflect the response of the system to inhalation of 1 liter of gas mixture containing 1% \( CO_2 \), or simply to the single-breath inhalation of 0.01 liter of \( CO_2 \) (22). Our values represent response to the single-breath inhalation of the same gas mixture with the inhaled volume equal to the average \( V_T \) rather than 1 liter. Therefore, before comparing the amplitude of the response obtained from our study with the literature value, we correct it by multiplying the amplitude by a factor equal to the ratio of 1 liter divided by the average value of \( V_T \) from our study. The corrected experimental value is included in Table 2. In general, the values of both parameters of the closed-loop ventilatory response from our study were of the same order as those reported by Lai and Bruce.

The value of the amplitude of the open-loop response from our study is somewhat lower than that reported by Lai and Bruce (19). Nevertheless, taking into account standard deviations associated with each value, we believe that our results are comparable with those from other studies. Although no direct comparison is available from literature data for the value of 95% duration time, indirect data from Lai and Bruce suggest that the upper limit for the value of this parameter is below 300 s. Our value of 304.5 s is comparable with this estimate.

The ARMAX model structure was better than B-J in describing our closed- and open-loop data. Comparing Eqs. 1 and 2, one can see that both structures are very similar and that ARMAX is a special case of more general B-J. We believe that both model structures provide enough flexibility in describing deterministic and stochastic parts of the transfer function as to avoid obtaining biased estimates.

Other investigators have not performed a comprehensive search for an appropriate model structure but rather chose one arbitrarily (12, 16, 17, 22). They based their model choice on the previous knowledge of the system and, in some cases, on the results from computer simulations employing dynamic computer models of the respiratory control system. Some authors opted for a B-J model structure in their studies (12, 19, 22), but others selected model structures as simple as autoregressive model with external input (16, 17).

Summarizing, we believe that comparison between our results obtained for normal human subjects with the results from the literature support the notion that our system identification technique provides a robust, reliable method that can be used to evaluate dynamic characteristics of the central chemoreflex loop in two groups of CHF patients, one with and one without CSA during sleep.

Characteristics of the respiratory control system for both groups of CHF patients. The results of this study using a \( CO_2 \) as a PRBS perturbation signal in hyperoxia show a significantly greater amplitude response for CHF patients with CSA than CHF patients without CSA during wakefulness. This difference was observed in both closed- and open-loop responses.

The respiratory control system consists of three major components each characterized by a separate gain

### Table 2. Comparison of peak amplitude of the response and \( T_{95\%} \) for the normal subjects with the literature values

<table>
<thead>
<tr>
<th>Source of the Data</th>
<th>Closed Loop</th>
<th>Open Loop</th>
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<tbody>
<tr>
<td></td>
<td>Amplitude, l/min</td>
<td>( T_{95%}, s )</td>
</tr>
<tr>
<td>Lai and Bruce (19)</td>
<td>0.079 ± 0.034</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>0.066 ± 0.013</td>
<td>344.7 ± 127.7</td>
</tr>
<tr>
<td>Data from our experiments</td>
<td>(0.089 ± 0.017)</td>
<td></td>
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</table>

Values are means ± SD. Values in parentheses reflect a correction process applied to the data from our experiments. \( T_{95\%} \), 95% duration time.
and time constant: the peripheral chemoreceptors, the central chemoreceptors, and the respiratory plant. Assuming that inhalation of 95% O\textsubscript{2} functionally eliminates peripheral chemoreceptors, our dynamic closed-loop response should reflect interaction between two remaining components and can be approximated by the product of the peak responses for the plant and central controller. This value was 2.63 times larger in CHF patients with CSA than in the CHF patients without CSA ($P < 0.01$). The closed-loop response 95% duration time reflects the dynamics of the plant (i.e., transport time of CO\textsubscript{2} from the lungs via the arterial blood to the site of the central chemoreceptors) further modified by the dynamics of the controller (i.e., additional delay and possible integration of the arterial signal by the brain compartment) as well as the dynamics of the central controller ventilatory response to the washout of CO\textsubscript{2} from the region of the central chemoreceptors. The value of the closed-loop response 95% duration time did not differ between the two groups of CHF patients.

The open-loop ventilatory response most likely reflects the dynamics of the central ventilatory controller. Thus the peak magnitude of the response should be dependent on the sensitivity of the chemoreceptors. The value of this parameter was 3.1 times higher for the CHF patients with CSA compared with the CHF patients without CSA ($P < 0.01$). The 95% duration time of the response probably reflects a delay associated with the transport of arterial P\textsubscript{CO\textsubscript{2}} signal to the brain compartment and the subsequent washout of CO\textsubscript{2}. The value of this parameter did not differ between the two groups of CHF patients. The long response duration times observed in the present study support the speculation that the CO\textsubscript{2} responses were mediated by central chemoreception, because peripheral chemoreceptors responses would have occurred in a fraction of the response time observed here (19).

Central sensitivity to CO\textsubscript{2} has been reported to be significantly increased in patients who demonstrate CSA during sleep (14, 33, 34). These investigators report values consistent with a two- to threefold increase in the central chemoreflex loop gain. The single-breath method (34) is hampered by the typically large ventilatory variability relative to the small ventilatory responses elicited by such brief chemical stimuli. The rebreathing test (14, 33, 34), which typically ends at the level of maximum tolerated ventilation, involves relatively high CO\textsubscript{2} levels and may be distorted by cortical influences. Our method overcomes these limitations by employing PRBS chemical stimulation with mean CO\textsubscript{2} level of only 2.5%. The design of our method ensures that the subject’s awareness of the fact that he breathes a gas mixture with an increased level of CO\textsubscript{2} is minimized. Finally, the method is optimized to provide closed-loop chemoreflex dynamics in the face of noise and in the presence of a normal operating signal. Two of mentioned above studies have further limitations. In the study of Wilcox et al. (33), only a group of CHF patients with CSA was studied, and therefore increased CO\textsubscript{2} sensitivity could not be compared with a value for non-CSA patients. Patients from the study of Xie et al. (34) suffered from idiopathic CSA. Therefore, only the study of Javaheri (14) offers similar comparison between two groups of CHF patients. Despite significantly different experimental technique, increase in central sensitivity to CO\textsubscript{2} from our study is almost identical to this reported by Javaheri.

The PRBS method of evaluating chemoreflex loop gain examines the transient response to imposed perturbations of CO\textsubscript{2} rather than a sustained response to a prolonged CO\textsubscript{2} stimulus. The magnitude and delay of the PRBS responses presumably reflect the dynamic behavior of the chemoreflex loop under conditions in which transient “errors” in arterial P\textsubscript{CO\textsubscript{2}} appear spontaneously. In particular, factors such as ventilatory adaptation and facilitation that likely occur during a sustained stimulus, perhaps as a result of slow dynamics of cerebral blood flow or alterations in neuromodulators, will influence the response. The closed-loop dynamic response also allows evaluation of the interaction of plant and controller dynamics that may importantly influence stability of the system. In this regard, we observe a similar ratio between open- and closed-loop values for gain of the CO\textsubscript{2} response, suggesting that differences in plant behavior, which would be reflected in the closed-loop but not the open-loop gain, are small between the two groups of CHF patients and, thus, play little role in the genesis of CSA in CHF (4).

The lack of a significant difference in the 95% response duration time between the CHF/CSA group and the group of non-CSA patients supports the finding by Naughton et al. (24) that prolonged circulatory delay in patients with CHF does not correlate with the presence of CSA. The magnitude of the circulatory delay prolongation depends on the severity of CHF. Because the majority of our patients from both groups were diagnosed as New York Heart Association Class II subjects, we may expect that their circulatory delay time under supine resting conditions may be the same. The pseudorandom binary CO\textsubscript{2} stimulus method is not well suited for detection of differences in absolute delay because its resolution is limited by the respiratory cycle duration. Accordingly, we have made no comparison of absolute delay for the two groups of CHF patients.

Hyperoxia clearly suppresses the sensitivity of the carotid body to changes in arterial P\textsubscript{CO\textsubscript{2}} in humans (8). On the other hand, several investigators report significant contribution of the peripheral chemoreceptors to the ventilatory response to CO\textsubscript{2} in cats during hyperoxia (1, 6, 18). A recent study by Pedersen et al. (25) involving human subjects also indicates that some small component of the CO\textsubscript{2} chemoreflex response may be mediated by the peripheral chemoreceptors. Lai and Bruce (19) used the PRBS method in normoxia and hyperoxia to derive the ventilatory response to a brief CO\textsubscript{2} disturbance in the population of nine healthy, awake humans. For hyperoxia, their closed- and open-loop estimates of the response duration time were in the range of 200–300 s (see Table 2). For normoxia,
estimated response duration time for closed- and open-loop conditions was significantly shorter and limited to the 80- to 150-s range. The authors postulate that observed difference could be explained by the fact that under normoxic conditions the predominant part of the response originates from the fast peripheral chemoreceptors, whereas under hyperoxia this component is greatly reduced, exposing a much slower component originating from the central chemoreceptors. Because our estimates of the response duration time match these found by Lai and Bruce in hyperoxia, we infer that the response we measure is predominantly related to the central chemoreceptors.

We stress the fact that we have no means of estimating the possible contribution from the peripheral chemoreceptors to the overall response we measure. Therefore, we cannot exclude the notions presented by Sun et al. (30, 31) regarding increased activity of the peripheral chemoreceptors in conscious rabbits with pacing-induced heart failure. Nevertheless, we believe that our data provide a reasonable basis for a speculation about predominant role of the central chemoreceptors in the pathogenesis of the CSA in CHF patients.

Several factors not measured or controlled in this study may have influenced the observed difference in chemoreflex response to CO2. An unmeasured factor is resting arterial PCO2, which may have been lower in the CSA than in the non-CSA group (22). A reduction in alveolar PCO2, whatever the cause, will tend to depress the closed-loop response to CO2 because a unit change in ventilation elicits a smaller change in alveolar PCO2. However, if the CSA group has a compensated hypocapnia, the reduced plasma bicarbonate concentration might result in an increased open-loop hypercapnic response, owing to a larger change in pH for a unit change in arterial PCO2. Although the CSA group tended to be older and to have a higher BMI than the non-CSA group, these differences were not statistically significant. A higher BMI would be expected to be associated with a higher obstructive RDI, although patients with obstructive sleep apnea were excluded from the study. A higher BMI would also be associated with a lower lung volume, which would tend to increase the closed-loop gain. Overall, the trend toward differences in BMI and age would not be expected to produce the observed difference in open-loop gain.

Summarizing, we report a significant increase in the sensitivity of the central chemoreflex loop in CHF patients with CSA during sleep. This increase was 2.6-fold for the closed-loop response and 3.1-fold for the open-loop response. Whether or not an increase in central chemoreflex loop gain is an adequate explanation for the development of CSA in CHF remains to be explored.

REFERENCES


