Does the Severity of Central Sleep Apnea Correlate With Respiratory Gas Indexes During Cardiopulmonary Exercise Testing?

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SUMMARY

Central sleep apnea (CSA) is thought to arise as a consequence of chronic heart failure. We have attempted to determine the relationship between the severity of CSA and the respiratory gas indexes during cardiopulmonary exercise testing (CPX), indexes well-known to reflect the severity of heart failure. Twenty consecutive cardiac patients (59.0 ± 15.3 years) with CSA underwent CPX. End-tidal PCO$_2$ (PETCO$_2$) was measured at rest and at peak exercise as a substitute for PaCO$_2$, along with the peak oxygen uptake (VO$_2$) and the ratio of the increase in ventilation to the increase in CO$_2$ output (VE/VCO$_2$ slope). Peak VO$_2$, % peak VO$_2$, and the VE/VCO$_2$ slope of the subjects were 15.5 ± 5.8 mL/min/kg, 52.8 ± 16.7%, and 37.9 ± 12.5, respectively, showing moderate to severely decreased exercise capacity. While PETCO$_2$ at both rest and peak exercise significantly correlated with peak VO$_2$ ($r = 0.63$ and $r = 0.51$, respectively) and the VE/VCO$_2$ slope ($r = -0.77$ and $r = -0.91$, respectively), none of these 3 parameters correlated with the apnea-hypopnea index. The apnea-hypopnea index in the subjects with lower resting PETCO$_2$ was not notably different from that in the subjects with relatively high PETCO$_2$.

Although the severity of CSA is assumed to correlate with the severity of heart failure, and a lowering of PaCO$_2$ during wakefulness is considered to be one of the mechanisms behind CSA, the severity of CSA does not correlate with the respiratory gas indexes of CPX or the level of PETCO$_2$ in cardiac patients with moderate to severely decreased exercise capacity. (Int Heart J 2006; 47: 889-900)

Key words: Central sleep apnea, Exercise testing, PaCO$_2$, Respiratory gas analysis

OSCILLATORY breathing alternating between hyperpnea and hypopnea during sleep has been recognized for more than a century in cardiac patients. This disordered breathing, commonly referred to as Cheyne-Stokes respiration, is now classified as central sleep apnea (CSA). Several hypotheses have been proposed as
the mechanisms of this abnormal breathing, such as an instability of the ventilatory control system,\(^1\) a decrease in the PaCO\(_2\) regulatory set point,\(^2,3\) or fluctuations in the pulmonary blood flow.\(^4,5\) However, the mechanisms of this breathing pattern are not fully understood.

Formerly, risk stratification of heart failure was based on functional assessment and resting hemodynamic measurements.\(^6,7\) However, the former is subject to the physician's bias, and the latter does not necessarily correlate with the clinical manifestations of heart failure.\(^8,9\) To compensate, cardiopulmonary exercise testing (CPX) has become important for stratifying patients with heart failure\(^10,11\) and identifying those with a poor prognosis.\(^12-15\)

Sleep apnea can be classified either as CSA or obstructive sleep apnea (OSA). OSA is assumed to play an independent role in the pathogenesis and progression of cardiovascular disease.\(^16\) On the other hand, it is believed that CSA itself worsens the heart failure, and also becomes more severe according to the severity of the heart failure. It remains controversial, however, as to whether the severity of CSA correlates with respiratory gas indexes during CPX. These indexes are well-known to reflect the severity of heart failure.

In this study, we attempted to determine the relationship between the severity of CSA and the indexes of CPX in patients with cardiovascular disease. We also evaluated in these patients whether the degree of CSA is related to the end-tidal PCO\(_2\) (PETCO\(_2\)) obtained from the respiratory gas analysis during CPX, a parameter reflecting arterial PCO\(_2\).

**METHODS**

**Study patients:** We studied 20 consecutive patients with cardiovascular disease and with CSA at the Cardiovascular Institute. All subjects were screened for suspected sleep apnea through clinical findings or symptoms. They were diagnosed as having sleep apnea with an apnea-hypopnea index > 10/h, in which the central type was dominant (Table). No patients with unstable angina, a myocardial infarction within the preceding month, documented lung disease, cerebrovascular disease, or orthopedic difficulty in performing the exercise testing were included in this population. The committee on the ethical use of human subjects at the Cardiovascular Institute approved the protocol and procedures for this study. Informed consent was obtained from each patient prior to enrollment.

Coronary artery disease was diagnosed by the presence of significant coronary stenosis, defined as a ≥ 75% reduction in the luminal diameter of coronary vessels. The presence of a myocardial infarction was diagnosed according to the World Health Organization (WHO) criteria.\(^17\)

**Exercise protocol and respiratory gas analysis:** An incremental exercise test was
performed using an upright, electromagnetically braked cycle ergometer (Corival 400, Lode, Holland). The exercise test began with a 4-minute rest on the ergometer followed by a 4-minute warm-up at 20 watts, and then the load was increased incrementally by 1 watt every 6 seconds (10 W/min). Breath-by-breath oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), and minute ventilation ($\dot{V}E$) were measured from 4 minutes prior to starting the exercise until the end of the exercise using an AE-300S Respiromonitor (Minato Medical Science, Osaka, Japan), as previously described.\textsuperscript{18,19} PETCO$_2$, which is known to reflect arterial PCO$_2$, was also measured using this device.

Prior to calculating the parameters from the respiratory gas analysis, a 5-point moving average of the breath-by-breath data was performed. Peak $\dot{V}O_2$ was defined as the average value obtained during the last 15 seconds of incremental

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Mean: 59.0 618.1 70.2 24.8 31.8 40.9 15.5 52.8 37.9
SD: 15.3 5.9 14.0 4.7 12.8 21.8 5.8 16.7 12.5

Percentage of peak $\dot{V}O_2$ was calculated by dividing peak $\dot{V}O_2$ by predicted peak $\dot{V}O_2$. AHI indicates apnea-hypopnea index; AR, aortic regurgitation; AV block, atrioventricular block; AVR, aortic valve replacement; BMI, body mass index; CAD, coronary artery disease without myocardial infarction; DCM, idiopathic dilated cardiomyopathy; HHD, hypertensive heart disease; LVEF, left ventricular ejection fraction obtained from echocardiography; MR, mitral regurgitation; OMI, old myocardial infarction; Peak $\dot{V}O_2$, peak oxygen uptake; and $\dot{V}E$/VCO$_2$ slope, the ratio of the increase in ventilation to the increase in CO$_2$ output.
exercise. The percentage of peak $\dot{V}O_2$ was calculated by dividing the measured peak $\dot{V}O_2$ by the predicted peak $\dot{V}O_2$. The predicted peak $\dot{V}O_2$ was determined based on a normal Japanese population. The slope of the increase in $\dot{V}O_2$ to the increase in the work rate ($\Delta\dot{V}O_2/\Delta WR$), which is a reflection of the rate of the increase in cardiac output, was calculated from the data recorded between 30 seconds after the start of incremental exercise to 30 seconds before the end of the exercise by least squares linear regression. The ratio of the increase in $\dot{VE}$ to the increase in $\dot{V}CO_2$ ($\dot{VE}/\dot{V}CO_2$ slope), which is known to become steeper according to the severity of heart failure, was calculated from the start of incremental exercise to the respiratory compensation point also by least squares linear regression. The respiratory compensation point was determined by the following criteria: 1) The ratio of $\dot{VE}$ to $\dot{V}CO_2$ starts to increase after a period of decrease or stasis; and 2) the PET$CO_2$ starts to decrease after a period of stasis. When the respiratory compensation point could not be clearly identified, the $\dot{VE}/\dot{V}CO_2$ slope was calculated from the data recorded between the start of incremental exercise to the end of the exercise.

Sleep apnea screening: A Respiratory Monitor, Morpheus R (Teijin Pharma Limited, Tokyo) was used for sleep apnea screening. With this device, thoracoabdominal excursions, nasal airflow, snoring, and pulse oximetry were monitored during sleep. The recorded data was analyzed by a specially-trained technician without any knowledge of a subject’s clinical data. Apnea was defined as a cessation of inspiratory airflow for ≥ 10 seconds. Hypopnea was defined as a > 50% reduction of airflow or thoracoabdominal excursions lasting ≥ 10 seconds along with a ≥ 3% drop in pulse oximetric saturation. CSA was defined as a cessation of thoracoabdominal excursions. OSA was defined when nasal airflow was absent despite the presence of thoracoabdominal excursions. In this study, we enrolled only patients with an apnea-hypopnea index > 10.0/h in which the central type was dominant.

Statistics: Data are presented as the mean ± SD. Intergroup differences for measured variables were compared using the unpaired t test. Linear regression analysis was used to correlate the measured variables. For all comparisons, $P < 0.05$ was considered statistically significant.

RESULTS

The apnea-hypopnea index in the subjects was 31.8 ± 12.8 /h (Table), indicating moderate to severe sleep apnea. The peak $\dot{V}O_2$ and percentage of peak $\dot{V}O_2$ were 15.5 ± 5.8 mL/min/kg and 52.8 ± 16.7%, respectively, showing a moderate to severely decreased exercise capacity. The patients had a relatively high $\dot{VE}/\dot{V}CO_2$ slope (37.9 ± 12.5), and a relatively low $\Delta\dot{V}O_2/\Delta WR$ (8.9 ± 2.7 mL/min/
Figure 1. Correlation between the apnea-hypopnea index and respiratory gas indexes obtained from cardiopulmonary exercise testing. Peak VO\textsubscript{2} indicates peak oxygen uptake; ΔVO\textsubscript{2}/ΔWR, slope of the increase in oxygen uptake to the increase in work rate; and VE/\textit{V}CO\textsubscript{2} slope, the ratio of the increase in ventilation to the increase in CO\textsubscript{2} output.

Figure 2. Correlation between the central apnea index and respiratory gas indexes obtained from cardiopulmonary exercise testing. Peak VO\textsubscript{2} indicates peak oxygen uptake; ΔVO\textsubscript{2}/ΔWR, slope of the increase in oxygen uptake to the increase in work rate; and VE/\textit{V}CO\textsubscript{2} slope, the ratio of the increase in ventilation to the increase in CO\textsubscript{2} output.

W), as compared to generally accepted normal values.

Figure 1 shows the relationship between the indexes obtained from CPX and the level of the apnea-hypopnea index. There was no significant correlation between peak VO\textsubscript{2} and the apnea-hypopnea index. Similarly, the apnea-hypopnea index did not correlate either with ΔVO\textsubscript{2}/ΔWR, or with the VE/\textit{V}CO\textsubscript{2} slope. We also analyzed the relationship between the central apnea component of the total
apnea-hypopnea index and the indexes of CPX. The central apnea index did not correlate with peak $\dot{V}O_2$, $\Delta \dot{V}O_2/\Delta WR$, or the $\dot{V}E/\dot{V}CO_2$ slope (Figure 2).

Figure 3 shows the relationship between $\text{PETCO}_2$ measured at rest before CPX on a cycle ergometer and the respiratory gas indexes obtained from CPX. $\text{PETCO}_2$ at rest significantly positively correlated with peak $\dot{V}O_2$ ($r = 0.63$, $P = 0.003$) and $\Delta \dot{V}O_2/\Delta WR$ ($r = 0.71$, $P < 0.001$). $\text{PETCO}_2$ at rest significantly nega-
Correlation between end-tidal PCO₂ (PETCO₂) at rest and at peak exercise and the apnea-hypopnea index.

Comparison of the apnea-hypopnea index between patients with lower end-tidal PCO₂ (PETCO₂) at rest (< 34 mmHg, n = 9) and those with higher PETCO₂ at rest (> 34 mmHg, n = 11).

PETCO₂ at peak exercise also positively correlated with peak VO₂ (\(r = 0.51, P = 0.02\)) and \(\Delta\)VO₂/\(\Delta\)WR (\(r = 0.69, P < 0.001\)), and negatively correlated with the \(\dot{V}E/\dot{V}CO₂\) slope (\(r = -0.91, P < 0.0001\)) (Figure 4). However, PETCO₂ either at rest or at peak exercise did not correlate with the apnea-hypopnea index (Figure 5).

We also compared the apnea-hypopnea index after dividing the subjects into 2 groups according to their PETCO₂ at rest: Patients with lower PETCO₂ at rest
(<34 mmHg, \(n = 9\)) and those with higher PETCO2 at rest (> 34 mmHg, \(n = 11\)). There was no significant difference in the level of the apnea-hypopnea index between the 2 groups (Figure 6).

**DISCUSSION**

The severity of CSA has been thought to correlate with the severity of heart failure in cardiac patients. However, in the present study, we found that severity of sleep apnea does not correlate with the novel indexes of CPX in cardiac patients with CSA. Although a ventilatory hypersensitivity to PaCO2 is considered to be one of the key mechanisms for CSA, the severity of sleep apnea did not correlate with the \(\dot{V}E/\dot{V}CO2\) slope obtained from CPX, which is considered to reflect central chemosensitivity to CO2. Although PETCO2 both at rest and at peak exercise, a parameter reflecting PaCO2, significantly correlated with the indexes of cardiopulmonary exercise testing, it did not correlate with the severity of sleep apnea.

**Proposed mechanisms of CSA:** It is believed that the CSA in cardiac patients arises as a consequence of heart failure. Several investigators have noted that approximately 50% of patients with symptomatic congestive heart failure have CSA. Although CSA has been considered a sign of a poor prognosis, this is still a question under debate. Several investigators have postulated that CSA in cardiac patients may have a causal relationship with prolonged circulation time, impaired systolic and/or diastolic functions, and left ventricular enlargements.

While awake, heart failure patients tend to hyperventilate due to stimulation of pulmonary vagal irritant receptors by pulmonary congestion and enhanced central and peripheral chemosensitivity. During sleep, CSA is usually initiated by a spontaneous arousal which results in a further increase in ventilation and fall in PaCO2 below the apneic threshold. Apnea persists until PaCO2 rises above this threshold level. In patients with higher ventilatory sensitivity to PaCO2, a slight rise in PaCO2, even within the physiological fluctuation, would cause hyperventilation, resulting in a drop of PaCO2 to the apneic threshold. By these mechanisms, Cheyne-Stokes respiration, alternating between hyperpnea and hypopnea, is assumed to persist. Lower waking PaCO2 is considered to be one of the strong risk factors of CSA, since the CSA is easily initiated when the set point of PaCO2 is low and close to the apneic threshold.

**Respiratory gas analysis:** Parameters obtained from cardiopulmonary exercise testing are known to reflect activities of daily living and the severity of heart failure in cardiac patients. Among these parameters, peak \(\dot{V}O2\) has been considered a gold standard for identifying patients with a poor prognosis and selecting
candidates for cardiac transplantation. The VE/\dot{V}CO_2 slope is thought to range from approximately 24 to 34 in normal subjects. This slope becomes steeper according to the severity of heart failure. The steeper VE/\dot{V}CO_2 slope is assumed to be related to a hyperchemosensitivity to CO_2, a decrease in the regulatory set point for PaCO_2, an increase in the ratio of pulmonary dead space to tidal volume, or the development of lactic acidosis during exercise. In healthy subjects, \Delta \dot{V}O_2/\Delta WR is known to be approximately 10 mL/min/W. Since \Delta \dot{V}O_2/\Delta WR is determined by the rate of the increase in cardiac output and the rate of the difference in arterial-mixed venous O_2 during incremental exercise, the lower \Delta \dot{V}O_2/\Delta WR implies an insufficient cardiac reserve and/or insufficient vasodilator capacity in the skeletal muscle. The slopes of \Delta \dot{V}O_2/\Delta WR and VE/\dot{V}CO_2 both reflect cardiopulmonary and circulatory adaptation during exercise and are known to be strong predictors of mortality in patients with left ventricular dysfunction.

PETCO_2 reflects PaCO_2 both at rest and during exercise, with PETCO_2 being slightly lower than PaCO_2 while at rest and slightly exceeding PaCO_2 during exercise in healthy subjects. In patients with heart failure, the arterial-end tidal PCO_2 difference (P[a-ET]CO_2), which reflects a ventilation-perfusion mismatch, becomes higher due to the lower PETCO_2 according to the severity of heart failure. With regard to the relationship between the level of PETCO_2 and the CPX parameters, our present study corroborated the findings of a previous study performed by Wasserman, et al. Similar to our study, they found a positive correlation between the PETCO_2 at peak exercise and peak \dot{V}O_2 in chronic heart failure patients. Patients with CSA would have lower PaCO_2 while awake according to the severity of the CSA, if the CSA is truly related to a lower set point of PaCO_2. The lower PaCO_2 along with higher P[a-ET]CO_2 must further decrease PETCO_2 in patients with CSA. However, in the present study, there was no relationship between the severity of sleep apnea and the level of PETCO_2.

Study limitations: With only 20 patients being enrolled in the present study, larger patient populations are necessary to confirm our data. Although the peak \dot{V}O_2 in the patients of the present study was considerably low, they did not necessarily exhibit symptoms of heart failure. LVEF in our patients (40.9 ± 21.8%) was higher than previous investigations reporting the relationship between the severity of CSA and the indexes of CPX. The discrepancy between the present findings and the previous reports might be attributed to the severity of heart disease of the enrolled subjects. Although we could not measure PaCO_2 in the present study, its measurement is warranted to confirm whether the set point of PaCO_2 has a causal relationship with CSA.

In addition to the chemosensitivity to CO_2, there are several possible factors influencing CSA, such as the metabolic rate, pulmonary pressure, functional...
residual capacity, and prolonged circulation time. Although the $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope is assumed to be regulated by the central chemosensitivity to CO$_2$, the correlation between the $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope and a parameter reflecting central chemosensitivity has been reported to be relatively weak.\textsuperscript{25} Also, the $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope can be influenced by other factors, such as input from the ergoreceptors in exercising muscles.\textsuperscript{44} PETCO$_2$ may be influenced not only by the chemosensitivity to CO$_2$ but also by the levels of PaO$_2$ and blood bicarbonate. For these reasons, the severity of CSA might not correlate with the $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope or the level of PETCO$_2$.

**Conclusions:** Although the severity of CSA is assumed to correlate with the severity of heart failure, and a lowering of PaCO$_2$ during wakefulness is considered to be one of the mechanisms behind CSA, the severity of CSA does not correlate with the respiratory gas indexes of CPX or the level of PETCO$_2$ in cardiac patients with moderate to severely decreased exercise capacity.

**REFERENCES**


