—Original—

Sleep-Disordered Breathing with Nighttime Hypocapnia Relates to Daytime Enhanced Ventilatory Response to Exercise in Patients with Heart Disease

Nagaharu Fukuma, Hiroko Hayashi, Juri Sugaya,
Tomohiro Aida, Masatoshi Kato, Kazuyo Kato,
Yuko Kato, Hiroshi Takahashi and Kyoichi Mizuno

Division of Cardiology, Department of Internal Medicine, Nippon Medical School

Abstract

Background: Sleep-disordered breathing (SDB) induces nighttime disturbance of arterial gases, such as carbon dioxide. However, it is still unclear whether nighttime SDB-related gas abnormality is related to respiratory dysregulation in daytime. Therefore, we examined the relationship between the arterial partial pressure of carbon dioxide ($PaCO_2$) at nighttime and the respiratory response to exercise in daytime.

Methods: Eighteen men (age, mean ± SD; 55 ± 11 years) with heart disease underwent multichannel respiratory monitoring through the night with transdermal measurement of $PaCO_2$ ($PtcCO_2$) reflecting $PaCO_2$ and a cardiopulmonary exercise test in daytime. The ventilatory equivalent (VE)/carbon dioxide production (VCO_2) slope as an index of ventilatory response to exercise and peak oxygen consumption (VO_2) were obtained with a cardiopulmonary exercise test.

Results: Of the 18 patients, 10 patients had obstructive SDB, 5 had central SDB, and 3 patients did not have SDB. The mean apnea-hypopnea index was 21 ± 17. Minimum nighttime saturation of O_2 was positively correlated with peak VO_2, but not with VE/VCO_2. Nighttime $PtcCO_2$ was not correlated with peak VO_2 but was negatively correlated with the VE/VCO_2 slope of the daytime cardiopulmonary exercise test ($r=-0.53$).

Conclusion: Nighttime lowering of $PaCO_2$ in SDB is related to an abnormal ventilatory response to exercise testing in the daytime. This finding suggests that nighttime hyperventilation in SDB alters both nighttime and daytime pathophysiological conditions in patients with heart disease.

(J Nippon Med Sch 2012; 79: 409–415)

Key words: sleep apnea, hypocapnia, ventilatory response, heart disease

Correspondence to Nagaharu Fukuma, MD, Division of Cardiology, Department of Internal Medicine, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan
E-mail: fukuma@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

Introduction

In patients with both obstructive and control sleep-disordered breathing (SDB), which includes symptomatic and asymptomatic sleep apneas, and those with central SDB, abnormal arterial partial pressure of carbon dioxide ($PaCO_2$), including hypocapnia and hypercapnia, frequently develops at night through disturbed ventilatory regulation during sleep[1–3]. Additionally, patients with heart disease often have an enhanced ventilatory response to exercise in the daytime. These 2 phenomena have common features, such as frequent occurrence and poor prognosis, among patients with heart disease. The relationship between these 2 ventilatory abnormalities, however, has not been sufficiently examined.

In previous studies, daytime hypocapnia and hyperventilation during exercise were observed in patients with heart failure and central SDB, and nighttime hypercapnia and a hyperventilatory response to exercise were observed in patients with obstructive SDB[4–6]. In these studies, however, the nighttime $PaCO_2$ was not continuously examined. Furthermore, patients with obstructive SDB and those with central SDB have been separately examined, although the overlap between central and obstructive SDBs has recently attracted attention[7]. Therefore, in the present study we examined nighttime hyperventilation using continuous transdermal measurement of $PaCO_2$ ($PtcCO_2$) and daytime respiratory disturbance by means of cardiopulmonary exercise testing in patients with heart disease. Then, we evaluated the relationship between $PtcCO_2$ in the nighttime and the respiratory response to exercise in the daytime.

Materials and Methods

Study Population

The study population consisted of 18 men (age, mean ± SD; 55 ± 11 years) with stable heart disease including 14 with old myocardial infarctions, 2 with dilated cardiomyopathy, 1 with hypertrophic cardiomyopathy, and 1 with hypertensive heart disease. All subjects underwent multichannel respiratory monitoring with recording of $PtcCO_2$ in the nighttime and cardiopulmonary exercise testing in the daytime. Patients were excluded if they had exercise-induced ischemia, exercise-induced serious arrhythmia, decompensated heart failure, respiratory disease, arteriosclerosis obliterans, or peripheral edema. Furthermore, patients were excluded if they had had a myocardial infarction within 10 days before the study or were older than 70 years or both. Subjects were eligible for this study if exercise was limited only by symptoms of leg fatigue or dyspnea but not by angina, syncope, or claudication. All aspects of the study were carefully explained to the study subjects before informed consent for participation was obtained.

Assessment of SDB and $PtcCO_2$

All subjects underwent an overnight sleep study with a computerized sleep apnea diagnosis set (Morpheus R, Compumedics Ltd., Victoria, Australia) to evaluate SDB. Oronasal signals detected with a thermistor were used as the respiratory sensors, and thoracic and abdominal effort was measured with 2 belt sensors. Percutaneous oxygen saturation (SpO_2) was recorded with digital pulse oximetry (sampling frequency, 1 Hz). Detection of respiratory events and oximetry analysis were performed manually. Apnea was defined as a cessation of airflow for at least 10 seconds, and hypopnea was defined as a reduction in airflow by more than 50% compared with that at baseline for more than 10 seconds, which was accompanied by at least a 3% decrease in the SpO_2. The apnea-hypopnea index (AHI) was defined as the number of episodes per hour of apnea or hypopnea. An AHI $\geq$5 times/hr was considered to indicate SDB. An episode of obstructive SDB was defined as the cessation of airflow in the presence of thoracic and abdominal wall motion. An episode of central SDB was defined as the cessation of both airflow and thoracic and abdominal wall motion.

The $PtcCO_2$ was noninvasively and continually measured with a transdermal monitor (9900MKII, Kohken Medical Co. Ltd., Tokyo, Japan). The $PtcCO_2$ as measured with this method has been reported to be closely correlated with the actual $PaCO_2$ in

Table 1 Comparison of clinical characteristics between patients with low or normal minimum $PtcCO_2$

minMinimum $PtcCO_2$	<37 mm Hg, n = 8	≥37 mm Hg, n = 10	Statistics
Age (mean ± SD), years	57 ± 12	54 ± 8	ns
Body-mass index, kg/m^2	25 ± 3	27 ± 5	ns
Left ventricular ejection fraction, %	43 ± 15	40 ± 11	ns
Brain natriuretic peptide, pg/mL	270 ± 341	221 ± 253	ns
Diabetes mellitus	2/8 (25%)	3/10 (30%)	ns
Hypertension	5/8 (63%)	5/10 (50%)	ns

MinMinimum $PtcCO_2$, minimum partial pressure of carbon dioxide using the transdermal method during night sleep; ns, not significant

arterial blood samples[8–10]. To measure the $PtcCO_2$, the sensor was placed on the inside of the upper arm through a glass electrode. This sensor is kept heated during the test to maintain a sensor temperature of 42℃ because of arterialization of the capillary network at the measurement site. In the present study, we evaluated the minimum SpO_2 and minimum $PtcCO_2$ during a single night.

Cardiopulmonary Exercise Test

All subjects underwent a symptom-limited cardiopulmonary exercise test.

Cardiopulmonary exercise testing was performed with a cycle ergometer (StrengthErgo 240, Mitsubishi Electric Engineering Co., Ltd., Tokyo, Japan) with the subject in the sitting position. After a 4-minute rest period, exercise began with a 4-minute warm-up at 10 or 20 W and 60 revolutions per minute, after which the intensity was increased incrementally by 1 or 2 W every 6 seconds according to the ramp protocol. Heart rate (HR) and 12-lead electrocardiogram were monitored continuously (ML-5000, Fukuda Denshi, Tokyo, Japan). During testing, blood pressure was measured every minute with an automatic indirect cuff manometer (STBD-780B, Nihon Collin Co., Ltd., Aichi, Japan). Exercise was stopped upon symptoms of exhaustion. During exercise no patient experienced angina, syncope, ischemic ST segment changes, or serious arrhythmia. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and the ventilatory equivalent (VE) were measured with a breath-by-breath gas analyzer (AE-300, Minato Medical Science, Osaka, Japan), and then we determined the anaerobic threshold (AT) with the V-slope method, peak VO_2, and the VE/VCO_2 slope as an index of ventilatory response to exercise.

Statistical Analysis

We examined the relationships between $PtcCO_2$ during sleep and cardiopulmonary exercise test variables, such as the VE/VCO_2 slope. All values are expressed as the mean ± standard deviation (SD). Variables were compared between groups by means of the unpaired Student's *t*-test and chi-square analysis. Correlations were assessed with the Pearson least-squares correlation test, and results are presented as coefficients of correlation. Differences were considered statistically significant at p-values of less than 0.05.

Results

Among the 18 patients with stable heart disease, 10 patients had obstructive SDB, 5 patients had central SDB, and 3 patients had an AHI of less than 5. The mean AHI was 21 ± 17.

To clarify whether the nighttime $PtcCO_2$ abnormality due to SDB affects the clinical background, the 22 patients were classified into 2 groups according to the minimum $PtcCO_2$: 8 patients had a low minimum $PtcCO_2$ (minimum $PtcCO_2$ <37 mmHg) and 10 patients had a normal minimum $PtcCO_2$ (minimum $PtcCO_2$ ≥37 mmHg). There were no significant differences in clinical characteristics, such as age, body-mass index, and left ventricular ejection fraction, between the low $PtcCO_2$ group and the normal $PtcCO_2$ group (**Table 1**). Concerning the sleep study, the AHI and the type of SDB had no significant difference between the low $PtcCO_2$ and

Table 2 Comparison of the overnight sleep study findings between patients with low or normal minimum $PtcCO_2$

minMinimum $PtcCO_2$	<37 mm Hg, n = 8	≥37 mm Hg, n = 10	Statistics
minMinimum $PtcCO_2$, mm Hg	34.0 ± 2.9	40.1 ± 3.9	P<0.001
Apnea hypopnea index, times/hr	43 ± 15	40 ± 11	ns
Obstructive SDB	3 of 8 (34%)	7 of 10 (70%)	ns
Central SDB	4 of 8 (40%)	1 of 10 (10%)	ns

MinMinimum $PtcCO_2$, minimum partial pressure of carbon dioxide using transdermal continuous method during night sleep; SDB, sleep-disordered breathing

Table 3 Comparison of cardiopulmonary exercise test findings between patients with low or normal minimum $PtcCO_2$

minMinimum $PtcCO_2$	<37 mm Hg, n = 10	≥37 mm Hg, n = 12	Statistics
Peak load, W	84 ± 44	102 ± 40	ns
HR Heart rate at peak exercise (beats/minute)	134 ± 7	121 ± 14	ns
Systolic blood pressure at peak exercise (mm Hg)	160 ± 34	171 ± 32	ns
Anaerobic threshold, mL/kg/minimum	13.3 ± 2.3	13.0 ± 3.3	ns

CPEX, cardiopulmonary exercise test; Minimum $PtcCO_2$, minimum partial pressure of carbon dioxide using the transdermal method during night sleep

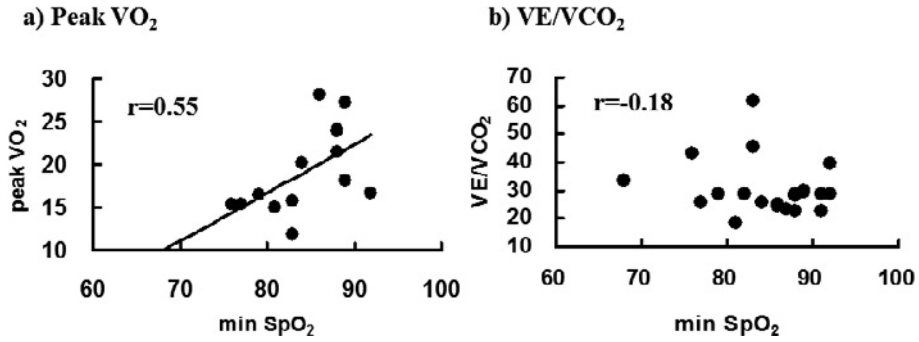

Fig. 1 Relationship between min SpO_2 and CPEX parameters
Although min SpO_2 was positively correlated with peak VO_2, min SpO_2 had no relationship with VE/VCO_2.
Min SpO_2, minimum saturation of oxygen using transdermal method during night sleep; CPEX, cardiopulmonary exercise test; Peak VO_2, peak oxygen uptake during CPEX; VE/VCO_2, ratio of ventilation to carbon dioxide output during CPEX.

normal $PtcCO_2$ groups (**Table 2**). On cardiopulmonary exercise testing there was no difference in exercise load, including watt and peak heart rate, between the low $PtcCO_2$ and normal $PtcCO_2$ groups (**Table 3**).

The nighttime minimum SpO_2 was positively correlated with peak VO_2 but was not correlated with the VE/VCO_2 slope (**Fig. 1**). The nighttime minimum $PtcCO_2$ was not correlated with peak VO_2 ($r=0.100$, not significant) but was negatively correlated with the VE/VCO_2 slope on daytime cardiopulmonary exercise testing ($r=-0.530$, $p<0.05$) (**Fig. 2**).

Discussion

The present study examined the relationship between abnormal $PtcCO_2$ during nighttime sleep and ventilatory regulation during daytime cardiopulmonary exercise testing in patients with heart disease. We found that nighttime hypocapnia in patients with SDB was related to daytime

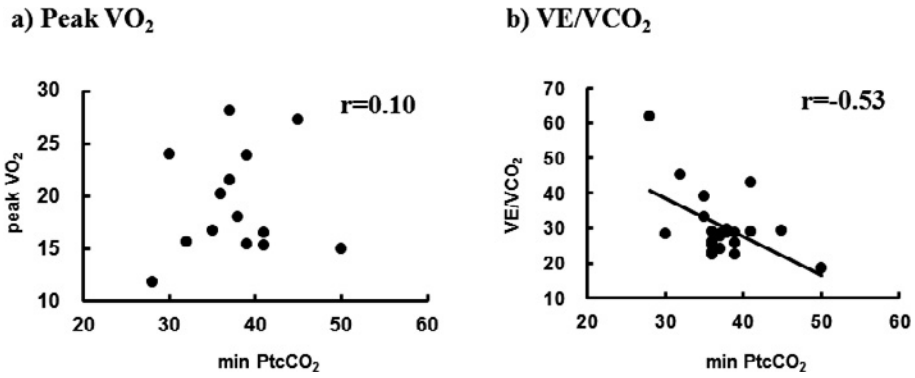

Fig. 2 Relationship between min $PtcCO_2$ and CPEX parameters
Although min $PtcCO_2$ was not correlated with peak VO_2, min $PtcCO_2$ was negatively correlated with VE/VCO_2.
Min $PtcCO_2$, minimum partial pressure of carbon dioxide using the transdermal method during night sleep; CPEX, cardiopulmonary exercise test; Peak VO_2, peak oxygen uptake during CPEX; VE/VCO_2, ratio of ventilation to carbon dioxide output during CPEX.

hyperventilation during exercise testing regardless of whether the patient had obstructive or central SDB. This finding may indicate that nighttime hyperventilation with SDB, which is thought to be influenced by hyperchemosensitivity, leads to an enhanced daytime ventilatory response to exercise.

Previous studies have documented nighttime hypercapnia in patients with obstructive SDB, daytime hypocapnia in patients with central SDB, and exercise hyperventilation in patients with either type of SDB[5,11,12]. However, these previous studies did not sufficiently clarify the relationship between disturbed nighttime respiratory regulation with SDB and daytime abnormal ventilatory control. Problems included the methods of classifying SDB and measuring $PaCO_2$ at a single time point. Although the AHI is usually determined in studies of SDB, the AHI can indicate only the frequency of apnea and hypopnea events but not actual ventilatory efficacy, such as the minute volume of ventilation. Therefore, we should mention the limitation of AHI. Additionally, the $PaCO_2$ during nighttime is thought to undergo time-dependent changes and should be measured repeatedly. We thought that nighttime minimum $PtcCO_2$ has clinical significance because it reflects actual ventilatory efficacy under pathophysiological conditions. Another problem concerns the disregard of overlap between obstructive and central SDBs. Recent reports have revealed that a part of SDB has a serial feature, which is named "complex sleep apnea"[7], from obstructive SBD to central SDB. This continuity from obstructive SBD to central SDB is thought to be induced mainly by chemoreflex hypersensitivity. To solve these problems, therefore, the present study classified SDB of the basis of $PtcCO_2$ and examined the total population, including patients with obstructive or central SDB.

In the present study, we found that SDB with hypocapnia leads to an enhanced daytime ventilatory response to exercise in both patients with obstructive SDB and patients with central SDB. Our first finding was that nighttime hypocapnia develops in patients with central SDB and patients with obstructive SDB. Hypocapnia, even in patients with obstructive SDB, was negatively correlated with AHI, although the patients with a low AHI tended to have hypercapnia. Consistent with this worsened hypercapnia, severe obstructive SDB is thought to have renewed character, such as enhanced chemosensitivity, and results in ventilatory overshoot after an obstructive episode. Our second finding was that nighttime hypocapnia in both patients with obstructive SDB and patients with central SDB was related to daytime hyperventilation during exercise testing. Chemoreflex hypersensitivity in both central SDB and severe obstructive SDB has been suggested to

induce both nighttime hypocapnia and daytime hyperventilation[13,14].

In patients with heart disease, both hypocapnia and the enhanced ventilatory response to exercise have been reported to be prognostic factors. Previous studies have suggested that hypocapnia has a harmful effect on the cardiovascular system through disturbed myocardial oxygenation, cardiac arrhythmia, vasoconstriction, and enhanced platelet aggregation[15–17]. Furthermore, previous studies of central SDB have indicated that hypocapnia is related to the development of ventricular arrhythmia[18,19]. Concerning hyperventilation during exercise, an increased VE/VCO_2 slope indicates a poor prognosis in patients with heart disease[20]. Therefore, we can speculate that a common mechanism between the nighttime hypocapnia and exercise hyperventilation exists in patients with heart disease.

One limitation of the present study concerns measurement of $PaCO_2$. We used $PtcCO_2$ as a variable reflecting $PaCO_2$, but this is not a direct measurement. Previous studies that have compared $PaCO_2$ and $PtcCO_2$ have shown a strong correlation[8–10]. Although we believe that this noninvasive and successive method is precise, we thought that it should be confirmed by a more direct technique. Another limitation is that subanalysis of central and obstructive SDBs is impossible because of the small study population. Therefore, we believe the present results do not fully indicate each feature of SDBs. In the future, we should perform further studies and confirm both the similarities and differences of ventilation abnormalities between central and obstructive SDBs.

This is, to our knowledge, the first study to show the continuing ventilation abnormalities through both central and obstructive mechanisms in patients with heart disease and SDB. Our results suggest that both types of SDB may worsen the pathophysiological condition of patients with heart disease. Therefore, we conclude that respiratory disturbances throughout the day should be considered in patients with heart disease obstructive SDB or central SDB or both.

References

1. Yokhana SS, Gerst DG 3rd, Lee DS, Badr MS, Qureshi T, Mateika JH. Impact of repeated daily exposure to intermittent hypoxia and mild sustained hypercapnia on apnea severity. J Appl Physiol 2011 Nov 3. [Epub ahead of print].
2. Kaw R, Hernandez AV, Walker E, Aboussouan L, Mokhlesi B: Determinants of hypercapnia in obese patients with obstructive sleep apnea: a systematic review and metaanalysis of cohort studies. Chest 2009; 136: 787–796.
3. Nopmaneejumruslers C, Kaneko Y, Hajek V, Zivanovic V, Bradley TD: Cheyne-Stokes respiration in stroke: relationship to hypocapnia and occult cardiac dysfunction. Am J Respir Crit Care Med 2005; 171: 1048–1052.
4. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD: Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med 1999; 160: 1101–1106.
5. Hargens TA, Guill SG, Aron A, et al.: Altered ventilatory responses to exercise testing in young adult men with obstructive sleep apnea. Respir Med 2009; 103: 1063–1069.
6. Koike A, Nagayama O, Goda A, et al.: Does the severity of central sleep apnea correlate with respiratory gas indexes during cardiopulmonary exercise testing? Int Heart J 2006; 47: 889–900.
7. Gilmartin GS, Daly RW, Thomas RJ: Recognition and management of complex sleep-disordered breathing. Curr Opin Pulm Med 2005; 11: 485–493.
8. Senn O, Clarenbach CF, Kaplan V, Maggiorini M, Bloch KE: Monitoring carbon dioxide tension and arterial oxygen saturation by a single earlobe sensor in patients with critical illness or sleep apnea. Chest 2005; 128: 1291–1296.
9. Maniscalco M, Zedda A, Faraone S, Carratù P, Sofia M: Evaluation of a transcutaneous carbon dioxide monitor in severe obesity. Intensive Care Med 2008; 34: 1340–1344.
10. Rauhala E, Himanen SL, Saastamoinen A, Polo O: Prolonged spiking in the Emfit sensor in patients with sleep-disordered breathing is characterized by increase in transcutaneous carbon dioxide. Physiol Meas 2007; 28: 1163–1173.
11. Hanly P, Zuberi N, Gray R: Pathogenesis of Cheyne-Stokes respiration in patients with congestive heart failure. Relationship to arterial PCO2. Chest 1993; 104: 1079–1084.
12. Arzt M, Harth M, Luchner A, et al.: Enhanced ventilatory response to exercise in patients with chronic heart failure and central sleep apnea. Circulation 2003; 107: 1998–2003.
13. Imadojemu VA, Mawji Z, Kunselman A, Gray KS, Hogeman CS, Leuenberger UA: Sympathetic chemoreflex responses in obstructive sleep apnea and effects of continuous positive airway pressure therapy. Chest 2007; 131: 1406–1413.
14. Javaheri S: A mechanism of central sleep apnea in patients with heart failure. N Engl J Med 1999; 341: 949–954.

15. Laffey JG, Kavanagh BP: Hypocapnia. N Engl J Med 2002; 347: 43–53.
16. Snow JB, Kitzis V, Norton CE, et al.: Differential effects of chronic hypoxia and intermittent hypocapnic and eucapnic hypoxia on pulmonary vasoreactivity. J Appl Physiol 2008; 104: 110–118.
17. Kazmaier S, Weyland A, Buhre W, et al.: Effects of respiratory alkalosis and acidosis on myocardial blood flow and metabolism in patients with coronary artery disease. Anesthesiology 1998; 89: 831–837.
18. Leung RS, Diep TM, Bowman ME, Lorenzi-Filho G, Bradley TD: Provocation of ventricular ectopy by cheyne-stokes respiration in patients with heart failure. Sleep 2004; 27: 1337–1343.
19. Javaheri S, Corbett WS: Association of low PaCO2 with central sleep apnea and ventricular arrhythmias in ambulatory patients with stable heart failure. Ann Intern Med 1998; 128: 204–207.
20. Corrà U, Pistono M, Mezzani A, et al.: Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence. Circulation 2006; 113: 44–50.

(Received, January 23, 2012)
(Accepted, March 28, 2012)