J Cardiol 2005 Aug; 46(2): 53–61

Effectiveness of Short-Term Treatment With Nocturnal Oxygen Therapy for Central Sleep Apnea in Patients With Congestive Heart Failure

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Abstract

Objectives. To evaluate the short term effects of inhalation of oxygen at night in 51 patients with congestive heart failure(CHF)and sleep apnea syndrome(SAS).

Methods. Fifty-one patients with stable CHF(31 males, 20 females, mean age 79.0±11.9 years; brain natriuretic peptide level of＞100 pg/m*l*)were evaluated between September 2003 and August 2004, using a Morpheus monitor. The complication rate of SAS in patients with CHF was assessed and apnea hypopnea index, oxygen desaturation index 3%, heart rate, and autonomic nerve activity under room air compared to supplemental O_2(2 *l*/min)over two consecutive nights.

Results. Thirty-eight(75%)of the CHF patients had SAS. Of these SAS patients, 49% suffered from central SAS and 51% had obstructive SAS. Apnea hypopnea index and oxygen desaturation index 3% improved remarkably with supplemental oxygen($p<0.001$), in particular, the central SAS group demonstrated prominent improvement($p<0.001$). Obstructive SAS patients exhibited no significant changes ($p=0.3356$), but tended to exacerbate the episodes of sleep apnea. Total heart rate was decreased($p=0.0079$). Nevertheless, heart rate variability analysis showed little effect of nocturnal oxygen therapy on the autonomic nervous system during sleeping.

Conclusions. Nocturnal oxygen therapy improved the number of sleep apnea episodes and decreased total heart rate during sleep time for the CHF patients with central SAS, despite little influence on the autonomic nervous system, based upon assessment of heart rate variability. Obstructive SAS might exacerbate the episodes of sleep apnea.

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Key Words

■**Heart failure** ■**Oxygen consumption**(**home oxygen therapy, nocturnal oxygen therapy**)
■**Autonomic nervous system**

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Manuscript received December 24, 2004; revised February 8 and March 15, 2005; accepted April 4, 2005

INTRODUCTION

Patients with congestive heart failure (CHF) are commonly treated with inhibitors of the renin-angiotensin system and β-blockers have been introduced based on clinical evidence, but some patients still have less than the expected improvement of quality of life and require repeated hospitalization. As one of the exacerbating factors of CHF, 30 to 40% of the CHF patients exhibit complications of Cheyne-Stokes respiration during sleeping at night, which is predictive of the clinical condition and prognosis of heart failure[1-3]. Although the efficacy of nocturnal oxygen therapy reduces the number of sleep apnea episodes for CHF patients with central sleep apnea[4-6], the effect of oxygen therapy on the autonomic nervous activity has not been evaluated using heart rate variability analysis. The present study investigated the complication rate of sleep apnea syndrome (SAS) in patients with heart failure, and the effectiveness of short-term nocturnal oxygen therapy on improving sleep apnea and autonomic nervous activity in patients with CHF with SAS.

PATIENTS AND METHODS

Patients

Patients in stable condition in our hospital were examined for their status of sleep apnea and autonomic nervous activity from September 2003 to August 2004. These parameters were compared with (O_2 2 *l*/min) and without (room air) oxygen therapy during sleep. Fifty-one patients (31 males, 20 females, mean age 79.0 ± 11.9 years, body mass index 22.1 ± 3.3 kg/m^2) who exhibited symptoms in accordance with the Framingham Clinical Criteria[7,8] and brain natriuretic peptide (BNP) > 100 pg/m*l* (Shionogi) were enrolled in this study, excluding those with chronic obstructive pulmonary disease and cerebral vascular disease (**Table 1**). The causes of their heart failure were as follows: 34 patients with ischemic heart disease, 12 with valvular impairment, 3 with dilated cardiomyopathy, 1 with hypertrophic cardiomyopathy, and 6 with hypertension, except for arrhythmia (atrial fibrillation, sick sinus syndrome and high advanced atrioventricular block) (**Table 2**). The mean BNP level was 816.8 ± 862.6 pg/m*l* (maximum 3,870 pg/m*l*, minimum 100 pg/m*l*). Ejection fraction measured on the short axis by transthoracic echocardiography was 43.3 ± 17.9% (**Table 1**).

Table 1 Characteristics of 51 patients with heart failure

Age (yr)	79.0±11.9
Sex (male/female)	31/20
Body mass index (kg/m^2)	22.1±3.3
Brain natriuretic peptide (pg/m*l*)	816.8±862.6
Ejection fraction (%)	43.3±17.9

Continuous values are mean±SD.

Table 2 Etiology of heart failure

Etiology	Rate (number)
Ischemic cardiomyopathy	67% (34)
Valvular heart disease	24% (12)
Dilated cardiomyopathy	6% (3)
Hypertrophic cardiomyopathy	2% (1)
Others (including hypertension)	12% (6)

Table 3 Medication

Medication	Rate
Beta-blockers	41%
Angiotensin II receptor blockers or angiotensin converting enzyme inhibitors	80%
Diuretics	61%
Nitrates	57%
Digitalis	16%
Amiodarone hydrochloride	6%

These patients were receiving various medications, such as β-blockers 41%, angiotensin II receptor blockers or angiotensin converting enzyme inhibitors 80%, diuretics 61%, nitrates 57%, digitalis 16%, and amiodarone hydrochloride 6%, excluding other antiarrhythmic agents, especially short-acting drugs (**Table 3**). Narcoleptics were excluded on the first day of examination.

Methods

Patients who were admitted to our hospital under a diagnosis of heart failure were tested in stable condition, with medication, immediately before discharge and without any supplemental oxygen. We used a Holter electrocardiography (ECG) and Respiratory Monitor, Morpheus (Teijin Pharma Ltd.) under the following conditions: day 1, no oxygen therapy (room air); day 2, nocturnal oxygen therapy (O_2 2 *l*/min). Patients were evaluated continuously during sleep to assess sleep apnea

(obstructive and central), apnea hypopnea index (AHI), oxygen desaturation index (ODI) 3%, and autonomic nervous activity, using Holter ECG, mean heart rate and heart rate variability analysis.

Sleep apnea was defined as cessation of air current for more than 10 sec, and hypopnea was defined as reduction of normal ventilation $>$ 50%, as well as decrease in oxygen saturation $>$ 3%. AHI shows the incidence of apnea and hypopnea per hour, and ODI 3% shows the incidence of 3% or greater decrease in oxygen saturation per hour. SAS was identified as: AHI $<$ 10: normal; AHI $\geq$ 10: abnormal. Furthermore, SAS was categorized as: AHI 10−20: mild hypopnea group; AHI $>$ 20: severe hypopnea group (requiring treatment). Thoracic and abdominal breathing movement and simultaneous nasal air current were measured to determine central or obstructive apnea. Central apnea was identified when both nasal air current and thoracic and abdominal breathing movement were stopped. Obstructive apnea was identified when nasal air current was stopped but thoracic and abdominal breathing movement was not. The analysis was performed manually[9] in consideration of the potential for underestimation by automatic analysis. Normal R-R interval (NN interval) during sleeping with normal heart rate, excluding arrhythmia, was assessed for heart rate variability using fast Fourier transform. The time domain measures of heart rate variability were assessed by pNN50, which is the NN50 at the normal heart rate interval (the proportion of change in successive R-R intervals was greater than 50 msec)[10] as an index of parasympathetic activity, and SDNN which is the standard deviation in normal heart rate as an index of prognosis for sudden death. The frequency domain measures of heart rate variability were assessed by low frequency power [the change of NN interval in the low-frequency (0.04−0.15 Hz)] and high frequency power [the change of NN interval in the high-frequency (0.15−0.40 Hz)]. Autonomic activity was evaluated by high frequency power, which is an index of vagal activity and low frequency power/high frequency power ratio which is an index of sympathetic activity[11−13].

Statistical analysis

StatView J-5.0 was used for statistical analyses. Continuous variables were described as the mean ± SD, and paired *t*-test was used for comparison between groups. Statistical significance was defined as $p < 0.05$.

Table 4 Patients with congestive heart failure complicated by sleep apnea syndrome

Frequency of CHF complicated with SAS	Rate (number) (n=51)
Normal	
AHI $<$ 10 (normal)	25% (13)
SAS	
AHI $\geq$ 10	75% (38)
10 $\leq$ AHI $\leq$ 20: mild SAS	25% (13)
AHI $>$ 20: severe SAS (required treatment)	49% (25)

CHF = congestive heart failure; SAS = sleep apnea syndrome; AHI = apnea hypopnea index.

Table 5 Classification of sleep apnea syndrome

Classification of SAS	Rate (number) (n=51)
Obstructive SAS	51% (26)
Central SAS	49% (25)

Abbreviation as in Table 4.

RESULTS

Thirty-eight (75%) of the 51 CHF patients had SAS (AHI $\geq$ 10; **Table 4**). Twenty-five (49%) of these 38 patients had severe SAS (AHI $>$ 20) and 13 (25%) had mild SAS (AHI 10−20). Of these SAS patients, 25 patients (49%) had central SAS and 26 (51%) had obstructive SAS (**Table 5**). To evaluate the efficacy of short-term oxygen therapy, oxygen (O_2 2 *l*/min) was supplied for all 51 patients with heart failure. In all patients, AHI ($p < 0.001$), ODI 3% ($p < 0.001$), total apnea rate ($p = 0.007$), and total hypopnea rate ($p < 0.001$) improved significantly (**Fig. 1**). AHI in central SAS was significantly improved by nocturnal oxygen therapy ($p < 0.001$). AHI in obstructive sleep apnea was worsened by nocturnal oxygen therapy, although not statistically significant ($p = 0.3356$; **Fig. 2**). Total heart rate was decreased ($p = 0.0079$) by nocturnal oxygen therapy, whereas the average heart rate was not significantly reduced ($p = 0.3557$; **Fig. 3**). Nevertheless, in the time domain measure of heart rate variability, SDNN ($p = 0.9432$) and pNN50 ($p = 0.4987$) was not changed by nocturnal oxygen therapy. In addition, in the frequency domain measure of heart rate variability, high frequency power

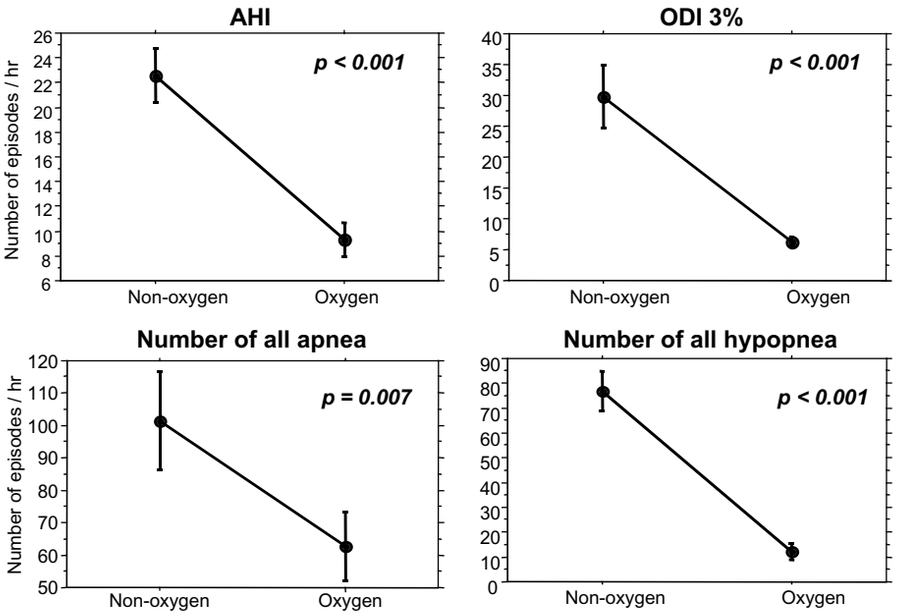

Fig. 1 Effect of oxygen therapy
ODI 3% = oxygen desaturation index 3%. Other abbreviation as in Table 4.

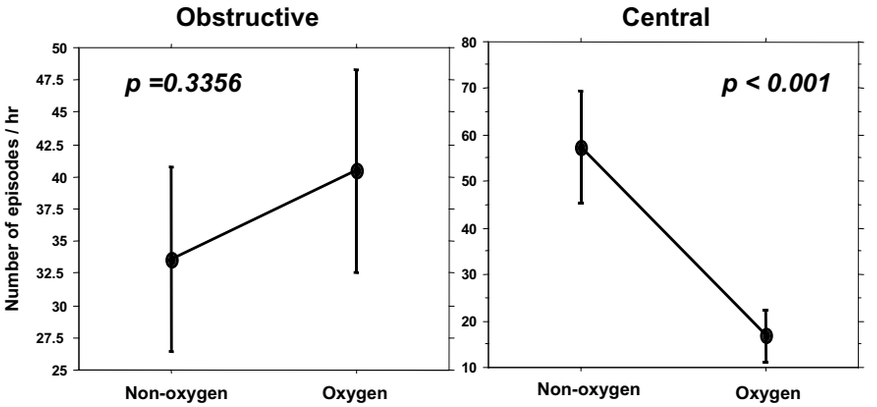

Fig. 2 Effect of oxygen therapy: Classification of sleep apnea syndrome

($p = 0.6167$) and low frequency power/high frequency power ratio ($p = 0.9760$) was not changed by nocturnal oxygen therapy (**Fig. 4**).

DISCUSSION

Thirty to 40% of the CHF patients exhibit complications of Cheyne-Stokes respiration during sleeping time[1–3]. There are three mechanisms for heart failure related to respiratory pattern[14–16]: Mechanical pumping dysfunction leads to a reduction in renal blood flow and consequent stimulation of renin-angiotensin system results in activation of sympathetic nerve activity; pulmonary congestion and interstitial edema stimulate J-receptors causing hyperventilation through afferent C fibres; and cardiomegaly causes a decrease in functional residual volume and reduces oxygen reserve volume in the lung. However, hypoxemia is compensated by hyperventilation during the daytime. Therefore, CHF patients exhibit hypocapnia during the day as a result of activation of sympathetic nerve activity and chemoreceptors. During sleeping, however, rapidly decreased sensitivity of central chemoreceptors and increased $PaCO_2$ concentration cause supraliminal stimulation of apnea. CHF patients

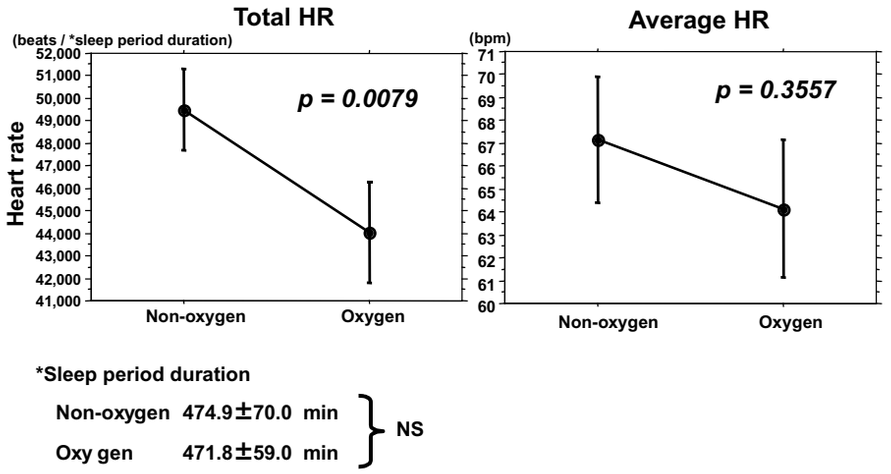

Fig. 3 Effect of oxygen therapy: Total heart rate, average heart rate
HR = heart rate; bpm = beats/min.

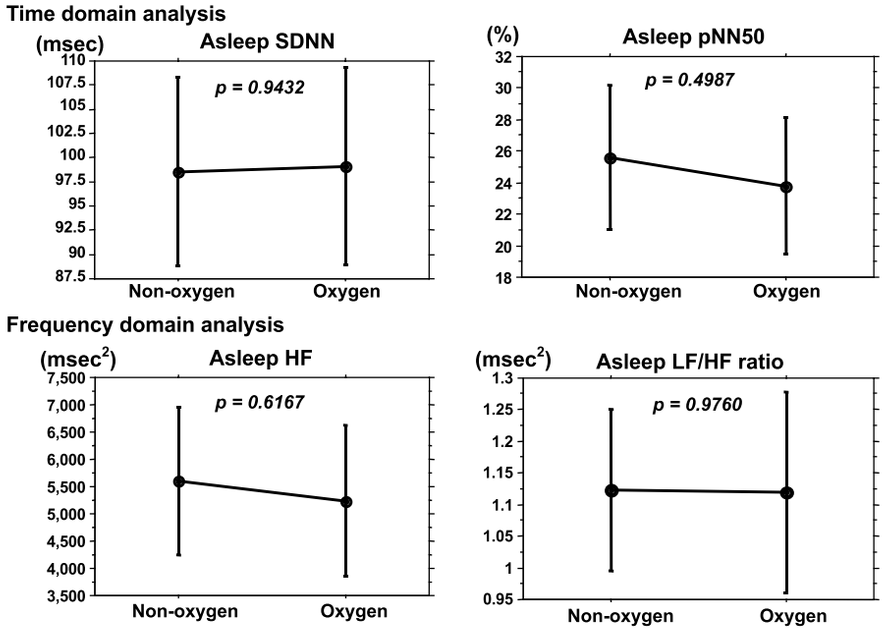

Fig. 4 Effect of oxygen therapy: Time domain analysis and frequency domain analysis
Asleep SDNN = standard deviation of all normal R-R intervals during recording of electrocardiogram during sleeping, used as a prognosis index for sudden death; Asleep pNN50 = percentage of differences between adjacent normal R-R intervals that are > 50 msec computed during the recording of electrocardiogram during sleeping, that is used as an index of parasympathetic activity; Asleep HF = asleep high frequency power, energy in the heart period power spectrum between 0.15 and 0.40 Hz during sleeping; Asleep LF = asleep low frequency power, energy in the heart period power spectrum between 0.04 and 0.15 Hz during sleeping; Asleep LF/HF ratio = ratio of low to high frequency power during sleeping.

take longer to sense this information because of delayed circulation due to pumping dysfunction. Marked elevation of $PaCO_2$ concentration stimulates the central chemoreceptors and leads to hyperventilation. Prolonged apnea causes hypoxia that promotes hyperventilation through peripheral chemoreceptors. This mechanism causes Cheyne-Stokes respiration, which results in a malignant cycle during sleeping at night (**Fig. 5**)[17,18]. Nocturnal sympathetic activation stimulates ner-

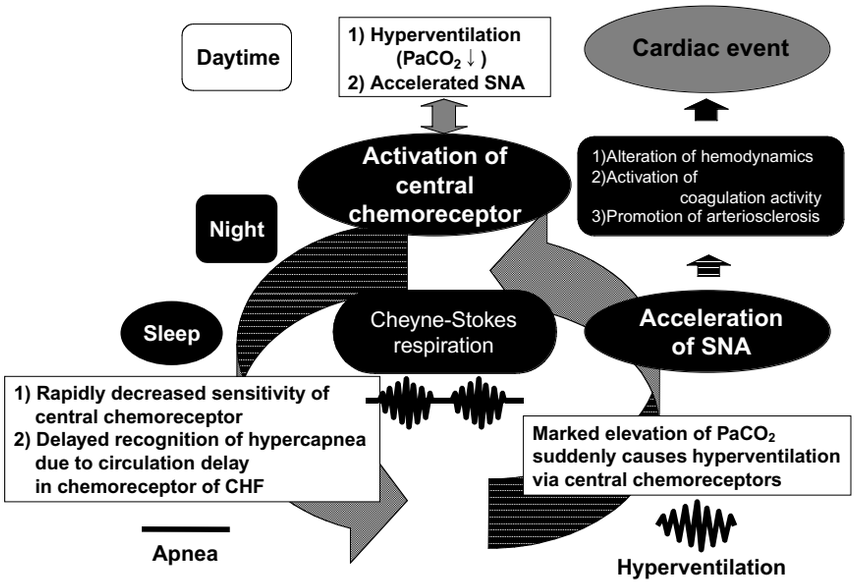

Fig. 5 Malignant cycle of congestive heart failure patients with Cheyne-Stokes respiration
SNA = sympathetic nerve activity. Other abbreviation as in Table 4.

vous or humoral hormones[4,19,20], and can lead to more cardiac events[21,22]. Therefore, in consideration of this mechanism, the main purposes of adjunctive therapy for CHF patients with central SAS are stabilization of circulation time and improvement of respiratory conditions.

Treatments for central SAS have included: Theophylline, atrial pacing, and nasal continuous positive airway pressure(CPAP). The efficacy of theophylline[23]and atrial overdriving pacing[24]certainly improved the number of sleep apnea episodes in the short term, but have not proved a positive effect on cardiac function(ejection fraction, BNP etc.)or long-term outcome was not evaluated. Nasal CPAP[25,26]is the ideal therapy because positive intrathoracic pressure leads to increased oxygen reserve volume by improvement of pulmonary functional residual volume, and alveolus enlargement by improvement of cardiac function and decreased blood circulation period, following reduction of cardiac pre- and after-load. However, this device must be fixed on the face and requires both patient compliance and adherence. In particular, elderly patients occasionally do not tolerate this procedure.

The present study evaluated the effectiveness of oxygen therapy as one of the therapies for the CHF patients with central SAS. All patients agreed to and tolerated the administration of nocturnal oxygen by nasal cannula. The main purposes of this therapy are the improvement of peripheral oxygen during sleep time and breaking the malignant cycle of central SAS. These results suggest remarkable improvement of AHI and ODI 3%, as well as significantly decreased total heart rate. In contrast to our expectations, heart rate variability analysis using Holter ECG recordings during sleep demonstrated no influence on the autonomic nervous system. Although we will discuss this reason further in the" study limitations ", the relationship between sleep conditions and autonomic activity might be underestimated. Moreover, because an inverse relationship was demonstrated between age and heart rate variability[27], the fact that most patients were elderly in this study might have a negative effect on our results. However, oxygen therapy lowered the total heart rate during sleep, suggesting some positive effects on stabilization of autonomic nerve activity, and so may be expected to decrease the number of cardiac events in the long term. Oxygen therapy and nasal CPAP therapy were equally effective in improving nocturnal apnea[28].This oxygen therapy might be expected to provide better compliance and adherence for elderly patients than nasal CPAP.

The efficacy of nocturnal oxygen therapy in the long term is unclear.[4−6,29]. Our group is also currently exploring the effectiveness of nocturnal oxygen therapy in long-term prognosis and the appropriate indications for nocturnal oxygen therapy. In

particular, because this study demonstrated that obstructive SAS using nocturnal oxygen might tend to exacerbate the episodes of sleep apnea, although the mechanism is unknown, we should carefully make decisions for the indications in the future. If some CHF patients with obstructive SAS or chronic obstructive pulmonary disease are carelessly given oxygen therapy, CO_2 narcosis may be caused. Moreover, nocturnal oxygen supplement is one of the adjunctive therapies for CHF patients with central SAS. First of all, stabilization of heart failure by sufficient conventional therapy is the most important because of improving circulation time. In order to safely start nocturnal oxygen therapy, obtaining information about blood arterial gas and the simplified sleep test as well as Morpheus are at least needed in the stable phase of heart failure.

Study limitations

There are several limitations in the present study. The records of sleeping period and awake period were based on patient declarations, despite the fact that most patients were elderly, with a mean age 79.0 ± 11.9 years. The Holter ECG and Respiratory Monitor, Morpheus, used in the current study, unlike polysomnography, cannot record electroencephalograms that dispense with the evaluation of sleeping stages. Thus, elucidation of the association between autonomic nervous activities measured by Holter ECG and sleep conditions would appear difficult. Since cardiovascular events are closely related to autonomic activity, improvement of the Holter ECG and Respiratory Monitor, Morpheus, is necessary to elucidate any association between heart rate variability and sleep.

CONCLUSIONS

Nocturnal oxygen therapy improved the episodes of sleep apnea for the CHF patients and decreased total heart rate during sleep time, despite little influence on the autonomic nervous system, based upon assessment of heart rate variability. Obstructive SAS might exacerbate the episodes of sleep apnea. We should strictly determine the indications for nocturnal oxygen therapy in CHF patients in consideration of the long-term outcome.

Acknowledgment

We are grateful to Mr. Akio Fukuda and Mr. Makoto Kanzawa in Teijin Parma Inc. for their considerable assistance.

要　　約

慢性心不全患者の中枢性睡眠時無呼吸に対する夜間酸素療法による短期改善効果

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目　的: 睡眠時無呼吸症候群を有する心不全患者に対して夜間酸素投与による短期改善効果および自律神経活動への影響を検討した．

方　法: 入院中の心不全患者（脳性Na利尿ペプチド＞100 pg/m*l*）51例（男性31例，女性20例）で，平均年齢は79.0 ± 11.9歳を対象とした．症状安定期に終夜簡易生体モニターを使用し，夜間就寝中に，酸素なしと酸素投与下（2 *l*/min経鼻カニューレによる）での比較検討を行った．心不全患者における睡眠時無呼吸症候群の併発率を明らかにした．さらに，酸素投与による循環動態，無呼吸（閉塞性，中枢性），無呼吸低呼吸指数，1時間当たりの3%以上動脈血酸素飽和度の低下回数（ODI 3%）の改善効果および付属のホルター心電図を用い心拍変動解析による自律神経活動への影響に関して検討した．

結　果: 心不全患者おける睡眠時無呼吸症候群は38例（75%）と高率に合併し，そのうち49%が中枢性，51%が閉塞性無呼吸であった．酸素投与により，無呼吸低呼吸指数およびODI 3%の顕著な改善が認められた（$p < 0.001$）．中枢性無呼吸については有意な改善がみられたが（$p < 0.001$），閉塞性無呼吸は改善が認められず，むしろ有意差はないものの増悪傾向であった（$p = 0.3356$）．また，総心拍数の徐拍化が認められた（$p = 0.0079$）．しかし，心拍変動解析では自律神経活動に対する影響は認められなかった．

結　論: 中枢性無呼吸を併発した心不全患者への夜間酸素療法は，睡眠中の無呼吸を改善し心拍

数の徐拍化も認められたが，心拍変動解析では自律神経活動に対する影響は認められなかった．閉塞性無呼吸患者への夜間酸素療法は増悪の可能性が危惧された．

J Cardiol 2005 Aug; 46(2): 53−61

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