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

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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/ml) 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 O2 (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). 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.

Key Words
- Heart failure
- Oxygen consumption (home oxygen therapy, nocturnal oxygen therapy)
- Autonomic nervous system

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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. Although the efficacy of nocturnal oxygen therapy reduces the number of sleep apnea episodes for CHF patients with central sleep apnea, 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 patients were compared with and without 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/m²) who exhibited symptoms in accordance with the Framingham Clinical Criteria and brain natriuretic peptide (BNP) > 100 pg/mL (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/mL (maximum 3,870 pg/mL, minimum 100 pg/mL). 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

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Rate (number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>67% (34)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>24% (12)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>6% (3)</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>2% (1)</td>
</tr>
<tr>
<td>Others (including hypertension)</td>
<td>12% (6)</td>
</tr>
</tbody>
</table>

Continuous values are mean ± SD.

Table 2 Etiology of heart failure

<table>
<thead>
<tr>
<th>Medication</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>41%</td>
</tr>
<tr>
<td>Angiotensin receptor blockers or angiotensin converting enzyme inhibitors</td>
<td>80%</td>
</tr>
<tr>
<td>Diuretics</td>
<td>61%</td>
</tr>
<tr>
<td>Nitrates</td>
<td>57%</td>
</tr>
<tr>
<td>Digitalis</td>
<td>16%</td>
</tr>
<tr>
<td>Amiodarone hydrochloride</td>
<td>6%</td>
</tr>
</tbody>
</table>

These patients were receiving various medications, such as β-blockers 41%, angiotensin 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 (O₂ 2 l/min). Patients were evaluated continuously during sleep to assess sleep apnea...
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 ≥ 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 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 intervals [the proportion of change in successive R-R intervals was greater than 50 msec] 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. Defined as $p < 0.05$.

**RESULTS**

Thirty-eight (75%) of the 51 CHF patients had SAS (AHI ≥ 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 (2 l/min) was supplied for all 51 patients with heart failure. In all patients, AHI ( $p < 0.001$), ODI ( $p < 0.001$), 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

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

<table>
<thead>
<tr>
<th>Frequency of CHF complicated with SAS</th>
<th>Rate( number )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>AHI &lt; 10(normal)</td>
<td>25%(13)</td>
</tr>
<tr>
<td>SAS</td>
<td></td>
</tr>
<tr>
<td>AHI ≥ 10</td>
<td>75%(38)</td>
</tr>
<tr>
<td>10 ≤ AHI ≤ 20: mild SAS</td>
<td>25%(13)</td>
</tr>
<tr>
<td>AHI &gt; 20: severe SAS (required treatment)</td>
<td>49%(25)</td>
</tr>
</tbody>
</table>

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

**Table 5** Classification of sleep apnea syndrome

<table>
<thead>
<tr>
<th>Classification of SAS</th>
<th>Rate( number )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive SAS</td>
<td>51%(26)</td>
</tr>
<tr>
<td>Central SAS</td>
<td>49%(25)</td>
</tr>
</tbody>
</table>

Abbreviation as in Table 4.
( \( p = 0.6167 \) ) 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
take longer to sense this information because of delayed circulation due to pumping dysfunction. Marked elevation of PaCO₂ 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)\textsuperscript{17,18}.

\textbf{Fig. 3} Effect of oxygen therapy: Total heart rate, average heart rate

\begin{itemize}
  \item Total HR = heart rate; bpm = beats/min.
\end{itemize}

\textbf{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.
vous or humoral hormones, and can lead to more cardiac events. 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 and atrial overdriving pacing 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 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, the relationship was demonstrated between age and heart rate variability, 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. 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. 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, CO₂ 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
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