Effect of Respiratory Therapy on the Prognosis of Chronic Heart Failure Patients Complicated With Sleep-Disordered Breathing
– A Pilot Efficacy Trial –

Hiroyuki Satake, MD, PhD; Koichiro Sugimura, MD, PhD; Yoshihiro Fukumoto, MD, PhD; Koji Fukuda, MD, PhD; Makoto Nakano, MD, PhD; Masateru Kondo, MD, PhD; Shigefumi Fukui, MD, PhD; Hiromasa Ogawa, MD, PhD; Tsuyoshi Shinozaki, MD, PhD; Hiroaki Shimokawa, MD, PhD

Background: Sleep-disordered breathing (SDB) has been reported to influence mortality and occurrence of ventricular tachyarrhythmia in patients with chronic heart failure (CHF). It remains to be elucidated, however, whether respiratory therapy (RT) can affect the occurrence of fatal ventricular tachyarrhythmia in CHF patients with SDB.

Methods and Results: We prospectively examined whether the severity of SDB was associated with fatal cardiac events in CHF patients and, if so, whether RT for SDB improved prognosis. We enrolled 95 patients with stable CHF, in whom SDB was examined on overnight polygraphy. The severity of SDB was quantified using the apnea-hypopnea index (AHI). All patients with AHI ≥10 (n=42) at initial evaluation were recommended to have RT, such as home oxygen therapy and continuous positive airway pressure, and 24 agreed to this. During the follow-up period of 29±17 months, 8 ventricular tachyarrhythmias occurred and 14 of the 95 patients died. On multivariate proportional hazard analysis AHI ≥5 was a risk factor for fatal arrhythmic events (P=0.026). Although RT significantly reduced AHI, it did not significantly reduce the event rates, but 4 patients with AHI <5 on RT had no fatal arrhythmic events or death.

Conclusions: SDB is an independent prognostic factor and thus an important therapeutic target in CHF patients.
(Circ J 2016; 80: 130–138)

Key Words: Chronic heart failure; Respiratory therapy; Sleep-disordered breathing

Sleep-disordered breathing (SDB) is frequently observed in patients with chronic heart failure (CHF), with a prevalence of up to 70%. It has been reported that SDB adversely affects cardiovascular functions due to overnight hypoxia and sympathetic nervous system activation, which can worsen prognosis in patients with CHF. Previous studies reported that both obstructive sleep apnea (OSA) and central sleep apnea (CSA) increase the frequency of ventricular premature beats, a surrogate marker of ventricular irritability. Also, several reports found that OSA and CSA are associated with impaired cardiac autonomic function and increased cardiac arrhythmia, and that treatment of SDB reduces sympathetic nervous activity. Furthermore, it has been reported that home oxygen therapy (HOT) and continuous positive airway pressure (CPAP) decrease the number of nocturnal premature ventricular contractions and couplets in responders, but not in non-responders, in CHF patients complicated with SDB. Although the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP) showed that CPAP did not improve the prognosis of CHF patients with CSA, post-hoc analysis suggested that CPAP may be effective for CSA when apnea-hypopnea index (AHI) is reduced to <15/h in terms of both left ventricular ejection fraction (LVEF) and transplant-free survival. Recently, it has been reported that the long-term prognosis of CHF patients tended to be improved...
with increased use of medications for heart failure such as $\beta$-blockers and aldosterone, but it still remains to be elucidated whether respiratory therapy (RT) for SDB in CHF patients could reduce the fatal ventricular tachyarrhythmias associated with poor prognosis in CHF patients. Indeed, there is no current evidence available as to the extent to which AHI needs to be reduced in CHF patients with SDB in order to improve prognosis.

**Methods**

This study conformed to the principles outlined in the Declaration of Helsinki, and the ethics committee of Tohoku University Hospital approved the study protocol. All patients provided written informed consent.

**Study Subjects**

We enrolled 95 patients with CHF who were referred between August 2000 and November 2008, based on the inclusion criteria, including LVEF $\leq$50%, at least 1 previous episode of hospitalization, stable clinical conditions for at least 3 months with optimal medication, no prior history of ventricular tachycardia or ventricular fibrillation (VT/VF), and no implantable cardioverter defibrillators (ICD) for secondary prevention. Furthermore, we excluded the patients with acute myocardial infarction, unstable angina or cardiac surgery within the previous 3 months or obstructive lung disease. At study entry, the patients underwent blood tests for brain natriuretic peptide (BNP), echocardiography and sleep study, before starting nocturnal RT.

**Data Collection**

We obtained demographic data such as New York Heart Association (NYHA) functional class, morbidity period, medications (angiotensin-converting enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB], $\beta$-blockers, loop diuretics, spironolactone, digitalis, and amiodarone), smoking habit, comorbidities (hypertension, diabetes mellitus, dyslipidemia), ischemic events, and echocardiographic parameters including LV end-diastolic dimension (LVDd), left atrial (LA) dimension and LVEF. In the present study, hypertension was defined as the use of any anti-hypertensive agent and/or systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg; diabetes mellitus as the use of anti-diabetic agents, fasting glucose $\geq$110 mg/dl and/or glucose $\geq$200 mg/dl 2 h after a 75-g oral glucose tolerance test; and dyslipidemia as the use of lipid-lowering agents, plasma low-density lipoprotein cholesterol $\geq$140 mg/dl, triglycerides $\geq$150 mg/dl, and/or high-density lipoprotein cholesterol <$40$ mg/dl.

**Echocardiography**

Two-dimensional (2-D) echocardiography and Doppler ultrasound were performed according to the standard techniques following the American Society of Echocardiography guidelines. LVEF was measured according to the Teichholz or modified Simpson method. LA dimension and LVDd were also measured in M-mode and corrected on 2-D echocardiography.

**Sleep Study**

Patient enrollment is shown in Figure 1. First, all 95 patients underwent overnight polygraphy (Morpheus, Teijin, Osaka, Japan). This system carries out non-attached type 3 monitor-
ing and has been validated against 12-channel polysomnography for quantifying SDB. 18–23 Episodes of apnea and hypopnea and mean and lowest arterial oxygen saturation levels were assessed according to uniform methods with an unattended system. 18,24 Respiratory effort was measured with airflow using nasal pressure. Total cessation of airflow at the nose and mouth for at least 10 s was classified as apnea (obstructive apnea if respiratory effort was present and central apnea if the effort was absent). Partial airway closure, which was associated with both a reduction of airflow by >30% and oxygen desaturation of >4%, was classified as hypopnea. 25 AHI was defined as the number of episodes of apnea/hypopnea per hour of sleep. 18,24,25 SDB was defined as AHI \( \geq 5 \). 26 CSA was defined as a \( \leq 50\% \) obstructive component in AHI, and OSA as a >50% obstructive component in AHI. 26 In the present study, almost all apnea-hypopnea episodes consisted of both central and obstructive components, thus AHI represents both OSA and CSA.

### RT

After the initial sleep evaluation, all 42 patients with AHI \( \geq 10 / h \) were recommended to receive RT, including HOT and CPAP in order to determine whether RT can reduce the prevalence of fatal arrhythmic events or improve long-term prognosis of CHF patients with SDB. Of 31 CSA patients, 18 agreed to receive HOT, and out of 11 OSA patients, 6 agreed to receive CPAP. Regardless of the severity of SDB, an oxygen dose of 3 L/min was used for HOT. CPAP was carried out with auto-CPAP (AutoSet; ResMed, Sydney, NSW, Australia). All CPAP patients underwent automatic titration, which was performed with the auto-CPAP device. It automatically increases or decreases mask pressure in response to snoring (inspiratory airflow contour morphology) or the presence of apnea or hypopnea, thus acting to completely restore airway patency. In the present study, the lower pressure limit was set to 4 mmHg and the upper limit to 12 mmHg to avoid too high a pressure because this could cause adverse effects in CHF patients.

### Endpoints

Patients visited the outpatient clinic every 4–8 weeks for follow-up (mean follow-up period, 29±17 months). The primary outcome of this study was defined as fatal arrhythmic events (VF, sustained VT and sudden death).
We defined sudden death as instantaneous, unexpected death or death within 1 h of symptom onset not related to circulatory failure; VF as polymorphic ventricular tachyarrhythmia with RR interval <200 ms; and VT as tachycardia lasting >30 s or unstable hemodynamic tachycardia. The secondary outcome was defined as all-cause death. In order to determine specific confounding factors, we examined clinical and medical history and NYHA functional class and echocardiographic and laboratory data at baseline. Patients were prospectively observed, and all events were surveyed using the outpatient visit data or pacemaker records during the follow-up period.

If the primary endpoint was met without death, the patient continued to be monitored for the secondary endpoint, and if the secondary endpoint was fulfilled, the study was completed for the patient.

Statistical Analysis
Continuous variables are expressed as mean±SD. All analyses were performed with JMP® Pro 12 (SAS Institute, Cary, NC, USA). Continuous variables were compared using Welch’s t-test for normally distributed variables, or Wilcoxon rank sum test for variables with non-normal distribution. Fisher’s exact test was used to compare categorical variables. Kaplan-Meier analysis and log-rank test were used to compare survival rates in patients with AHI <5/h and those with AHI ≥5/h. We used AHI calculated from polygraphy after nocturnal RT when it was introduced. The predictors of fatal arrhythmic events (VF, sustained VT and sudden death) and all-cause death were examined in univariate and multivariate Cox proportional hazard models. The covariates for multivariate analysis (stepwise method) included age, sex, body mass index (BMI), hypertension, diabetes mellitus, hyperlipidemia, smoking, AHI ≥5, serum BNP, more than NYHA class III, LVDd, LA dimension, LVEF, β-blockers, renin-angiotensin system inhibitors, loop diuretics and amiodarone. A trend analysis was also performed to analyze whether increased severity of SDB was associated with an increased risk of the events. P<0.05 was considered to be statistically significant.

Results

Subject Clinical Characteristics
Ninety-five consecutive patients with CHF, including 72 men (76%) and 23 women (24%), were prospectively enrolled and then underwent sleep study. Ischemic cardiomyopathy was noted in 19 and non-ischemic cardiomyopathy in 76, and mean LVEF was 33±10%. The patients were treated with optimal medical therapy, including β-blockers (84%) and ACEI/ARB (91%), loop diuretics (63%), spironolactone (26%), and digoxin (27%) to control heart rate (HR) or improve LV function, and amiodarone (11%) for non-sustained VT.

Figure 2. Effects of respiratory therapy. Apnea-hypopnea index (AHI) in patients with central sleep apnea (CSA) and obstructive sleep apnea (OSA) at baseline and follow-up. Home oxygen therapy (HOT) and continuous positive airway pressure (CPAP) significantly reduced AHI.

Table 2. Fatal Arrhythmic Events and All-Cause Death in 95 CHF Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Fatal arrhythmic event</th>
<th>All-cause death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AHI &lt;5 (n=39)</td>
<td>AHI ≥5 (n=56)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>1 (3)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Heart failure death</td>
<td>3 (8)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Death of non-cardiac cause</td>
<td>1 (3)</td>
<td>4 (7)</td>
</tr>
</tbody>
</table>

Causes of non-cardiac death included lung cancer (n=1), pneumonia (n=2), cerebral bleeding (n=1) and unknown case (n=1). AHI, apnea-hypopnea index; CHF, chronic heart failure.

Primary Endpoint
In the AHI <5 group, 4 patients with improved AHI (<5/h) on RT had no cardiac event (Table 2), but one patient had fatal arrhythmic event (VT) in the non-SDB group and 9 in the AHI ≥5 group (VT in 5, VF in 2, and sudden death in 2; Table 2).

A trend analysis showed a stepwise increase in the risk of fatal arrhythmic events as the severity of SDB increased (2.6,
Figure 3. Frequency of (A) fatal arrhythmic events and (B) all-cause death according to severity of sleep-disordered breathing (SDB). There was a stepwise increase in the risk of both (A) fatal arrhythmic events and (B) all-cause death as severity of SDB increased (fatal arrhythmic events, 2.6, 13.6 and 17.6%; all-cause death, 10.2, 4.6, and 26.5%, in patients with apnea-hypopnea index [AHI] >5/h, 5/h ≤ AHI <10/h, and AHI ≥10/h, respectively).

Figure 4. Kaplan-Meier survival curves of primary and secondary endpoints in all patients. Kaplan-Meier survival curves of (A) fatal arrhythmic events and (B) all-cause death in patients with chronic heart failure. The event-free survival rates for primary endpoints were significantly lower in the apnea-hypopnea index (AHI) ≥5 group than in the AHI <5 group.
13.6 and 17.6% in patients with AHI <5/h, 5/h ≤ AHI <10/h, and AHI ≥10/h, respectively; Figure 3A). The prevalence of fatal arrhythmic events during sleep was 0% and 44% in patients with AHI <5/h and AHI ≥5/h, respectively. The event-free survival rate for primary endpoints was significantly lower in the AHI ≥5 group than in the AHI <5 group (P=0.02, log-rank test; Figure 4A). On Cox proportional hazards model analysis AHI ≥5/h was the only independent predictor of fatal arrhythmic events (P=0.03; hazard ratio, 11.4; Table 1).

**Secondary Endpoint**

Four patients died in the non-SDB group (HF death in 3 and non-cardiac death in 1) and 10 in the AHI ≥5 group (VF in 2, sudden death in 2, HF death in 2, and non-cardiac death in 4; Table 2).

A trend analysis showed that the prevalence of all-cause death was higher in the patients with AHI ≤10/h than in those with 5≤ AHI <10/h, 5/h ≤ AHI <10/h, 5/h ≤ AHI <10/h, and AHI ≥10/h, respectively; Figure 3B). Survival free from all-cause death tended to be lower in the AHI ≥5 group (P=0.16, log-rank test; Figure 4B). On Cox proportional hazards model analysis AHI ≥10/h was the only independent predictor of all-cause death (P=0.01, hazard ratio, 11.4; Table 3).

**Effects of RT**

In 42 patients with AHI ≥10/h at initial evaluation, 24 were treated with RT (RT group), and the remaining 18 did not receive RT (non-RT group). Although RT significantly reduced AHI (Figure 2), there were no significant differences in fatal arrhythmic events or all-cause death between the 2 groups (Figures 5A,B). Among the 24 patients who received the RT, 4 with AHI <5 in response to RT were defined as the responders and the remaining 20 who did not reach AHI <5 as the non-responders (Figure 1). Importantly, there were no fatal arrhythmic events or all-cause deaths in the responder group, whereas 4 fatal arrhythmic events occurred and 3 patients died in the non-responder group. On Kaplan-Meier survival analysis, the non-responder group tended to have worse prognosis than the responder group (Figures 5C,D).

**Discussion**

It has been previously reported that RT for SDB in CHF patients might improve prognosis or reduce non-fatal ventricular arrhythmias. It has not, however, been demonstrated to what extent AHI needs to be reduced in CHF patients with SDB in order to prevent fatal arrhythmic events. Novel findings of the present study were that SDB, defined as AHI ≥5, is an independent predictor of fatal arrhythmic events in CHF patients, and that RT improved SDB but only tended to improve long-term prognosis in those patients.

To the best of our knowledge, this is the first study demonstrating that SDB is an independent predictor of fatal arrhythmic events in CHF patients, if these patients have residual SDB after nocturnal RT. The present results also suggest the importance of aggressive therapy for SDB to achieve AHI <5/h in CHF patients.

**SDB and Fatal Arrhythmias**

Normal sleep is associated with a low occurrence of ventricular arrhythmias. SDB, however, may interrupt normal sleep patterns and disrupt the protective effects of sleep. OSA and CSA exert potent modulatory effects on the autonomic nervous system at night, predisposing to cardiac arrhythmias through a number of mechanisms. Somers et al reported that SDB can increase sympathetic activity and blood pressure. It has been reported that SDB is associated with abnormalities in cardiac autonomic response, such as HR variability, and the resultant hypoxemia can lead to nocturnal cardiac isch-

### Table 3. Significant Indicators of Fatal Arrhythmic Events and All-Cause Death

|                  | Fatal arrhythmic events | All-cause death |
|------------------|-------------------------|-----------------|----------------|
|                  | Univariate analysis     | Multivariate analysis | Univariate analysis | Multivariate analysis |
|                  | P-value | HR  | P-value | HR  | P-value | HR  | P-value | HR  |
| Age              | 0.85    | 1.01| 0.07    | 1.04| 0.50    | 1.01|        |      |
| Sex              | 0.86    | 1.16| 0.72    | 1.23|        |     |        |      |
| BMI              | 0.86    | 1.02| 0.06    | 0.88| 0.07    | 0.86|        |      |
| Hypertension     | 0.89    | 1.13| 0.85    | 0.84|        |     |        |      |
| Diabetes mellitus| 0.65    | 1.58| 0.28    | 2.24|        |     |        |      |
| Hyperlipidemia   | 0.75    | 0.70| 0.38    | 2.64|        |     |        |      |
| Smoking          | 0.09    | 5.67| 0.21    | 2.61|        |     |        |      |
| AHI ≥ 5          | 0.03    | 12.6| 0.03    | 11.4| 0.16    | 2.21|        |      |
| AHI ≥10          | 0.05    | 3.47| 0.01    | 4.63| 0.01    | 4.79|        |      |
| Brain natriuretic peptide | 0.26    | 1.00| 0.31    | 1.00|        |     |        |      |
| NYHA class III–IV | 0.55  | 0.58| 0.10    | 2.43|        |     |        |      |
| LV end-diastolic dimension | 0.34  | 0.97| 0.83    | 1.00|        |     |        |      |
| Left atrial dimension | 0.12  | 1.08| 0.64    | 1.68|        |     |        |      |
| LVEF             | 0.12    | 0.95| 0.91    | 0.99|        |     |        |      |
| ACEI/ARB         | 0.98    | 0.56| 0.42    | 0.51|        |     |        |      |
| β-blockers       | 0.94    | 1.31| 0.05    | 0.29|        |     |        |      |

AHI ≥5/h was an independent predictor of fatal arrhythmic events and AHI ≥10/h was a predictor of all-cause death. Further, β-blocker was a negative risk factor for all-cause death. HR, hazard ratio. Other abbreviations as in Table 1.
SATAKE H et al.

independently associated with an increased risk of ventricular arrhythmia and appropriate ICD therapy. These reports support the notion that SDB is an independent risk factor for the occurrence of malignant ventricular arrhythmia. Indeed, in the present study, SDB was associated with the occurrence of malignant ventricular arrhythmia and poor prognosis.

The beneficial effects of RT have been reported for SDB-related malignant ventricular arrhythmias. Javaheri reported

Figure 5. Kaplan-Meier survival curves of primary and secondary endpoints. Kaplan-Meier survival curves of (A) fatal arrhythmic events and (B) all-cause death in the respiratory therapy (RT) and non-RT groups. In 42 patients with AHI >10 at initial evaluation, there were 24 patients in the RT group and 18 in the non-RT group. There were no significant differences between the two groups for both endpoints. (C,D) Kaplan-Meier survival curves for (C) fatal arrhythmic events and (D) all-cause death according to response to RT. In 24 patients with AHI >10 at initial evaluation who underwent RT, AHI was reduced to <5 in 4 patients (responder group) and was not reduced to <5 in 20 patients (non-responder group). There were no significant differences between the two groups for both endpoints, but the responder group (4 patients) with AHI <5 on RT had neither fatal arrhythmic events nor all-cause death during the follow-up period.
an association between SDB and ventricular arrhythmia in patients with HF and subsequently observed that improvement of SDB by CPAP was accompanied by a significant reduction in ventricular arrhythmias. 11 In the present study, however, AHI after nocturnal RT was the only predictor of fatal arrhythmic events, suggesting that patients with high AHI are associated with poor prognosis and high risk of malignant ventricular arrhythmia even after RT. In contrast, in the present study, there were no fatal arrhythmic events or all-cause deaths in the responder group, and the mean HR and 3% oxygen desaturation index (ODI) during the second sleep study were significantly decreased compared with the first polygraphy study in the patients treated with RT (mean HR, 70 ± 10.6 beats/min vs. 64 ± 9.8 beats/min, P = 0.031; 3% ODI, 3.4 ± 8.6% vs. 9.9 ± 10.2%/h, P = 0.028). This was partially because sympathetic activity and hypoxemia during sleep were improved by the RT. Moreover, the present results suggest that AHI ≥ 5/h could identify patients at very high risk for fatal arrhythmic events (Figure 3A).

SDB and Long-Term Prognosis

Previous studies have shown that CSA is an independent predictor of long-term prognosis in CHF patients. Lanfranchi et al reported that non-sustained VT appeared more often in patients with CHF and severe CSA than in those with mild or no CSA. 12 As mentioned here, the stratified analysis in the CPNPAP study showed that prognosis was improved in patients who achieved AHI < 15 in response to CPAP. 14 Kasai et al also reported that CPAP significantly reduced the risk of death and hospitalization in patients with CHF and OSA. 38 Moreover, the event-free survival rate was significantly higher in more compliant patients. 38 The confirmatory, multicenter, randomized, controlled study of adaptive servo-ventilation (ASV) in patients with CHF (SAVIOR-C) showed that ASV therapy was not superior to guideline-directed medical therapy with regard to cardiac function-improving effect but did have a clinical status-improving effect. 39 These results suggest that nocturnal RT can reduce fatal events and improve prognosis in CHF patients with SDB.

Recently, an interim analysis of the SERVE-HF Study for ASV therapy in patients with CSA and CHF found a statistically significant 2.5% increase in annual risk of cardiovascular mortality for those with LVEF ≤ 45% compared with the control group. 27,40 In response to that report, the Japanese Circulation Society issued the first statement on appropriate use of ASV in CHF patients with reduced LVEF. 41 It should be noted, however, that the SERVE-HF Study did not examine the effects of nocturnal RT (eg, CPAP or HOT).

No evidence is yet available as to what extent AHI needs to be reduced in CHF patients with SDB in order to improve prognosis. In the present study, there was no significant difference in long-term prognosis between the RT and the non-RT groups. This was probably due to the relatively small number of patients treated with nocturnal RT and the low incidence of events. Furthermore, there was no significant difference in prognosis between the responder and the non-responder groups, probably due to the small number of patients in the responder group. There were, however, no fatal arrhythmic events or all-cause deaths in the responder group (AHI < 5). Although the number of patients in the responder group was small, AHI ≥ 5 was found to be an independent predictor of fatal arrhythmic events and it may be important to reduce AHI to < 5 with RT.

Study Limitations

Several limitations should be mentioned for the present study. First, the diagnosis and classification of SDB were based on cardiorespiratory polygraphy, not on polysomnography, which is considered to be the gold standard for diagnosis of SDB. 26 The non-attached type 3 monitoring system, however, has been reported to be reliable. Cunningham et al reported a good correlation between AHI measured on polysomnography and that by the portable device, 45 and that the type 3 monitoring system could correctly evaluate OSA as defined on polysomnography with a sensitivity of 96% and specificity of 83%. 22

Further, El Shayeb et al reported in their meta-analysis that the type 3 portable devices showed good diagnostic performance compared with the type 1 polysomnography in adult patients with a high pretest probability of moderate to severe OSA. 23 Second, the present study was a prospective but not a randomized trial and was performed in a single center with a small number of patients. Third, in the present study, we used the Teichholz method or modified Simpson method to calculate LVEF. The Teichholz method, however, could cause measurement error in calculation of LVEF due to the involvement of different cardiac ultrasound testers. Fourth, the present study did not evaluate the effect of ASV, which has been reported to be effective for CHF and various types of sleep apnea. 42,43

Conclusions

SDB in CHF patients was an independent predictor of fatal arrhythmic events. Conventional RT might improve prognosis if it is able to reduce AHI to <5/h.

Acknowledgments

This work was supported in part by Grants-in-Aid from the Japanese Ministry of Education, Culture, Sports, Science, and Technology, Tokyo, Japan.

Disclosures

The authors declare no conflict of interest.

References

9. Lanfranchi PA, Somers VK, Braghirolni A, Corra U, Deleuteri E,


