Long-Term Prognosis of Adaptive Servo Ventilation Therapy for Patients with Heart Failure -Consideration in Severity of Sleep-Disordered Breathing

Keita Goto¹,², Noriaki Takama², Masahiko Kurabayashi²

1. Division of Cardiology, Isesaki Municipal Hospital, Isesaki, Japan
2. Department of Cardiovascular Medicine, Gunma University School of Medicine, Maebashi, Japan

Corresponding author:
Keita Goto, MD
Division of Cardiology, Isesaki Municipal Hospital, 12-1, Tsunatorihonmachi, Isesaki, Gunma, Japan
Tel. +81-27-220-8153
Fax +81-27-220-8159
E-mail: k.goto@goto.ivory.ne.jp

Abstract

Background
Adaptive servo-ventilation (ASV) is used to treat sleep apnea in heart failure (HF). However, it is unclear whether ASV improves the long-term prognosis for all patients with HF, regardless of the severity of sleep-disordered breathing (SDB). We therefore aimed to estimate the long-term prognosis associated with ASV therapy for patients with HF by the severity of SDB.

Methods
Sixty-one consecutive patients with HF (mean age ± standard deviation: 70 ± 10 years) were initiated on ASV therapy for HF treatment after polysomnography. Patients were then classified into the following three groups based on their apnea–hypopnea index (AHI): a severe group with an AHI of ≥40/h (n = 28); a moderate group with an AHI of ≥20/h but <40/h (n = 20); and a mild group with an AHI of <20/h (n = 13). To estimate long-term prognosis, we reviewed the 3-year follow-up data, including that concerning fatal cardiovascular events (death from myocardial infarction, cardioembolic stroke, and fatal cardiac arrhythmias).

Results
No significant differences were observed between the three study groups in the risk of fatal cardiovascular events (p = 0.207).

Conclusions
Our results suggest that ASV therapy is associated with a good prognosis and that ASV therapy is effective, regardless of the severity of SDB.

Keywords: Adaptive servo-ventilation; Sleep apnea; Heart failure; Prognosis

Citation:

Introduction
Sleep-disordered breathing (SDB) has a close relation to heart failure (HF), the incidence of fatal cardiovascular events, and mortality.¹ Adaptive servo-ventilation (ASV) therapy has been shown to be effective for central sleep apnea (CSA) and Cheyne-Stokes respiration (CSR).² ³ Recently, ASV therapy has also been used to treat patients with HF who also have CSA and CSR² ³ ⁴ ⁵ as well as patients with SDB, including those with obstructive sleep apnea.⁶ ⁷ Cowie et al.⁶ reported that the ASV therapy for the patients with HF and reduced ejection fraction increased all-cause and cardiovascular mortality. However, previously, we reported that ASV therapy for patients with mild SDB resulted in almost equal improvements in brain natriuretic peptide (BNP) and left ventricular ejection fraction (LVEF) compared with patients with moderate and severe SDB, thus demonstrating that ASV therapy was effective for all patients with HF.⁷ Similarly, other reports suggested that the ASV therapy improved the LVEF, BNP, and the prognosis of patients with HF.⁸ ⁹ ¹⁰ ¹¹ However, previous reports have suggested that there is a negative relationship between the severity of SDB and prognosis.¹ ² ³ It remained unclear as to whether ASV could improve the long-term prognosis of patients with HF, regardless of the severity of SDB. We aimed to clarify whether ASV therapy improved the short- and long-term prognosis in patients with HF, regardless of the severity...
of SDB. We hypothesized that both the short- and long-term prognosis of patients with HF could be improved by improving their SDB.

**Methods**

**Study design and ethical considerations**

The present study was a single-center, prospective cohort study of HF patients that was conducted between April 2007 and April 2010 at Isesaki Municipal Hospital. This study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki. The research protocol was approved by the Institutional Review Board for Human Research of Isesaki Municipal Hospital, and all patients gave written consent to the study.

We included 61 consecutive patients with HF who were initiated on ASV therapy after polysomnography to screen for SDB. All patients had a history of HF, such as, coronary artery disease, valvular disease, and cardiomyopathy, and were classified into class II–IV, according to the criteria of the New York Heart Association.

All patients were treated with optimal medical therapy for HF before undergoing full-night polysomnography and were prescribed ASV therapy. For analysis, patients were classified into the following three groups based on the apnea–hypopnea index (AHI): a severe group with an AHI of ≥40/h (n = 28); a moderate group with an AHI of ≥20/h but <40/h (n = 20); and a mild group with an AHI of <20/h (n = 13). To estimate long-term prognosis, we reviewed the 3-year follow-up data, including that concerning fatal cardiovascular events (death from myocardial infarction, cardio-embolic stroke, and fatal cardiac arrhythmias). Sleep evaluation and treatment devices

We conducted full-night polysomnography as screening to analyze SDB for all patients with HF, using a digital polygraph (P-Series Plus; Compumedics, Abbotsville, Australia) according to a commonly used method. SDB is common for patients with HF because 51 percent of patients with HF suffer from SDB. We measured nasal airflow with an airflow pressure transducer, arterial oxygen saturation by pulse oximetry with a finger probe (Nonin 8000J Adult Flex Sensor), and chest and abdominal movement using two bands (inductive respiratory bands), an electroencephalogram, an electrooculogram, and a chin electromyogram. We scored sleep staging and arousal according to generally accepted definitions and methods.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Severity of SDB</th>
<th>Mild SDB (n=13)</th>
<th>Moderate SDB (n=20)</th>
<th>Severe SDB (n=26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.5 ± 9.9</td>
<td>70.7 ± 10</td>
<td>70.9 ± 9.9</td>
<td>0.75</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>8 (62)</td>
<td>13 (65)</td>
<td>21 (75)</td>
<td>0.63</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>23.6 ± 8.6</td>
<td>23.2 ± 4.2</td>
<td>25.2 ± 4.6</td>
<td>0.50</td>
</tr>
</tbody>
</table>

**Underlying heart disease**

| ICM, n (%) | 6 (46) | 8 (40) | 12 (43) | 0.99 |
| Valvular heart disease, n (%) | 4 (31) | 4 (20) | 1 (3.6) | 0.04 |
| Cardiomyopathy, n (%) | 1 (7.7) | 1 (5) | 8 (29) | 0.08 |
| Others, n (%) | 2 (15) | 7 (35) | 7 (25) | 0.45 |

**Drug therapy**

| ß-blocker/ARBs/ACE inhibitors | 8 (62) | 9 (53) | 14 (64) | 0.77 |
| Diuretics | 10 (77) | 9 (53) | 13 (59) | 0.45 |

**Coronary risk factors**

| Hypertension | 10 (77) | 18 (90) | 20 (71) | 0.31 |
| Dyslipidaemia | 3 (23) | 4 (20) | 15 (54) | 0.04 |
| Diabetes mellitus | 4 (30.8) | 8 (40.0) | 7 (25.0) | 0.55 |
| Smokers | 2 (15.4) | 6 (31.6) | 7 (25.9) | 0.63 |

**Blood Pressure (mmHg)**

| Systolic | 117 ± 19 | 130 ± 18 | 124 ± 22 | 0.197 |
| Diastolic | 64.0 ± 10 | 69.6 ± 9.1 | 70.0 ± 13 | 0.246 |
| Triglycerides (mg/dl) | 109 ± 61.2 | 88.4 ± 38.4 | 129 ± 102 | 0.223 |
| HDL Cholesterol (mg/dl) | 45.8 ± 9.93 | 55.8 ± 18.2 | 50.5 ± 15.8 | 0.202 |
| LDL Cholesterol (mg/dl) | 112 ± 36.1 | 101 ± 29.3 | 110 ± 37.1 | 0.585 |
| Fasting blood sugar (mg/dl) | 98.9 ± 38.6 | 119 ± 30.3 | 128 ± 62.7 | 0.253 |
| LVEF (%) | 46.2 ± 17.2 | 43.9 ± 17.2 | 44.1 ± 17.9 | 0.917 |
| BNP (pg/ml) | 379 (260-503) | 590 (187-560) | 488 (202-629) | 0.481 |

Legend: Values are Means ± standard deviation; SDB = sleep disordered breathing, Mild (AHI ≤20); Moderate (AHI 20-40); Severe (AHI≥40); HF = heart failure; ICM = ischemic cardiomyopathy; ARBs = angiotensin receptor blockers; BNP = brain natriuretic peptide.
After confirmation of SDB and grading of severity by full-night polysomnography, we used an ASV device (AutoSet-CS; ResMed, Sydney, Australia) with a full facemask (ResMed) for all HF patients. We set the expiratory positive airway pressure at 4 cm H2O and the inspiratory support pressure at 3–8 cm H2O. The backup respiratory rate for apnea or hypopnea was 15 breaths/min. We checked patient compliance with ASV therapy from the ASV device. If apnea or hypopnea was observed, the ASV device modified the expiratory positive airway pressure and inspiratory support to fit the patients’ breathing as necessary.

Data collection
We defined underlying heart disease as ischemic cardiomyopathy, valvular heart disease, and cardiomyopathy. Patients with ischemic cardiomyopathy were defined as those with angina pectoris, unstable angina pectoris, or acute coronary syndrome by coronary angiography in the past. Patients with valvular heart disease were defined as those with uncontrolled refractory HF induced by valvular heart disease but without an indication for surgery. Patients with cardiomyopathy were defined as those with dilated or hypertrophic cardiomyopathy. We defined coronary risk factors as hypertension, dyslipidemia, and diabetes mellitus. Hypertension was defined as a blood pressure ≥140/90 mmHg or the use of antihypertensive medication. Dyslipidemia was defined as elevated low-density-lipoprotein cholesterol (≥120 mg/dL), reduced high-density-lipoprotein cholesterol (<40 mg/dL), triglycerides ≥150 mg/dL, or the use of antilipidemic drugs. Diabetes mellitus was defined as a fasting blood sugar ≥126 mg/dL and an HbA1c ≥6.5%, or the use of insulin or oral antihyperglycemic drugs.

Transthoracic echocardiography was performed to evaluate the LVEF in all patients before ASV therapy; LVEF was calculated by the modified Simpson's method. We also took a blood sample to evaluate the BNP level before ASV therapy. BNP and LVEF were then re-evaluated 6 months after ASV therapy to assess the effect on short-term prognosis. We also used LVEF and BNP to evaluate the severity of HF between patients with fatal cardiovascular event.

Outcomes
The primary endpoint was fatal cardiovascular mortality at 3 years, defined as death from myocardial infarction, cardioembolic stroke, or fatal cardiac arrhythmias. We excluded patients with non-cardiac fatal events.

Statistical analysis
All values are shown as mean ± standard deviation (SD) or median (25%–75% inter-quartile range). Normally distributed data were evaluated by Fisher’s exact test for binary variables or by one-way analysis of variance for continuous variables. Non-normally distributed data were evaluated by the χ² test for binary variables or by the Kruskal–Wallis test for continuous variables. The log-rank test was used to compare the fatal cardiovascular event-free rate among the three groups. Repeated-measures analysis of variance was used to evaluate whether ASV therapy improved BNP and LVEF among the three AHI groups. We considered P-values <0.05 to be significant in all comparisons. All statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). EZR is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) with a modified version R command designed to add statistical functions that are used frequently in biostatistics.
Results

Characteristics of patients

Table 1 shows the patient characteristics before ASV therapy. We enrolled 61 patients in this study and classified them into three groups by the severity of SDB. No significant differences were apparent among the three groups with respect to age and gender, body mass index, BNP, and LVEF. The mean age was 70 ± 10 years and men accounted for the majority of participants (68.9%). The median BNP levels before ASV therapy were as follows: 379 (260–503) pg/ml in the mild group, 590 (187–560) pg/ml in the moderate group, and 488 (202–629) pg/ml in the severe group (P = 0.481). The mean LVEF before ASV therapy were as follows: 46.2 ± 17.2% in the mild group, 43.9 ± 17.2% in the moderate group, and 44.1 ± 17.9% in the severe group (P = 0.917).

Sleep study

Table 2 shows the results of full-night polysomnography before ASV therapy. There were no significant differences in the total sleeping time or sleep efficacy among the three groups. As expected though, significant differences did exist in the arousal index, AHI, CSA index, and obstructive sleep index, which were positively correlated with the severity of SDB.

Fatal cardiovascular event-free rate

Figure 1 shows the Kaplan–Meier survival curves for the fatal cardiovascular event-free rate among the three groups by SDB severity. After the 3-year follow up, no significant difference was observed in the risk of fatal cardiovascular events (log-rank test: P = 0.207). ASV therapy was effective for all patients, regardless of the severity of SDB.

The differences between patients with fatal cardiovascular events and those with non-fatal cardiovascular events are summarized in Table 3. No significant differences were observed by age and gender, BNP, LVEF, or AHI between those with and without fatal cardiovascular events.

Improvement of LVEF and BNP level

The BNP level and LVEF were improved almost equally in the three groups after ASV treatment (fig. 2). Although the BNP level decreased significantly in each group from before to after ASV therapy (changes of BNP levels: mild group, 146 [25–240] pg/ml; moderate group; 286 [4.97–289] pg/ml; and severe group, 348 [82–509] pg/ml), there was no significant difference among the three groups (P = 0.339). Similarly, although the LVEF increased significantly in each group from before to after ASV therapy (changes of LVEF: mild group, 8.83 ± 11.9%; moderate group; 12.5 ± 12.0%; and severe group; 8.11 ± 12.5%), there was no significant difference among the three groups (P = 0.491).

Discussion

Findings and Data interpretation

In this study, we found that ASV therapy improved both the short- and long-term prognosis of patients with HF, regardless of the severity of SDB.

First, under ASV therapy there was no statistically significant difference between mild, moderate and severe sleep apnea patients, consistent with the hypothesis that ASV may improve the otherwise adverse long-term prognosis associated with the presence of increasingly severe sleep apnea in patients with HF, although the small sample size means we cannot prove...
this. To our knowledge, there are no reports on this relationship between the effects of ASV therapy and SDB severity. Cowie et al. reported that the ASV therapy for the HF patients with CSA was associated with the poorer long-term prognosis than the control therapy.6 The ASV therapy needs to be examined with the right selection of the patients since Coats suggested that the ASV therapy has a negative effect on the right sided preload and right ventricular function.17 Furthermore, in Japan, the ASV therapy was conducted for the patients with not only SDB but also HF. Furthermore, many reports showed that the ASV therapy for the patients with HF was effective.5,7,9,10,11,18-22 Although it is well known that the prognosis of patients is negatively correlated with the severity of SDB,17 little has been reported on the long-term prognosis in patients with HF after initiating ASV therapy. Earlier, we showed that ASV therapy was effective for patients with HF and that it improved their prognosis after one year.18 Furthermore, Yoshihisa et al. reported that ASV therapy improved the long-term prognosis of patients with chronic HF and CSR for about 3 years, and that of patients with HF, preserved LVEF, and SDB for about 4 years.10,12

Similar research also suggested that ASV therapy could improve the prognosis of patients with HF and comorbid chronic kidney disease and SDB.25 However, the present report differs from those reports10,18-22 in that we evaluated the relationship between long-term prognosis and SDB severity. Indeed, we found improved long-term prognosis regardless of SDB severity in a larger cohort (n = 61) than previously reported.

Second, ASV therapy for patients with HF improved the short-term prognosis, as determined by improvements in LVEF and BNP, regardless of the severity of SDB. Previously, we reported that ASV treatment for patients with mild SDB resulted in comparable improvements in BNP and LVEF for those with moderate and severe SDB.9 Koyama et al. have also reported that ASV therapy for patients with HF effectively improved the short-term prognosis (again, assessed by LVEF and BNP), irrespective of the SDB severity.21 Moreover, previous reports have revealed that ASV therapy improved both BNP and LVEF2,2,21,22 The results of the present study are therefore consistent with previous findings.

ASV therapy is usually used to treat CSA and CSR.2,3 However, ASV therapy increasingly appears to be appropriate for the management of all patients with HF because it improves both the short- and long-term prognosis, regardless of the severity of SDB. ASV therapy is therefore an effective non-pharmacological therapy for all patients HF, which is particularly relevant given that patients with SDB have a poorer prognosis than those without SDB.1,12

**Limitation**

The present study has two main limitations. First, this study was observational rather than randomized. The cohort may be biased by being enrolled from a single center; however, we made efforts to reduce this bias by applying ASV therapy to consecutive patients. Second, our study population was small. The results will therefore need to be confirmed in a larger clinical trial.

**Conclusion**

In conclusion, this study clearly revealed that ASV therapy for patients with HF improved both the short- and long-term prognosis, regardless of the severity of SDB. Our results suggest that ASV therapy is associated with a good prognosis and is effective for all patients with HF and SDB.

**Table 3. Fatal Cardiovascular Events and Clinical Parameters**

<table>
<thead>
<tr>
<th>Fatal cardiovascular events</th>
<th>Yes (n=11)</th>
<th>No (n=50)</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>70.2± 8.20</td>
<td>70.3± 10.2</td>
<td>0.960</td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>8 (72.7)</td>
<td>34 (68)</td>
<td>0.999</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>42.1 ± 16.0</td>
<td>45.0 ± 17.5</td>
<td>0.620</td>
</tr>
<tr>
<td>BNP, pg/ml</td>
<td>493 (389-584)</td>
<td>500 (175-597)</td>
<td>0.970</td>
</tr>
<tr>
<td>Drug therapy beta-blocker, n (%)</td>
<td>8 (20)</td>
<td>6 (14.6)</td>
<td>0.650</td>
</tr>
<tr>
<td>ARBs or ACE inhibitors n (%)</td>
<td>6 (64.5)</td>
<td>23 (56.1)</td>
<td>0.999</td>
</tr>
<tr>
<td>AHI (/hr)</td>
<td>43.7± 34.3</td>
<td>40.9± 23.7</td>
<td>0.744</td>
</tr>
</tbody>
</table>

**Abbreviations List**

- AHI = apnea-hypopnea index
- ASV = adaptive servo-ventilation
- BNP = brain natriuretic peptide
- CSA = central sleep apnea
- CSR = Cheyne–Stokes respiration
- CSW = Cheyne-Stokes breathing
- HF = heart failure
- LVEF = left ventricular ejection fraction
- ODI = oxygen desaturation index
- SDB = sleep-disordered breathing

**Declarations of Interest**

The authors declare no conflicts of interest.

**Acknowledgement**

The authors state that they adhere to the statement of ethical publishing in biomedical journals.23

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