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# Effect of Flow-Triggered Adaptive Servo-Ventilation Compared With Continuous Positive Airway Pressure in Patients With Chronic Heart Failure With Coexisting Obstructive Sleep Apnea and Cheyne-Stokes Respiration

Takatoshi Kasai, MD, PhD; Yasuhiro Usui, MD; Toru Yoshioka, MD, PhD; Naotake Yanagisawa, PhD; Yoshifumi Takata, MD; Koji Narui, MD; Tetsu Yamaguchi, MD; Akira Yamashina, MD; Shin-ich Momomura, MD; for the JASV Investigators

**Background**—In patients with chronic heart failure (CHF), the presence of sleep-disordered breathing, including either obstructive sleep apnea or Cheyne-Stokes respiration-central sleep apnea, is associated with a poor prognosis. A large-scale clinical trial showed that continuous positive airway pressure (CPAP) did not improve the prognosis of such patients with CHF, probably because of insufficient sleep-disordered breathing suppression. Recently, it was reported that adaptive servo-ventilation (ASV) can effectively treat sleep-disordered breathing. However, there are no specific data about the efficacy of flow-triggered ASV for cardiac function in patients with CHF with sleep-disordered breathing. The aim of this study was to compare the efficacy of flow-triggered ASV to CPAP in patients with CHF with coexisting obstructive sleep apnea and Cheyne-Stokes respiration-central sleep apnea.

**Methods and Results**—Thirty-one patients with CHF, defined as left ventricular ejection fraction <50% and New York Heart Association class  $\geq$ II, with coexisting obstructive sleep apnea and Cheyne-Stokes respiration-central sleep apnea, were randomly assigned to either CPAP or flow-triggered ASV. The suppression of respiratory events, changes in cardiac function, and compliance with the devices during the 3-month study period were compared. Although both devices decreased respiratory events, ASV more effectively suppressed respiratory events ( $\Delta$ AHI [apnea-hypopnea index],  $-35.4 \pm 19.5$  with ASV;  $-23.2 \pm 12.0$  with CPAP,  $P < 0.05$ ). Compliance was significantly greater with ASV than with CPAP ( $5.2 \pm 0.9$  versus  $4.4 \pm 1.1$  h/night,  $P < 0.05$ ). The improvements in quality-of-life and left ventricular ejection fraction were greater in the ASV group ( $\Delta$ LVEF [left ventricular ejection fraction],  $+9.1 \pm 4.7\%$  versus  $+1.9 \pm 10.9\%$ ).

**Conclusions**—These results suggest that patients with coexisting obstructive sleep apnea and Cheyne-Stokes respiration-central sleep apnea may receive greater benefit from treatment with ASV than with CPAP. (*Circ Heart Fail.* 2010;3:140-148.)

**Key Words:** heart failure ■ pressure ■ sleep ■ ventilation

It has been reported that  $\approx$ 50% of patients with chronic heart failure (CHF) have sleep-disordered breathing (SDB),<sup>1-4</sup> which consists of obstructive sleep apnea (OSA) caused by upper airway obstruction during sleep and Cheyne-Stokes respiration (CSR)-central sleep apnea (CSA) caused by respiratory control system instability. The presence of SDB, including both OSA and CSR-CSA, is known to be associated with increased mortality in patients with CHF.<sup>5-8</sup>

## Clinical Perspective on p 148

In patients with CHF, treatment of SDB has been shown to improve underlying cardiac dysfunction. In particular, treat-

ment with continuous positive airway pressure (CPAP) has been shown to suppress the abnormal breathing pattern, attenuate sympathetic overactivity, and improve left ventricular ejection fraction (LVEF) in patients with CHF with either OSA or CSR-CSA.<sup>9-12</sup> However, it remains controversial whether CPAP should be a specific therapeutic option in patients with CHF with SDB, because randomized clinical trials assessing the long-term efficacy of CPAP in patients with CHF with OSA are lacking. In addition, a large-scale randomized clinical trial, the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure, in which the long-term efficacy of CPAP in

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A list of all JASV investigators is given in the Appendix.

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patients with CHF with CSR-CSA was investigated, showed that CPAP did not improve transplant-free survival in association with its insufficient alleviation of SDB.<sup>13</sup> On the other hand, it is well recognized that compliance with CPAP can be problematic in treating SDB, particularly in patients with CHF. Therefore, other treatment options that can suppress SDB more effectively and can produce better compliance are needed to resolve the issue of whether patients with heart failure should be treated for SDB, when present.

From this perspective, adaptive servo-ventilation (ASV) may be an effective alternative for suppression of SDB.<sup>14</sup> Indeed, several groups have reported the efficacy of ASV for suppressing SDB using 2 different types of ASV: volume-triggered ASV, and the newer, flow-triggered ASV, which has been developed based on the concept of normalizing breathing in patients with both OSA and CSR-CSA.<sup>15–17</sup> Although several reports have demonstrated the efficacy of volume-triggered ASV for improving device compliance and cardiac function in patients with predominant CSR-CSA,<sup>18–20</sup> there are no similar data showing such efficacies using flow-triggered ASV. Moreover, no data about the efficacy of ASV for patients with CHF with coexisting OSA and CSR-CSA are available. Therefore, we hypothesized that, compared with CPAP, flow-triggered ASV would result in better compliance with the device and greater improvement in cardiac function in patients with CHF with coexisting OSA and CSR-CSA.

## Methods

### Subjects

This study was a prospective, parallel, randomized, multicenter trial. Subjects were enrolled based on the following criteria: (1) the presence of symptomatic CHF, which was defined as an LVEF <50% on echocardiography and New York Heart Association class  $\geq$ II; (2) stable clinical status, which was defined as receiving optimal medical therapy and no hospital admissions 1 month before study enrollment; and (3) diagnosed as having moderate-to-severe SDB, which was defined as  $\geq$ 15 apnea or hypopnea events per hour of sleep (ie, apnea-hypopnea index [AHI]) with coexisting OSA (obstructive AHI  $\geq$ 5 events/h) and CSR-CSA. The exclusion criteria were (1) age <20 or  $\geq$ 80 years; (2) CHF primarily because of organic valvular heart disease; (3) on cardiac resynchronization therapy; (4) the presence of chronic pulmonary disease; (5) on dialysis; (6) history of stroke with neurological deficit; and (7) patients who had already started or had previously tried positive airway pressure therapy. All patients gave their written informed consent to participate in this study. This study was approved by the ethics committees of the involved institutions.

### Sleep Study

SDB was diagnosed based on the results of overnight, in-laboratory, attended polysomnography. Generally accepted definitions and scoring methods were used.<sup>21–23</sup> Obstructive and central events were scored as previously described.<sup>24</sup> CSR was defined as follows: (1) at least 3 consecutive cycles of a cyclic crescendo-decrescendo change in the breathing amplitude and (2) central AHI  $\geq$ 5 events/h or a cyclic crescendo-decrescendo change in breathing amplitude lasting at least 10 consecutive minutes.<sup>23</sup>

### Intervention

After their baseline sleep study, the eligible subjects were randomly allocated into 2 groups: patients who received CPAP (REMStar Auto C-Flex, Respicronics, Murrysville, Pa) or those who received flow-triggered ASV (HEART PAP, Respicronics). Then, the patients

underwent a titration of the allocated device during a second, overnight, in-laboratory, attended polysomnography.

In the CPAP group, airway pressure was manually modulated from 4 cm  $\cdot$  H<sub>2</sub>O to the effective pressure, with a maximum of 12 cm  $\cdot$  H<sub>2</sub>O. The appropriate fixed pressure was chosen as the pressure abolishing or significantly decreasing both obstructive events (including apnea, hypopnea, and snoring) and CSR without arousal.

The principle of operation of the flow-triggered ASV has been described previously.<sup>15–17</sup> In summary, the flow-triggered ASV provides a manually set level of expiratory positive airway pressure (EPAP) to maintain upper-airway patency and automatically modulates the inspiratory positive airway pressure (IPAP) within a preset range to maintain a target inspiratory airflow, thereby eliminating CSR-CSA events. In addition, the device provides an automatic back-up rate, should sustained apnea be detected. In the ASV group, the EPAP was manually titrated from 4 cm  $\cdot$  H<sub>2</sub>O to the effective pressure, with a maximum of 10 cm  $\cdot$  H<sub>2</sub>O, using a similar titration method to that used for CPAP. The minimal IPAP was set at the determined EPAP level or to EPAP +2 cm  $\cdot$  H<sub>2</sub>O in patients with obstructive flow limitation. The maximal IPAP was set to 10 cm  $\cdot$  H<sub>2</sub>O greater than IPAP min. In addition, all subjects were initially set to an automatic back-up rate. When the central apneas were not corrected, the automatic back-up rate was changed to the fixed back-up rate of 10 breaths per minute or more. Subsequently, if continued periodic breathing (ie, CSR) was observed, maximal IPAP was raised by 2 cm  $\cdot$  H<sub>2</sub>O. A schema of the ASV titration algorithm is shown in Figure 1.

All subjects were assessed for compliance with treatment every month during the 3-month study period. Compliance was measured as the machine use (hours each night) given by the built-in counter. Provided pressure during use was also recorded in the device, and the mean value for the follow-up period was automatically calculated.

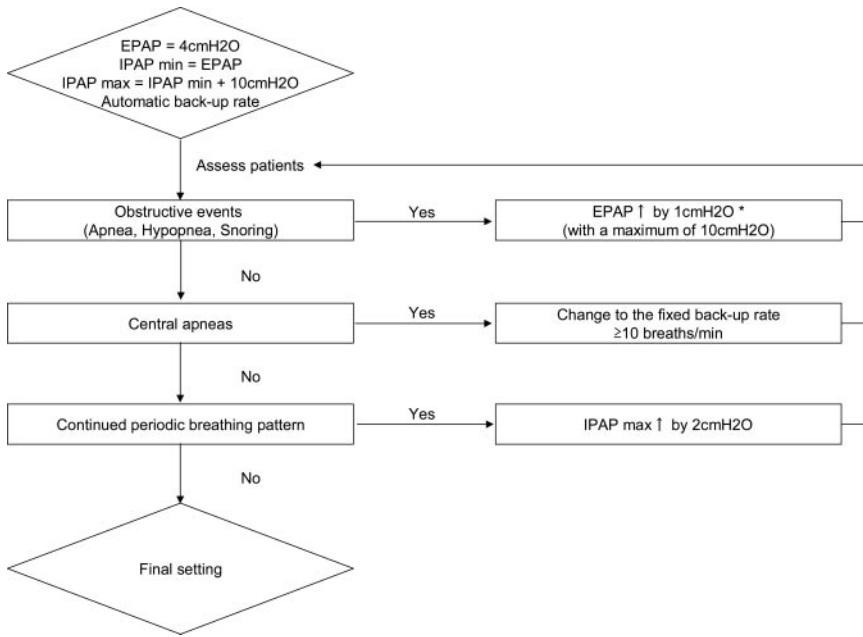
### Measurements

The effectiveness of treatment of SDB evaluated by overnight, in-laboratory, attended polysomnography was assessed 3 months after initiation of each treatment.

At the time of hospitalization for the diagnostic and follow-up sleep studies, body mass index, blood pressure, heart rate, LVEF, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, plasma brain natriuretic peptide (BNP), 24-hour urinary norepinephrine excretion, the distance walked in 6 minutes, sleepiness, and quality-of-life (QOL) were assessed. Two-dimensional echocardiographic images were obtained from the parasternal long and short axes, apical long axis, and apical 4-chamber views. The left ventricular end-diastolic diameter and left ventricular end-systolic diameter were determined, and the LVEF was calculated according to the modified Simpson method. The sonographers were blinded to the assignment of treatment and were not involved in the present study. Blood samples for the BNP measurement were obtained in the early morning after a 30-minute rest period, whereas the patient was in the supine position. An arterial blood gas sample was also collected at the time of each polysomnography. The protocol for the 6-minute walk test has been described elsewhere.<sup>25</sup> The total distance walked in 6 minutes was measured and assessed. Sleepiness was subjectively evaluated using the Epworth sleepiness scale. QOL was assessed using the 36-item short form 36 (SF-36) questionnaire.<sup>26</sup> The SF-36 consists of a 36-item questionnaire that evaluates 8 subscales.

### Statistical Analysis

All values are shown as the means  $\pm$  SD, and categorical variables are expressed as numbers and percentages. The baseline characteristics were compared using Student *t* test for normally distributed data and the Mann–Whitney *U* test for nonnormally distributed data for continuous variables, whereas the  $\chi^2$  test or Fisher's exact test was used for categorical variables. Within- and between-group comparisons of measurements were carried out using paired and unpaired Student *t* tests for normally distributed data, and the Mann–Whitney *U* test and the Wilcoxon–signed rank test for nonnormally distributed data. The correlation between changes in LVEF and compliance was



**Figure 1.** A schema of the ASV titration algorithm. The EPAP was increased with a maximum of 10 cm · H<sub>2</sub>O if obstructive events were observed. Then, when the central apneas were not corrected, the automatic back-up rate was changed to the fixed back-up rate of 10 breaths per minute or more. After that, if continued periodic breathing (ie, CSR) was observed, maximal IPAP was raised by 2 cm · H<sub>2</sub>O. \*When EPAP was increased, the difference between minimal and maximal IPAP was maintained. In cases with obstructive flow limitation, the minimal IPAP was set at 2 cm · H<sub>2</sub>O above EPAP. Even in such cases, the difference between minimal and maximal IPAP was maintained. IPAP min indicates minimal IPAP; IPAP max, maximal IPAP.

assessed using Pearson correlation analysis. A *P* value <0.05 was considered statistically significant. All statistical analyses were performed using a statistical software package (SPSS version 11.0 for Windows; SPSS Inc, Chicago, Ill).

**Table 1. Baseline Characteristics**

|                                       | ASV Group<br>(n=16) | CPAP Group<br>(n=15) |
|---------------------------------------|---------------------|----------------------|
| Age, y                                | 56.9±14.3           | 56.5±12.6            |
| Male gender                           | 16 (100)            | 15 (100)             |
| BMI, kg/m <sup>2</sup>                | 26.9±6.0            | 26.3±4.2             |
| Epworth sleepiness scale              | 8.2±4.8             | 8.4±3.9              |
| Cause of heart failure                |                     |                      |
| Ischemic/nonischemic                  | 5 (31.3)/11 (68.7)  | 4 (26.7)/11 (73.3)   |
| NYHA class                            |                     |                      |
| II                                    | 9 (56.2)            | 9 (60.0)             |
| III                                   | 7 (43.8)            | 6 (40.0)             |
| Left ventricular ejection fraction, % | 35.7±12.9           | 36.0±8.1             |
| Atrial fibrillation                   | 7 (43.8)            | 5 (33.3)             |
| ICD                                   | 2 (12.5)            | 2 (13.3)             |
| PaO <sub>2</sub> , Torr               | 83.5±10.9           | 83.0±8.2             |
| PaCO <sub>2</sub> , Torr              | 37.7±4.1            | 38.1±2.1             |
| Medications                           |                     |                      |
| ACE inhibitors/ARBs                   | 15 (93.8)           | 14 (93.3)            |
| β-blockers                            | 14 (87.5)           | 13 (86.7)            |
| Diuretics                             | 12 (75.0)           | 11 (73.3)            |
| Aldosterone blocker                   | 8 (50.0)            | 7 (46.7)             |
| Digoxin                               | 1 (6.3)             | 1 (6.7)              |
| Nitrates                              | 4 (25.0)            | 3 (20.0)             |

Values are represented as n (%). NYHA indicates New York Heart association; ICD, implantable cardioverter defibrillator; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker.

## Results

### Patients' Characteristics

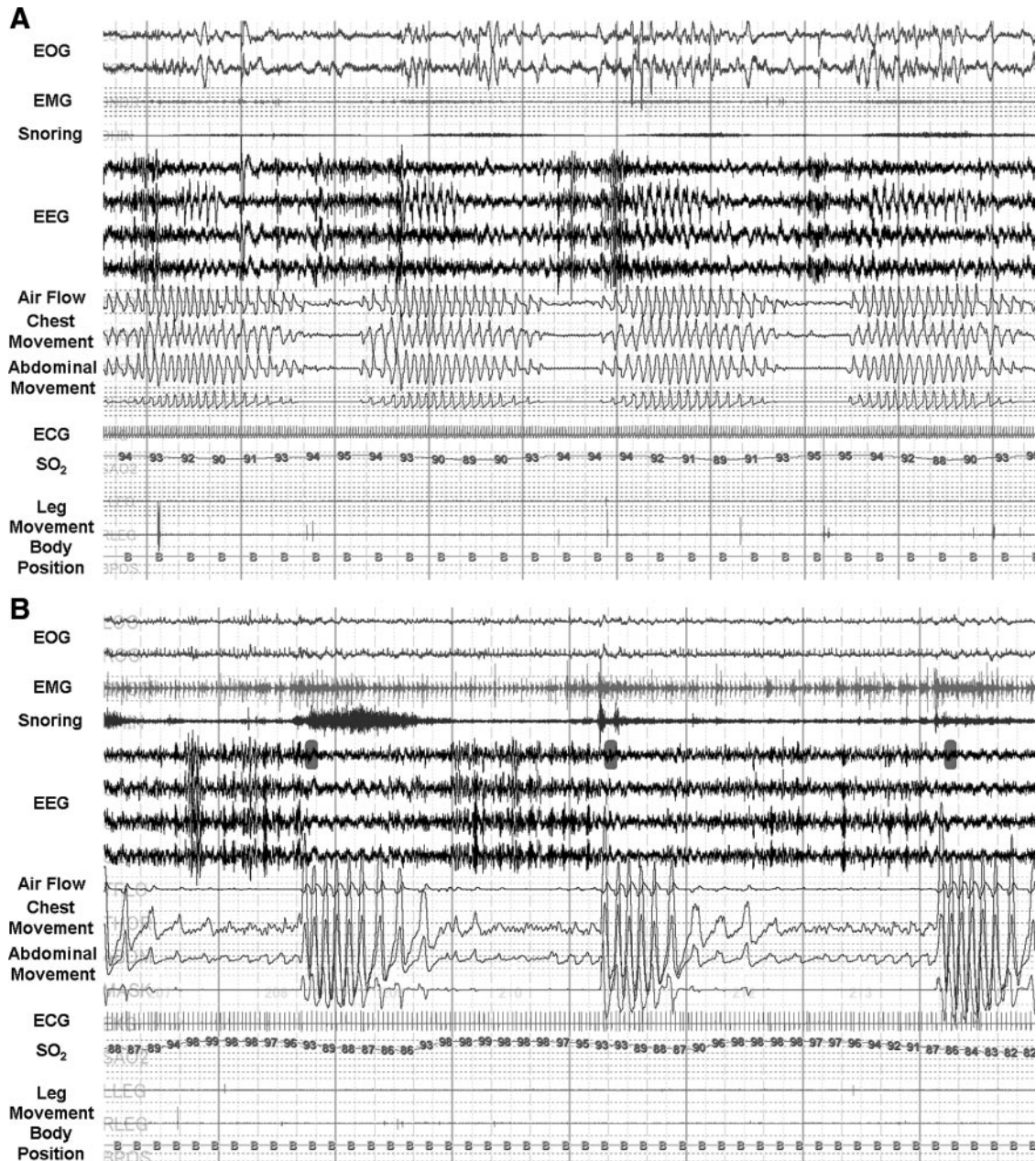
Of the 31 randomized patients, 16 were allocated to the ASV group and 15 to the CPAP group. Both groups were well matched for baseline characteristics (Table 1). The findings of the diagnostic sleep study are shown in Table 2. The mean AHI was similar in both groups and >50% of respiratory events were central. The representative respiratory events are shown in Figure 2.

One patient in the ASV group withdrew for personal reasons and failed to complete the trial, leaving 30 patients for complete analysis. No changes were made to patients' medications during the study period. There were no changes in body mass index and no difference in the body mass index changes between the 2 groups (+0.1±1.0 kg/m<sup>2</sup> in the ASV group, +0.3±1.3 kg/m<sup>2</sup> in the CPAP group; *P*=0.431). There were no changes in PaO<sub>2</sub> within each group and no difference in the PaO<sub>2</sub> changes between the 2 groups (-0.7 Torr in the ASV group, -1.1 Torr in the CPAP group; *P*=0.931). On the other hand, a signifi-

**Table 2. Findings of Sleep Study**

|  | ASV Group (N=16) | CPAP Group (N=15) |
|--|------------------|-------------------|
| TST, min                               | 341.2±70.0       | 345.6±61.2        |
| Apnea-hypopnea index, h                | 36.3±19.4        | 38.6±13.9         |
| Central events, %                      | 53.8±29.3        | 52.8±28.6         |
| Lowest SO <sub>2</sub> , %             | 80.6±4.7         | 80.2±7.7          |
| TST spent with SO <sub>2</sub> <90%, % | 22.7±30.4        | 23.0±25.6         |
| Arousal index, h                       | 40.7±20.4        | 38.7±13.7         |
| Sleep stage % of TST                   |                  |                   |
| Slow wave sleep                        | 9.5±8.6          | 9.9±5.1           |
| Rapid eye movement sleep               | 10.7±7.3         | 11.7±4.4          |

TST indicates total sleep time; SO<sub>2</sub>, oxyhemoglobin saturation.



**Figure 2.** Representative respiratory events during a diagnostic sleep study. A, Typical CSR-CSA; note 3 central apneas and subsequent hyperventilation. During central apneas, thoracoabdominal movements are absent. B, Typical OSA; note 3 obstructive apneas. During obstructive apneas, out-of-phase thoracoabdominal movements are observed. EOG indicates electro-oculogram; EMG, submental electromyogram; EEG, electroencephalogram; SO<sub>2</sub>, oxyhemoglobin saturation.

cant increase in the PaCO<sub>2</sub> was observed only in the ASV group (from 37.7 Torr to 40.7 Torr; *P*<0.001), and a significantly greater increase in the PaCO<sub>2</sub> was seen in the ASV group (+3.2±2.9 Torr) than in the CPAP group (+1.1±2.0 Torr; *P*=0.025).

**Effects on SDB and Sleepiness**

In both groups, treatment significantly reduced AHI (Figure 3A); however, the reduction of AHI was significantly greater in the ASV group than in the CPAP group at 3 months (Figure 3B).

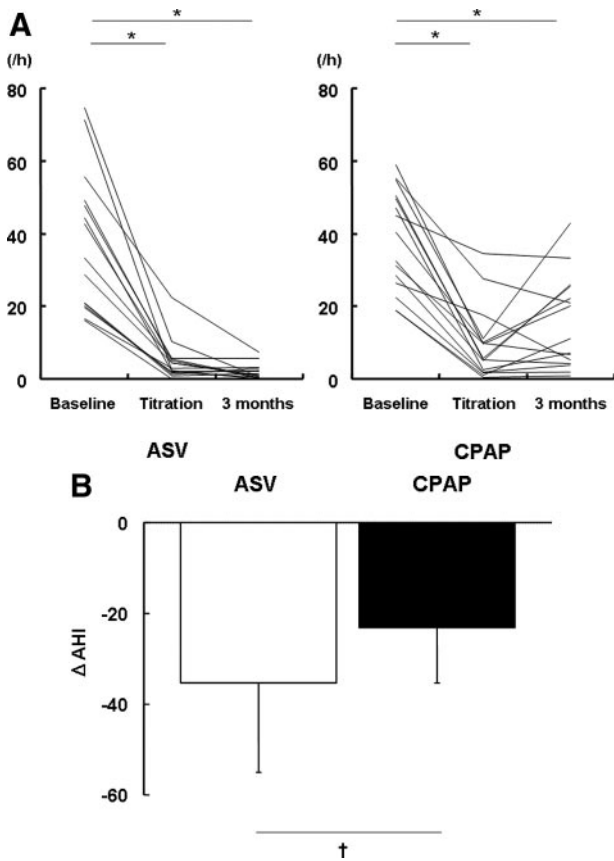
In the CPAP group, the mean provided pressure was 7.0±1.6 cm · H<sub>2</sub>O. On the other hand, in the ASV group, the

mean provided IPAP and EPAP were 9.5±2.3 cm · H<sub>2</sub>O and 7.3±2.4 cm · H<sub>2</sub>O, respectively.

There were no statistically significant differences in the Epworth sleepiness scale changes between the 2 groups (-3.2±3.4 in the ASV group and -2.7±3.5 in the CPAP group).

**Cardiac Function**

There were no significant differences in the blood pressure and heart rate changes between the 2 groups (Table 3). There were significant differences between the 2 groups in the increase in LVEF (Figure 4) and in the reduction



**Figure 3.** Efficacy of flow-triggered ASV and CPAP for AHI. A, Individual values for the AHI at baseline, titration study, and 3 months later. In the ASV group, AHI is significantly suppressed at the titration study, and further suppression is observed 3 months later ( $37.4 \pm 19.5/h$  at the baseline,  $4.7 \pm 5.5/h$  at the titration study, and  $1.9 \pm 2.1/h$ ). In contrast, in the CPAP study, AHI is also suppressed at the titration study; however, 3 months later, AHI is slightly increased ( $38.6 \pm 13.9/h$  at the baseline,  $9.6 \pm 10.0/h$  at the titration study, and  $15.4 \pm 12.8/h$  at 3 months later). B, Changes in AHI from baseline to 3 months later. Flow-triggered ASV induced a greater decrease in AHI than did CPAP ( $\Delta$ AHI,  $-35.4 \pm 19.5$  in the ASV group;  $-23.2 \pm 12.0$  in the CPAP group). \* $P < 0.01$ , † $P < 0.05$ .

of left ventricular end-systolic diameter and BNP (Table 3).

ASV significantly reduced urinary norepinephrine excretion, whereas CPAP did not. However, there were no significant differences in the reductions of urinary norepinephrine excretion between the 2 groups (Table 3).

The distance walked in 6 minutes increased significantly in the ASV group, whereas there was no such increase seen in the CPAP group. Thus, the increase in distance was significantly greater in the ASV group than in the CPAP group (Table 3).

### QOL Improvement

After 3 months of treatment, the improvement in QOL was significantly greater with ASV than with CPAP (Figure 5), especially in vitality and the subscales associated with the physical component score.

**Table 3. Blood Pressure, Heart Rate, and Cardiac Function**

|  | ASV Group (N=15) | CPAP Group (N=15) | P*    |
|--|------------------|-------------------|-------|
| <b>Systolic blood pressure, mm Hg</b>  |                  |                   |       |
| Baseline                               | 119.7 ± 17.0     | 120.3 ± 9.5       | 0.875 |
| 3 mo                                   | 118.2 ± 20.4     | 123.1 ± 10.0      |       |
| Δ                                      | -1.5 ± 11.0      | 2.8 ± 9.2         | 0.253 |
| <b>Diastolic blood pressure, mm Hg</b> |                  |                   |       |
| Baseline                               | 73.8 ± 12.7      | 75.7 ± 8.7        | 0.655 |
| 3 mo                                   | 74.7 ± 16.5      | 78.2 ± 7.4        |       |
| Δ                                      | 0.9 ± 11.2       | 2.5 ± 8.3         | 0.221 |
| <b>Heart rate, min</b>                 |                  |                   |       |
| Baseline                               | 70.0 ± 14.7      | 67.7 ± 11.4       | 0.575 |
| 3 mo                                   | 65.2 ± 13.3      | 68.3 ± 13.1       |       |
| Δ                                      | -4.8 ± 10.9      | 0.6 ± 13.7        | 0.243 |
| <b>Urinary norepinephrine, μg/L</b>    |                  |                   |       |
| Baseline                               | 177.2 ± 87.2     | 164.6 ± 86.4      | 0.693 |
| 3 mo                                   | 138.9 ± 75.5†    | 167.0 ± 90.2      |       |
| Δ                                      | -38.3 ± 87.3     | 2.5 ± 138.6       | 0.343 |
| <b>Plasma BNP, pg/mL</b>               |                  |                   |       |
| Baseline                               | 281.0 ± 303.9    | 235.8 ± 244.1     | 0.984 |
| 3 mo                                   | 245.5 ± 289.8†   | 239.3 ± 277.7     |       |
| Δ                                      | -35.5 ± 115.2    | -3.5 ± 119.2      | 0.006 |
| <b>Distance walked in 6 min, m</b>     |                  |                   |       |
| Baseline                               | 393.3 ± 61.5     | 409.3 ± 57.8      | 0.726 |
| 3 mo                                   | 428.3 ± 64.7†    | 400.6 ± 55.5      |       |
| Δ                                      | 35.0 ± 42.7      | -8.7 ± 70.1       | 0.008 |
| <b>LVEDD, mm</b>                       |                  |                   |       |
| Baseline                               | 62.9 ± 7.5       | 63.1 ± 7.2        | 0.829 |
| 3 mo                                   | 61.9 ± 8.1       | 62.9 ± 6.2        |       |
| Δ                                      | -1.0 ± 3.3       | -0.3 ± 2.6        | 0.504 |
| <b>LVESD, mm</b>                       |                  |                   |       |
| Baseline                               | 49.3 ± 10.6      | 50.3 ± 9.0        | 0.813 |
| 3 mo                                   | 45.5 ± 11.4†     | 49.9 ± 8.2        |       |
| Δ                                      | -3.7 ± 4.2       | -0.4 ± 3.7        | 0.028 |

LVEDD indicates left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter.

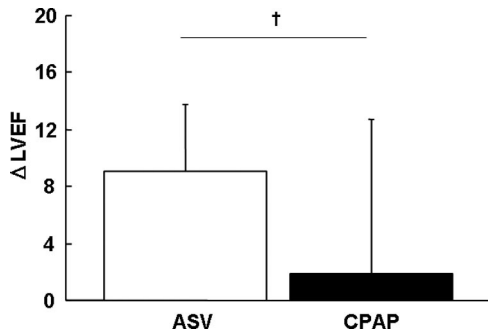
\* $P$  for between group comparisons.

† $P < 0.05$  vs baseline.

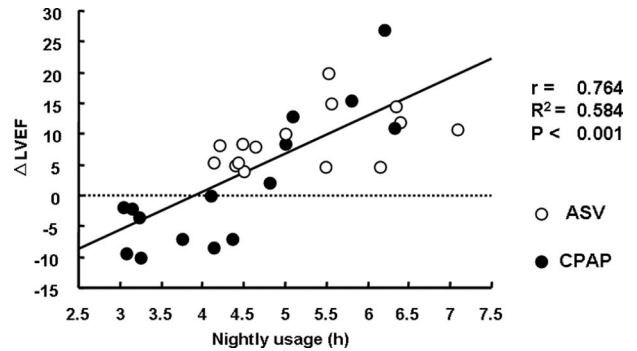
### Compliance With Treatment

During the study period, the compliance was  $5.2 \pm 0.9$  h/night with ASV and  $4.4 \pm 1.1$  h/night with CPAP group; compliance was significantly better with ASV than with CPAP.

A positive correlation between compliance and the increase in the LVEF was observed (Figure 6).



**Figure 4.** Efficacy of flow-triggered ASV and CPAP for changes in LVEF. There is a significant difference in the LVEF changes between the 2 groups ( $+9.1 \pm 4.7\%$  in the ASV group,  $+1.9 \pm 10.9\%$  in the CPAP group). † $P < 0.05$ .



**Figure 6.** Correlation between changes in LVEF and compliance. A significant positive correlation between  $\Delta$ LVEF and compliance (nightly usage [h]) is observed with flow-triggered ASV or CPAP at 3 months. The white circle indicates the ASV group, and the blue circle indicates the CPAP group.

**Discussion**

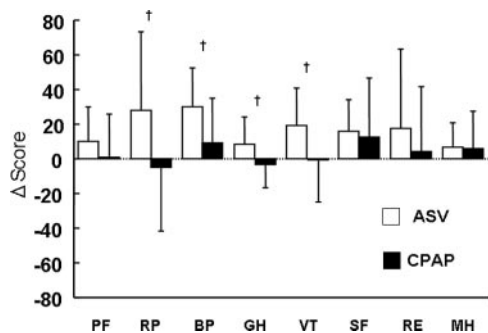
The presence of SDB is associated with higher mortality among patients with CHF,<sup>5-8</sup> and CPAP has been reported to be effective for both suppressing the abnormal breathing pattern and improving cardiac function in patients with CHF with either OSA or CSR-CSA.<sup>9-12</sup> However, there are insufficient data with regards to reductions in morbidity and mortality when treating SDB with CPAP in patients with CHF. A post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure trial demonstrated that increases in transplant-free survival were greater in patients in whom CPAP sufficiently suppressed SDB than in the control group.<sup>27</sup> This implies that CPAP treatment might improve long-term outcomes if SDB were sufficiently suppressed. On the other hand, poor compliance with CPAP is a major cause of concern. In the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure trial, CPAP use decreased after 12 months,<sup>13</sup> and it was suggested that decreased CPAP operating time might cause unanticipated results among patients with predominant

CSR-CSA. It was also reported that poor compliance with CPAP was associated with poor outcomes in patients with CHF with OSA.<sup>28</sup> Therefore, ASV, which was reported as a more effective option for suppressing abnormal breathing with better compliance than CPAP,<sup>14,19</sup> has been the focus of interest.

Based on this 3-month, randomized, parallel trial versus CPAP, flow-triggered ASV was superior for suppressing SDB, improving cardiac function, increasing the distance walked in 6 minutes, improving QOL, and compliance with the device. These results are comparable with those of other studies in which the efficacy of several positive airway pressure devices was investigated in patients with CHF with SDB,<sup>10-13,18-20,29-31</sup> but they differ in the following 2 aspects: flow-triggered ASV was not used; and patients with coexisting OSA and CSR-CSA were not enrolled.

The algorithm of this flow-triggered ASV differs from another type of ASV, volume-triggered ASV, in terms of the target parameter for the automatic adaptation, setting options, and pressure range. In particular, the algorithm for flow-triggered ASV allows the application of CPAP (minimal IPAP=EPAP) and enables one to define the back-up rate individually, whereas the volume-triggered ASV device applies a minimal difference of 3 cm · H<sub>2</sub>O between minimal IPAP and EPAP and has only an automatic back-up rate. Therefore, flow-triggered ASV is considered to be more practical for normalizing breathing in patients with coexisting OSA and CSR-CSA than volume-triggered ASV, which has been developed with a focus on patients with predominant CSR-CSA,<sup>16,17</sup> even though no studies have compared these 2 devices. Because patients with pure CSR-CSA are rare in the current clinical setting, it might be important to focus on patients with coexisting OSA and CSR-CSA. In fact, the percentage of central events was lower in this study than in other studies in which patients with  $\geq 70\%$  or  $80\%$  of central events were enrolled.<sup>18-20</sup> Therefore, it may be reasonable to presume that more patients can be regarded as candidates for treatment with this flow-triggered ASV.

In this study, SDB was sufficiently suppressed by flow-triggered ASV, whereas the efficacy of suppressing SDB in the CPAP group varied in each case. This varied response to CPAP is compatible with other studies.<sup>9,10,13,19,32</sup> Moreover,



**Figure 5.** Efficacy of flow-triggered ASV and CPAP for QOL assessed by SF-36. Of the 8 subscales of the SF-36, changes in RP ( $+28.3 \pm 45.2$  in the ASV group,  $-5.0 \pm 36.8$  in the CPAP group), BP ( $+30.1 \pm 22.0$  versus  $+9.3 \pm 25.7$ ), GH ( $+8.5 \pm 15.4$  versus  $-3.0 \pm 13.7$ ), and Vt ( $+19.0 \pm 22.2$  versus  $-0.3 \pm 23.7$ ) are significantly different, whereas changes in PF ( $+9.7 \pm 20.4$  versus  $+0.7 \pm 24.9$ ), SF ( $+15.7 \pm 18.5$  versus  $+12.6 \pm 33.8$ ), RE ( $+17.7 \pm 45.2$  versus  $+4.4 \pm 37.5$ ), and MH ( $+6.9 \pm 13.8$  versus  $+5.6 \pm 22.0$ ) show no significant difference between the 2 groups. † $P < 0.05$ . PF indicates physical functioning; RP, role limitations due to physical problems; BP, bodily pain; GH, general health perception; Vt, vitality; SF, social functioning; RE, role limitations due to emotional problems; MH, mental health.

some patients who responded to CPAP on the night of the titration study did not always sustain the response, whereas the response to the ASV was consistently good throughout the study period.

Compliance with the device was also of interest. Philippe et al<sup>19</sup> reported that compliance with volume-triggered ASV was greater than that with CPAP for 6 months after initiation in a prospective, parallel, randomized, multicenter trial. As well, in this study, compliance with flow-triggered ASV was significantly greater than with CPAP throughout the 3 months. Such greater compliance with flow-triggered ASV might be associated with (1) better comfort using the bilevel pressure setting, which might be induced by providing relatively lower pressure at expiration than at inspiration as described in the other studies using a bilevel device or volume-triggered ASV<sup>19,29,31</sup>; (2) automatic adaptation of pressure support, which may also be a source of better comfort; and (3) sufficient and constant alleviation of SDB, as shown in the other studies.<sup>18,19</sup>

Several studies have shown the efficacy of volume-triggered ASV for cardiac function in patients with CHF with predominant CSR-CSA. In a 1-month, randomized trial, volume-triggered ASV was reported to induce a significant reduction of plasma BNP and urinary catecholamine excretion compared with a subtherapeutic mode of volume-triggered ASV.<sup>18</sup> Philippe et al<sup>19</sup> also showed that improvements in the LVEF, and QOL, with this modality were greater than those with CPAP. Furthermore, Oldenburg et al<sup>20</sup> showed that volume-triggered ASV improved cardiopulmonary exercise testing parameters, in addition to other cardiac parameters, at 6 months in an observational cohort. On the other hand, data showing the efficacy of flow-triggered ASV in patients with CHF with SDB are sparse, and to date, no studies have investigated the efficacy of flow-triggered ASV for improvements in cardiac function. To the best of our knowledge, this study is the first to show the efficacy of flow-triggered ASV for changes in several parameters of cardiac function, such as LVEF, BNP level, and distance walked in 6 minutes.

There was a significantly greater improvement in LVEF in the ASV group ( $+9.1 \pm 4.7\%$ ) than in the CPAP group. This seems to be greater than that observed in other randomized studies that investigated the improvement in LVEF with several positive airway pressure devices in patients with CHF with CSR-CSA.<sup>10,13,18,19</sup> Reviewing previous studies, the improvement in LVEF by positive airway pressure in patients with CHF with predominant OSA was generally greater than that in patients with predominant CSR-CSA. Because patients with coexisting OSA and CSR-CSA were included, the improvement in LVEF was similar to that in patients with CHF with OSA rather than in patients with predominant CSR-CSA. Furthermore, such greater LVEF improvement in the ASV group in this study was corroborated by the slight reduction of left ventricular end-diastolic diameter and the significant reduction of left ventricular end-systolic diameter. Given this, ASV might be able to retard ventricular remodeling or reverse remodeling. However, the benefit for ventricular remodeling seems to still be controversial because of the relatively short follow-up periods. Therefore, a random-

ized trial assessing long-term outcomes including mortality, in addition to ventricular remodeling, is imminent.

Our primary hypothesis was that, compared with CPAP, flow-triggered ASV would result in better compliance with the device and greater improvement in cardiac function (ie, LVEF) in patients with CHF with coexisting OSA and CSR-CSA. In addition to the better compliance, this study showed significantly greater improvement in LVEF in the flow-triggered ASV group than in the CPAP group. Furthermore, there was a significant positive correlation between LVEF improvement and compliance with the device. This implies that better compliance with the device is an important factor for improvement of cardiac function in patients with CHF with SDB.

Another important finding of this study is that greater improvement in QOL assessed using the SF-36 was obtained with ASV than with CPAP. In particular, it has been reported that the vitality score was treatment sensitive in the OSA.<sup>26,33</sup> As anticipated and intuitively, the improvement in vitality was greater in the more effectively treated group, the ASV group.

### Limitations

This trial had several limitations. The first is the small number of patients, all of whom were men. However, despite this small number, significant superiorities in the improvement of cardiac function, QOL, and compliance were noted in the flow-triggered ASV group and were consistent with previous results obtained with volume-triggered ASV.<sup>18–20</sup> In addition, a recent study showed that male gender is a predictor of both OSA and CSR-CSA in patients with heart failure.<sup>34</sup> Hence, it is natural that male patients with heart failure with coexisting OSA and CSR-CSA were predominantly enrolled in this study. However, the efficacy of flow-triggered ASV for cardiac function among female patients with heart failure with coexisting OSA and CSR-CSA remains unknown.

The second limitation is the lack of a group with neither CPAP nor ASV. Given this, a further, randomized, prospective study that compares the changes in cardiac parameters of 3 groups (control, CPAP, and ASV groups) in patients with CHF with coexisting OSA and CSR-CSA is warranted.

The third is that blinding was not possible. However, the sonographers, the sleep specialists who scored the respiratory events, and the statistician who analyzed the data were completely blinded to the treatment assignment.

In conclusion, this showed that both CPAP and flow-triggered ASV reduced AHI, but flow-triggered ASV resulted in greater AHI reduction than CPAP, with consistent normalization of AHI. Compliance was significantly better with ASV than with CPAP. These differences may have contributed to the improvements in cardiac function and QOL in the ASV group and also suggest that patients with CHF may benefit more from treatment of coexisting OSA and CSR-CSA with flow-triggered ASV than with CPAP.

### Appendix

The following are all of the members of the Japanese trial to assess the effect of adaptive servo-ventilation in chronic heart failure



(JASV): Takatoshi Kasai, Koji Narui: Toranomon Hospital Sleep Center; Tomotaka Dohi, Sugao Ishiwata, Minoru Ohno, Tetsu Yamaguchi: Cardiovascular Center, Toranomon Hospital; Yasuhiro Usui, Yoshifumi Takata, Kihiko Asano, Kota Kato, Hirokazu Saruhara, Yuki Hashimura, Kazuki Shiina, Ryoko Asanuma, Akira Yamashina: Department of Cardiology, Tokyo Medical University; Kastuko Shoji: Central Clinical Laboratory, Tokyo Medical University; Toru Yoshioka, Yoshitaka Sugawara, Tomohiro Nakamura, Chikashi Suga, Shin-ichi Momomura: Cardiovascular Division, Saitama Medical Center, Jichi Medical University; Naotake Yanagisawa: Department of Cardiology, Juntendo University, School of Medicine.

## Disclosures

None.

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### CLINICAL PERSPECTIVE

In patients with chronic heart failure (CHF), the presence of sleep-disordered breathing, including either obstructive sleep apnea or Cheyne-Stokes respiration-central sleep apnea, is associated with a poor prognosis. A large-scale clinical trial showed that continuous positive airway pressure (CPAP) did not improve the prognosis of such patients with CHF, probably because of insufficient sleep-disordered breathing suppression. Recently, it was reported that adaptive servo-ventilation (ASV) can effectively treat sleep-disordered breathing. However, there are no specific data about the efficacy of flow-triggered ASV for cardiac function in patients with CHF with sleep-disordered breathing. The aim of this study was to compare the efficacy of flow-triggered ASV with CPAP in patients with CHF with coexisting obstructive sleep apnea and Cheyne-Stokes respiration-central sleep apnea. Thirty-one patients with CHF, defined as left ventricular ejection fraction <50% and New York Heart Association class  $\geq$ II, with coexisting obstructive sleep apnea and Cheyne-Stokes respiration-central sleep apnea, were randomly assigned to either CPAP or flow-triggered ASV. The suppression of respiratory events, changes in cardiac function, and compliance with the devices during the 3-month study period were compared. Although both devices decreased respiratory events, ASV more effectively suppressed respiratory events ( $\Delta$ AHI [apnea-hypopnea index]:  $-35.4 \pm 19.5$  with ASV,  $-23.2 \pm 12.0$  with CPAP,  $P < 0.05$ ). Compliance was significantly greater with ASV than with CPAP ( $5.2 \pm 0.9$  versus  $4.4 \pm 1.1$  h/night,  $P < 0.05$ ). The improvements in quality-of-life and LVEF were greater in the ASV group ( $\Delta$ LVEF:  $+9.1 \pm 4.7\%$  versus  $+1.9 \pm 10.9\%$ ). These results suggest that patients with coexisting obstructive sleep apnea and Cheyne-Stokes respiration-central sleep apnea may receive greater benefit from treatment with ASV than with CPAP.