Real-world Data of Adaptive Servo-ventilation Therapy for Patients with Heart Failure with Reduced Ejection Fraction: Three-year Follow-up Data Based on Comparison with Standard Medical Therapy

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Abstract

Background: Sleep-disordered breathing (SDB) is a cause of heart failure. Adaptive servo-ventilation (ASV) is one of the treatments for SDB. Recently, ASV has been applied to the treatment of patients with heart failure and SDB. The aim of this study was to estimate whether ASV therapy is effective and safe for patients with heart failure with reduced ejection fraction (HFrEF) compared with standard medical therapy in the real world, using three-year follow-up data.

Methods: The patients with HFrEF (n=186) were treated with standard medical therapy plus ASV therapy (ASV group; n=57) or standard medical therapy alone (control group; n=129). We followed up the patients for 3 years.

Results: The ASV group had significantly lower baseline left ventricular ejection fraction than the control group (27.9 ± 8.6% vs. 34.1 ± 8.8%; P<0.0001). Baseline brain natriuretic peptide (BNP) did not differ significantly between the groups. On follow-up, the changes in BNP level indicated that the ASV group showed significantly better improvement than the control group. There was no significant difference between the groups in the rate of fatal cardiovascular events (P=0.190, log-rank test).

Conclusion: ASV therapy was effective for the treatment of HFrEF, and the rate of fatal cardiovascular events were not higher in the ASV group in the real world.

Keywords: Adaptive servo-ventilation; Sleep-disordered breathing; Heart failure with reduced ejection fraction

Introduction

Sleep-disordered breathing (SDB) is a cause of heart failure. A previous report showed that SDB increased fatal cardiovascular events and all-cause mortality [1]. SDB in patients with cardiovascular disease is related to a poor long-term prognosis. Furthermore, the presence of obstructive sleep apnea is a strong predictor of fatal cardiovascular events [2].

Adaptive servo-ventilation (ASV) is one of the treatments for central sleep apnea (CSA) and Cheyne-Stokes respiration [3,4]. Recently, ASV has also been applied to the treatment of patients with heart failure and SDB [5-10]. ASV improves not only the short-term prognosis (symptoms, cardiac function, renal function, left ventricular ejection fraction (LVEF), and brain natriuretic peptide (BNP) levels) but also the long-term prognosis in patients with heart failure, regardless of the severity of SDB [8,9,11-24]. We previously reported that ASV therapy was effective for patients with heart failure and SDB [12,13,21,25].

However, the SERVE-HF trial showed that ASV therapy could not reduce mortality and morbidity in patients with heart failure with reduced ejection fraction (HFrEF) [26]. We reported the effectiveness and safety of ASV therapy for patients with HFrEF [13,21] before the SERVE-HF trial was published, and continue the follow-up of these patients compared with those treated with standard medical therapy. Our aim in this study was to determine whether ASV therapy is effective and safe for patients with HFrEF compared with standard medical therapy in the real world using three-year follow-up data.

Materials and Methods

The study enrolled 186 patients with HFrEF (mean age, 70 ± 12 yrs). The study was a single-center, retrospective observational cohort study conducted at Isesaki Municipal Hospital, Japan. We obtained informed consent from all patients and approval from the hospital’s Institutional Review Board for Human Research.

We defined patients with HFrEF as patients with heart failure and LVEF<45%. The underlying diseases for heart failure were coronary artery disease, valvular heart disease, cardiomyopathy, and arrhythmia. The patients had New York Heart Association Class II–IV symptoms. All patients were treated with standard medical therapy in the acute phase of heart failure. Standard medical therapy was the optimal medical therapy for heart failure, including beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin-converting enzyme receptor inhibitors, and diuretics. After their physical condition was stabilized, the patients were divided into two groups. ASV therapy for the patients with HFrEF (ASV group; n=57) was conducted in our team. The
patients with HFrEF using standard medical therapy alone in the same period of the ASV group were enrolled as control group (n=129).

We conducted a three-year follow-up between June 2006 and December 2015 to determine the rate of fatal cardiovascular events. The average period of observation was 1215 days (range, 848–1642) for the ASV group and 1004 days (range, 133–2579) for the control group. All patients in both groups were treated with optimal medical therapy during the observation period. We performed full-night PSG examination for all patients in the ASV group with a digital polygraph (P-Series Plus; Compumedics, Abbotsville, Australia). Arterial oxygen saturation was measured using pulse oximetry with a finger probe (Nonin 8000J Adult Flex Sensor). Thoracic and abdominal movements and nasal flow were measured as respiratory data with two inductive respiratory bands and an airflow pressure transducer. We evaluated sleep condition with an electroencephalogram, an electrooculogram, and a chin electromyogram from multiple electrodes placed at appropriate positions. We placed electrodes on both lower limbs to evaluate leg movements, including restless leg syndrome. We determined sleep stage and arousal based on generally accepted definitions and methods [27-29]. Apnea, hypopnea, sleep stage, and arousal were defined by the diagnostic criteria of the American Academy of Sleep Medicine Task Force [29].

Patients in the ASV group applied an ASV device (AutoSet-CS; ResMed, Sydney, Australia) with a full facemask (ResMed) (P-Series Plus; Compumedics, Abbotsville, Australia). Arterial oxygen saturation was measured at baseline and during the observation period. We performed full-night polysomnography. We set the expiratory and inspiratory backup respiratory rate for apnea or hypopnea worked at 15 breaths/min. The ASV device assisted the patient's breathing using expiratory positive airway pressure and inspiratory support in the presence of worsening respiratory status with increased apnea or hypopnea. We recorded the patient's compliance with the ASV device while they were using the device.

We diagnosed and defined hypertension, dyslipidemia, and diabetes mellitus as coronary risk factors according to standard criteria. LVEF was measured using transthoracic echocardiography with a modification of Simpson's method. LVEF and blood levels of BNP were measured at baseline and after 6 months.

The primary purpose of the study was to evaluate the long-term effects of ASV therapy, measured using the rate of fatal cardiovascular events, including death from myocardial infarction, cardioembolic stroke, and arrhythmia, over a period of 3 yrs. The secondary purpose was to evaluate the short-term effects of ASV therapy (using BNP levels and LVEF) at 6 months compared with baseline.

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The data are presented as mean ± standard deviation or median (interquartile range). Baseline characteristics were compared between the two groups using the t-test for normally distributed data and the Mann–Whitney U test for non-normally distributed continuous variables. Fisher's exact test or the χ² test was used for categorical variables. Paired t-tests were conducted to evaluate the short-term outcomes. The statistical tests were two-tailed, and a P value <0.05 was considered to indicate a statistically significant difference. Fatal cardiovascular event rates were analyzed using the Kaplan–Meier method, and comparisons between the two groups were conducted using the log-rank test. All statistical analyses were performed with JMP version 10 software.

### Results

#### Patient characteristics

Table 1 shows the baseline characteristics of the patients. The two groups differed significantly in age: 66 ± 10.4 yrs in the ASV group vs. 72 ± 11.4 yrs in the control group (P<0.01). The groups did not differ in sex ratio or body mass index.

|                        | Patients (n=186) | Heart failure | P value |
|------------------------|-----------------|---------------|---------|
| **ASV group**          |                 |               |         |
| Age, years             | 66 ± 10.4       | 72 ± 11.4     | 0.0011  |
| Male, n (%)            | 47 (82.5)       | 93 (72.1)     | 0.145   |
| Body mass index (kg/m²)| 25.0 ± 0.820    | 22.8 ± 0.783  | 0.0625  |
| **Control group**      |                 |               |         |
| New York Heart Association Classification                   |               |         |
| II, n (%)              | 12 (21.0)       | 96 (74.4)     | <0.001  |
| III, n (%)             | 38 (66.7)       | 30 (23.3)     | <0.001  |
| IV, n (%)              | 7 (12.2)        | 3 (2.30)      | <0.001  |
| **Underlying heart disease** |             |               |         |
| ICM, n (%)             | 21 (36.8)       | 70 (54.3)     | 0.0383  |
| Valvular heart disease, n (%) | 5 (8.77) | 10 (7.75) | 0.778  |
| Cardiomyopathy, n (%)  | 30 (52.6)       | 29 (22.5)     | <0.001  |
| Arhythmia, n (%)       | 0 (0)           | 4 (3.10)      | 0.314   |
| Others, n (%)          | 1 (1.75)        | 16 (12.4)     | 0.0245  |
| **Drug therapy**       |                 |               |         |
| β-blocker              | 25 (43.9)       | 49 (38.0)     | 0.516   |
| ARBs/ACE inhibitors    | 31 (54.4)       | 71 (55.0)     | 0.999   |
| **Coronary risk factors** |             |               |         |
| Hypertension           | 31 (54.3)       | 115 (89.2)    | <0.001  |
| Dyslipidemia           | 22 (38.6)       | 57 (44.2)     | 0.611   |
| Diabetes mellitus      | 21 (36.8)       | 31 (24.0)     | 0.0952  |
| Blood pressure (mmHg)  |                 |               |         |
| Systolic               | 122 ± 16.1      | 119 ± 19.3    | 0.29    |
| Diastolic              | 70.5 ± 10.3     | 67.2 ± 13.4   | 0.126   |
| Blood triglycerides (mg/dl) | 129 ± 83.1     | 122 ± 60.8    | 0.533   |
| HDL-cholesterol (mg/dl) | 48.3 ± 15.2    | 54.0 ± 14.4   | 0.0285  |
| LDL-cholesterol (mg/dl) | 110 ± 38.4     | 115 ± 34.0    | 0.585   |
| Fasting blood sugar (mg/dl) | 103 ± 22.0     | 136 ± 67.3    | <0.001  |
| LVEF (%)               | 27.9 ± 8.62     | 34.1 ± 8.83   | <0.001  |
We divided the underlying diseases for heart failure into five categories: ischemic cardiomyopathy (ICM), valvular heart disease, cardiomyopathy, arrhythmia, and others. The rates of ICM and cardiomyopathy were significantly different between the groups: ICM, 36.8% in the ASV group vs. 54.3% in the control group (P=0.0383); cardiomyopathy, 52.6% in the ASV group vs. 22.5% in the control group (P<0.01).

All patients received optimal medical therapy for heart failure (beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin-converting enzyme receptor inhibitors) before being enrolled in the present study. No significant differences in optimal medical therapy were observed between the two groups.

We recorded hypertension, dyslipidemia, and diabetes mellitus as coronary risk factors in all patients. The rate of hypertension was significantly lower in patients with ASV therapy than in those without ASV therapy (54.3% vs. 89.2%; P<0.001). There were no significant differences between the groups in blood triglycerides, low-density lipoprotein cholesterol, or BNP. High-density lipoprotein (HDL) cholesterol, fasting blood sugar, and LVEF were significantly lower in the ASV group than in the control group: HDL cholesterol, 48.3 ± 15.2 vs. 54.0 ± 14.4 mg/dl (P<0.0285); fasting blood sugar, 103.0±22.0 vs. 136 ± 67.3 mg/dl (P<0.001); LVEF, 27.9 ± 8.62% vs. 34.1 ± 8.83% (P<0.001).

Sleep study

Table 2 shows the sleep study with full-night polysomnography in the ASV group before ASV therapy. The average total sleeping time was 299 ± 121 min. The apnea hypopnea index was 43.3 ± 26.4/h. We also recorded the CSA index (14.7 ± 17.6/h) and obstructive sleep apnea (5.64 ± 9.87/h).

Table 1: Patients characteristics; Values are means ± standard deviation; HF: Heart Failure; ASV: Adaptive Servo Ventilation; ICM: Ischemic Cardiomyopathy; ARBs: Angiotensin Receptor Blockers; ACE inhibitors: Angiotensin Converting Enzyme inhibitors; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; LVEF: Left Ventricular Ejection Fraction; BNP: Brain Natriuretic Peptide.

Rates of fatal cardiovascular events

Figure 1 shows the fatal cardiovascular event-free rates in the groups over three years. No significant differences were observed between the two groups (P=0.190, log-rank test). Table 3 shows baseline LVEF and BNP in patients with fatal cardiovascular events. Among patients with fatal cardiovascular events, baseline LVEF was significantly lower in the ASV group than in the control group (27.9 ± 1.31% vs. 34.8 ± 0.823%; P<0.01). However, there was no significant difference between the groups in baseline BNP among patients with fatal cardiovascular events: ASV group, 349 (range, 164–647); control group, 272 (range, 90–598) (P=0.340).

Table 2: Polysomnography; Values are means ± standard deviation; HF: Heart Failure; SDB: Sleep Disordered Breathing, NREM: Non-rapid Eye Movement; REM: Rapid Eye Movement; AHI: Apnea Hypopnea Index; CSA: Central Sleep Apnea; OSA: Obstructive Sleep Apnea; ODI: Oxygen Desaturation Index.

Table 3: LVEF and BNP in the patients with Fatal Cardiovascular Events; Values are presented as means ± standard deviation or median (interquartile range); LVEF: Left Ventricular Ejection Fraction; BNP: Brain Natriuretic Peptide.
Changes in BNP level and LVEF

Figures 2A and 2B show changes in BNP levels (ΔBNP) and LVEF (ΔLVEF), respectively, from baseline to 6 months. ΔBNP and ΔLVEF were significantly different in the ASV and the control group. ΔBNP was -167 (–433 to –67) in the ASV group and -66 (–191 to –63.4) in the control group (P=0.017). ΔLVEF was 11.9 ± 2.10% in the ASV group and -3.36 ± 4.25% in the control group (P=0.0024).

Figure 2: Changes in (A) BNP levels (ΔBNP) and (B) LVEF (ΔLVEF) in 6 months in the ASV group and the control group; ΔBNP and ΔLVEF are significantly different between the two groups; ASV: Adaptive Servo-Ventilation; BNP: Brain Natriuretic Peptide; LVEF: Left Ventricular Ejection Fraction.

Changes in New York heart association (NYHA)
classification

Table 1 shows each NYHA classification in ASV group was significantly severe, compared to control group (P<0.001). Figures 3A and 3B show changes in NYHA classification from baseline to 6 months and 1 yr. However, ASV therapy improved the NYHA classification significantly after 6 months (P<0.001) and 1 year (P<0.001), rather than only standard medical therapy.

Figure 3: Changes of NYHA classification in (A) ASV group and (B) control group from baseline to 6 months and 1 year; NYHA classification was improved in the ASV group from baseline to 6 months (P<0.001) and 1 year (P<0.001); However, no significant difference of NYHA classification was observed in control group from baseline to 6 months and 1 year.

Discussion

This study had two important clinical results. First, ASV therapy did not significantly increase the rate of fatal cardiovascular events compared with optimal medical therapy alone, although LVEF was significantly lower in patients with ASV therapy than in patients without ASV therapy [30,31]. Second, ΔBNP and ΔLVEF were improved significantly in patients with ASV therapy, compared with patients without ASV therapy. First, ASV therapy did not significantly increase the rate of fatal cardiovascular events compared with optimal medical therapy alone, although LVEF was significantly lower in patients with ASV therapy than in patients without ASV therapy. Previous research suggested that SDB was related to heart failure, coronary artery disease, and mortality [1,2,32-38]. Various strategies against SDB have been developed in recent years. We previously reported that ASV therapy was effective in patients with heart failure and SDB with respect to BNP, LVEF, and prognosis [12,21,25]. Other researchers reported comparable results [5-11,14-20,22-24]. As far as we know, there are no reports of the effect of ASV therapy in patients with HFrEF, compared with control groups, with real-world data.

A recent randomized, controlled trial [26] suggested that ASV therapy in patients with HFrEF increased all-cause and cardiovascular mortality. However, the methods of the study had some limitations with respect to the inclusion criteria. The study included a selection bias. The ASV group included patients who discontinued ASV therapy along the way, whereas the control group included patients who started ASV therapy along the way. Our study does not have that selection bias, since we exactly divided all patients into an ASV group and a control group, due to retrospective study. Furthermore, adherence to ASV therapy in the present study was high compared with the recent study [26]. Our real-world data in the present study revealed that there was no significant difference between the two groups, although LVEF in the patients with ASV therapy was significantly lower than in the patients without ASV therapy.

Second, ΔBNP and ΔLVEF were significantly improved in patients with ASV therapy, compared with patients without ASV therapy. Previous studies reported that ASV therapy for patients with HFrEF improved BNP levels and the patients’ prognosis [39-41]. The present study showed that ASV therapy significantly improved BNP in patients with HFrEF, although baseline LVEF was significantly lower in the ASV group than in the control group.

The present study has two limitations. First, it does not have as strong evidence as a randomized, controlled trial because it is a retrospective observational study. There is a possibility that the present study has a selection bias in the results of fatal cardiovascular events. ASV therapy has a tendency to be applied to patients with relatively severe heart failure (Tables 1 and 3). However, Cowie et al. reported that ASV therapy was harmful to patients with HFrEF [26]. Therefore, we could not design a prospective study of ASV therapy for HFrEF. It was necessary to examine the effect of ASV therapy in patients with HFrEF in a retrospective study. The rate of use of beta-blockers in the present study may be low compared with that in our recent study due to old data, although no significant difference was observed in the rate of use of beta-blockers between the groups.

Second, there are significant differences in the underlying diseases between the groups in the present study. It is not clear whether ASV therapy is effective for specific underlying diseases, such as ICM or cardiomyopathy. Therefore, we cannot deny the possibility that the effect of ASV therapy on the specific underlying disease affects the result of this study. We need to clarify the effects of underlying disease in future studies.

ASV therapy did not significantly increase the rate of fatal cardiovascular events, compared with optimal medical therapy alone, although LVEF was significantly lower in patients with ASV therapy than in patients without ASV therapy. ΔBNP and ΔLVEF were
improved significantly in patients with ASV therapy, compared with patients without ASV therapy. There is a possibility that ASV therapy may be effective for patients with HFrEF with respect to long-term and short-term prognosis. ASV therapy for patients with HFrEF is worth considering in case of the more number of populations.

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