Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.7439-21
Intern Med 60: 3551-3558, 2021
http://internmed.jp

【 ORIGINAL ARTICLE 】

# Adaptive Servo-ventilation Therapy Results in the Prevention of Arrhythmias in Patients with Heart Failure Due to Ischemic Heart Disease

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**Abstract:**

**Objective** Whether or not adaptive servo-ventilation (ASV) is effective in preventing arrhythmias in patients with heart failure (HF) due to ischemic heart disease (IHD) is unclear. This study estimated the effects of ASV therapy on arrhythmias in patients with HF due to IHD.

**Methods** One hundred and forty-one consecutive hospitalized patients with HF due to IHD (mean age: 74.9 ±11.9 years old) were retrospectively assessed in this study. Of the 141 patients, 75 were treated with ASV (ASV group), and 66 were treated without ASV (Non-ASV group). We estimated the incidence of arrhythmias, including paroxysmal atrial fibrillation (PAF) and ventricular tachycardia (VT), during one-year follow-up in both groups using multivariable logistic regression models.

**Results** Men accounted for 55.3% of the study population. There were no significant differences in the baseline clinical characteristic data between the ASV and Non-ASV groups with respect to age, sex, heart rate, risk factors, oral medication, or laboratory data, including the estimated glomerular filtration rate (eGFR), brain natriuretic peptide, and left ventricular ejection fraction. ASV therapy was associated with a reduced incidence of arrhythmia after adjusting for demographic and cardiovascular disease risk factors (odds ratio, 0.27; 95% confidence interval, 0.11 to 0.63; $p<0.01$; compared to the Non-ASV group). In addition, at the 1-year follow-up, an improvement (increase) in the eGFR was found in the ASV group but not in the Non-ASV group.

**Conclusion** ASV therapy was able to prevent arrhythmias, including PAF and VT, with short-term improvements in the renal function in patients with HF due to IHD.

**Key words:** heart failure, adaptive servo-ventilation, sleep-disordered breathing, safety and efficacy

**(Intern Med 60: 3551-3558, 2021)**
**(DOI: 10.2169/internalmedicine.7439-21)**

## Introduction

Sleep apnea may be present in several cardiovascular diseases (CVDs), such as congestive heart failure (HF), arrhythmia, and coronary artery disease (1-4). Furthermore, sleep-disordered breathing (SDB) often accompanies HF and is closely related to the incidence of cardiovascular events and mortality. Adaptive servo-ventilation (ASV), a form of noninvasive positive pressure ventilation, offers superior tolerability and simple operability based on the provision of support pressure. The positive pressure is synchronized to the respiratory patterns of each patient through its device algorithm. ASV was developed to treat central sleep apnea (CSA), which is a subtype of SDB and accompanies congestive HF.

The Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo-Ventilation in Patients with Heart Failure (SERVE-HF) trial did not show a statistically significant difference between

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Received: March 2, 2021; Accepted: April 12, 2021; Advance Publication by J-STAGE: June 5, 2021
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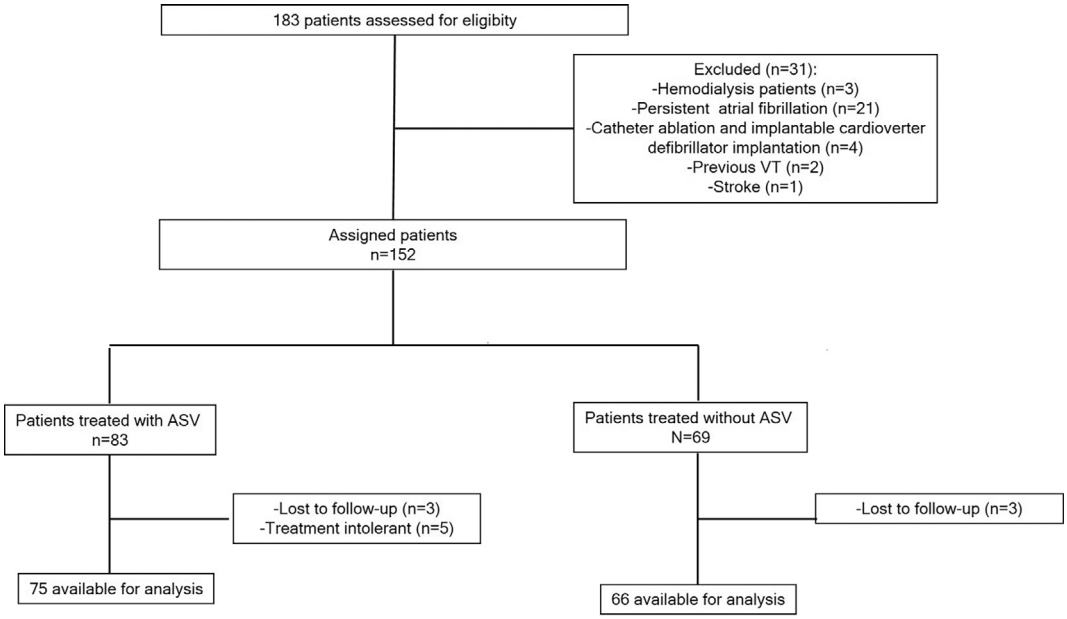


**Figure 1. Flow chart of the study participants. ASV: adaptive servo-ventilation, VT: ventricular tachycardia**

patients randomized to ASV and the control group with regard to the primary endpoint of time to all-cause mortality or unplanned hospitalization for worsening HF (5). However, many studies have revealed the benefits of ASV therapy in HF patients. In addition, several studies have shown that ASV therapy can prevent fatal cardiovascular events and improve the survival of HF patients and is beneficial even in patients who suffer from SDB (6-9). At present, ASV therapy is one of the most important methods for improving HF in clinical practice in Japan (9).

Arrhythmias often occur in patients with HF and affect the prognosis. Arrhythmias might be particularly severe and serious in patients with HF due to ischemic heart disease (IHD) (10, 11). While it has been increasingly recognized that ASV therapy is effective for HF, whether or not ASV therapy is effective in preventing arrhythmias in patients with HF remains unclear.

The present study explored whether or not ASV therapy exerted beneficial effects on arrhythmias in patients with HF due to IHD.

## Materials and Methods

### Study population

This was a multicenter, retrospective observational study. We retrospectively screened 183 consecutive patients with HF due to IHD hospitalized between April 2014 and March 2016 at Maebashi Red Cross Hospital and Gunma University Hospital. IHD patients were defined as patients who were diagnosed via coronary angiography or some other modalities, including treadmill stress tests, stress echocardiography, single-photon emission computed tomography, and computed tomography coronary angiography. After excluding patients with persistent, long-standing persistent, or permanent atrial fibrillation (AF) (n=21); a history of ventricular tachycardia (VT) (n=2); a history of catheter ablation and implantable cardioverter defibrillator implantation (n=4); stroke in the acute phase (n=1); and hemodialysis (n=3), 152 HF patients were divided into 2 groups of 83 patients treated with ASV (ASV group) and 69 treated without ASV (Non-ASV group).

The implementation of ASV therapy was decided by the attending physician based on the condition of each patient, regardless of the presence of SDB. In addition, we excluded patients who finished ASV treatment because of mask intolerance (n=5) and those who were lost to follow-up (n=3). Ultimately, 141 HF patients (75 in the ASV group and 66 in the Non-ASV group) were included (Fig. 1).

The study was conducted in accordance with the recommendations of the Declaration of Helsinki (1975). The protocol was approved by the Institutional Review Committee of Maebashi Red Cross Hospital and Gunma University Hospital, and the need to obtain informed consent was waived.

### Treatment devices/initiation of ASV

In this study, we used ASV (AutoSet-CS; ResMed, Sydney, Australia) together with a best-fitted full-face mask (ResMed). The device automatically detects the patient's breathing patterns and provides proper pressure support that is synchronized to these patterns through its fuzzy logic algorithms. It consisted of an expiratory positive airway pressure of 4 $cmH_2O$ and suitable minimum-maximum inspiratory support that was within the minimum manufacturer setting range of 3-8 $cmH_2O$. The backup respiratory rate was 15 breaths/min. Basically, the setting ranges, including the expiratory positive airway pressure and inspiratory support,

were fixed. If we detected persistent apnea during ASV therapy, ASV titration was performed as necessary. Compliance was assessed based on the ASV use (hours per night) obtained from the data recorded on a memory card built into the ASV device.

In the ASV group, ASV therapy was initiated immediately after admission with medication for acute decompensated HF.

### Outcomes

Patients were followed up for one year after hospitalization due to HF. The primary outcome was the incidence of arrhythmia events, including paroxysmal atrial fibrillation [PAF; defined as AF or atrial flutter on each monitoring or electrocardiogram (ECG) recording] and ventricular tachycardia (VT; defined as non-sustained or sustained VT on each monitoring or ECG recording) during the follow-up period.

### Baseline and follow-up examinations

The baseline was defined as the time of admission for HF. Baseline data, including demographic, laboratory, and echocardiographic variables, were obtained. Echocardiography and ECG recordings were performed at baseline and at the one-year follow-up. All patients were subjected to ECG monitoring to detect arrhythmias during hospitalization. Patients also underwent a Holter ECG at one month after discharge. The left ventricular ejection fraction (LVEF) was calculated using a modified Simpson's method with echocardiography. Conventional blood samples to determine the plasma brain natriuretic peptide (BNP) and creatinine levels were obtained at baseline and follow-up after ASV therapy. The estimated glomerular filtration rate (eGFR) was determined using the four-variable abbreviated modification of diet in renal disease formula. Each patient's blood pressure and heart rate were recorded three times in the supine position and averaged.

### Statistical analyses

In the results, continuous variables are expressed as the mean ± standard deviation (SD), and categorical variables are expressed as numbers and percentages. The differences in the baseline characteristics between the two groups were determined using the unpaired Student's *t*-test for continuous variables and the chi-square test for discrete variables.

We used multivariable logistic regression models to analyze the association between ASV therapy and arrhythmia events. Model 1 was adjusted for demographic factors (age, sex, and body mass index), and model 2 was adjusted for risk factors (New York Heart Association class, systolic blood pressure, heart rate, hypertension, diabetes, dyslipidemia, smoking, estimated GFR, LVEF, and anti-arrhythmia drug use). Significance was considered at a p-value of $< 0.05$. Statistical analyses were performed using the software programs IBM SPSS (Statistical Package for the Social Sciences) Statistics ver. 24.0 (International Business Machines Corporation, Armonk, USA) and Stata ver. 15.0 (Stata Corp, College Station, USA).

## Results

### Patient characteristics

The clinical characteristics of the ASV and Non-ASV groups are presented in Table 1. The mean age of the study population was 74±12 years old, and 55.3% of the patients were men. There were no significant differences in the baseline clinical characteristic data between the ASV and Non-ASV groups with respect to the age, sex, heart rate, risk factors (including diabetes mellitus, dyslipidemia, and hypertension), oral medication, laboratory data (including estimated GFR and plasma BNP levels), or LVEF.

### Incident arrhythmia (AF and VT)

A total of 67 patients (48%) experienced arrhythmia events, including PAF and VT. The ASV group had fewer arrhythmia events, including PAF and VT, than the Non-ASV group (36% vs. 61%, p=0.004; PAF, 23% vs. 44%, p=0.007; VT, 16% vs. 30%, p=0.043). The multivariable logistic regression models are presented in Table 2. ASV therapy was associated with a lower incidence of arrhythmias than the Non-ASV group after adjusting for demographic and CVD risk factors [odds ratio (OR), 0.27; 95% confidence interval (CI), 0.11 to 0.63; p<0.01; compared to the Non-ASV group]. The ASV group also had a significantly lower OR for PAF (OR, 0.27; 95% CI, 0.12 to 0.64; p<0.01) and tended to have a lower OR for VT (OR, 0.33; 95% CI, 0.11 to 1.01; p=0.052) than the Non-ASV group in the multivariable adjusted models.

### Changes in clinical parameters during the study period

At the one-year follow-up, there were no significant differences in the BNP, estimated GFR, or LVEF between the two groups (Table 3). However, an improvement (increase) in the estimated GFR was found in the ASV group, but not in the Non-ASV group. The adjusted mean for change in the eGFR in the ASV group after adjusting for demographic and CVD risk factors was higher than that in the Non-ASV group (3.3 vs. -3.0, p=0.043). There were no significant differences in the adjusted mean for change for BNP or the LVEF between the two groups (Fig. 2).

## Discussion

Our study results showed that ASV had beneficial effects in terms of preventing arrhythmia events, including PAF and VT, in HF patients.

In Japan, ASV is widely used in clinical practice to treat not only SDB but also HF, owing to its hemodynamics-improving effect, even if patients do not have SDB or only have mild SDB (12). However, the SERVE-HF study indi-

**Table 1. Comparisons of Baseline Characteristics between the Non-adaptive Servo-ventilation and Adaptive Servo-ventilation Groups.**

| | All participants (n=141) | ASV (n=75) | Non-ASV (n=66) | p value |
|---|---|---|---|---|
| Age (years) | 73.91 (11.96) | 72.77 (11.45) | 75.21 (12.48) | 0.23 |
| Male (n, %) | 78 (55.3%) | 42 (56%) | 36 (55%) | 0.86 |
| NYHA classes | | | | |
| I | 34 (24.1%) | 19 (25%) | 15 (23%) | 0.98 |
| II | 61 (43.3%) | 32 (43%) | 29 (44%) | |
| III | 37 (26.2%) | 19 (25%) | 18 (27%) | |
| IV | 9 (6.4%) | 5 (7%) | 4 (6%) | |
| BMI (kg/cm$^2$) | 21.92 (3.09) | 22.79 (3.02) | 20.93 (2.89) | <0.001 |
| SBP, mmHg | 118.63 (20.71) | 119.67 (20.69) | 117.45 (20.84) | 0.53 |
| Heart rate (bpm) | 72.74 (13.89) | 72.28(14.36) | 73.27 (13.42) | 0.67 |
| Hypertension (n, %) | 80 (56.7%) | 44 (59%) | 36 (55%) | 0.62 |
| Diabetes (n, %) | 69 (48.9%) | 41 (55%) | 28 (42%) | 0.15 |
| Dyslipidemia (n, %) | 41 (29.1%) | 21 (28%) | 20 (30%) | 0.76 |
| Smoking (n, %) | 54 (38.3%) | 30 (40%) | 24 (36%) | 0.66 |
| Medications | | | | |
| ACE inhibitors/ARBs (n, %) | 72 (51.1%) | 42 (56%) | 30 (45%) | 0.21 |
| Beta-blockers (n, %) | 78 (55.3%) | 43 (57%) | 35 (53%) | 0.61 |
| Diuretics (n, %) | 119 (84.4%) | 65 (87%) | 54 (82%) | 0.43 |
| Anti-arrhythmia drugs (n, %) | 10 (7.1%) | 4 (5%) | 6 (9%) | 0.39 |
| Laboratory data | | | | |
| BNP (pg/mL) | 941.26 (759.92) | 995.31 (812.67) | 879.85 (696.24) | 0.37 |
| eGFR (mL/min/1.73 cm$^2$) | 49.62 (24.02) | 50.07 (24.37) | 49.10 (23.78) | 0.81 |
| Cr (mg/dL) | 1.24 (0.61) | 1.23 (0.58) | 1.26 (0.65) | 0.71 |
| Echocardiographic data | | | | |
| LVEF (%) | 39.45 (14.87) | 37.93 (14.80) | 41.18 (14.88) | 0.2 |
| LAD (mm) | 40.62 (10.08) | 40.17 (10.91) | 41.14 (9.10) | 0.57 |
| LVD (mm) | 51.57 (11.48) | 50.96 (12.59) | 52.26 (10.12) | 0.5 |
| Arrhythmia | 67 (47.5%) | 27 (36%) | 40 (61%) | 0.004 |
| PAF | 46 (32.6%) | 17 (23%) | 29 (44%) | 0.007 |
| VT | 32 (22.7%) | 12 (16%) | 20 (30%) | 0.043 |
| Revascularization | | | | |
| PCI (n, %) | 90(63.8%) | 49(65.3%) | 41(62.1%) | 0.35 |
| CABG (n, %) | 3(2.1%) | 2(2.7%) | 1(1.5%) | 0.32 |

Results are expressed as the mean (standard deviation) unless specified otherwise.

ACE: angiotensin-converting enzyme, AF: atrial fibrillation, ARB: angiotensin II receptor blocker, ASV: adaptive servo-ventilation, BMI: body mass index, BNP: brain natriuretic peptide, CABG: coronary artery bypass grafting, Cr: creatinine, eGFR: estimated glomerular filtration rate, LAD: left atrial dimension, LVEF: left ventricle ejection fraction, LVD: left ventricular dimension, NYHA: New York Heart Association, PAF: paroxysmal atrial fibrillation, PCI: percutaneous coronary intervention, SBP: systolic blood pressure, VT: ventricular tachycardia

cated that study participants who received ASV therapy as treatment for moderate to severe predominant CSA had an increased risk of cardiovascular mortality compared to the control group. In addition, ASV therapy revealed no improvement in subjective symptoms (5). However, there are some differences, especially in the ASV setting, between the SERVE-HF study and clinical practice in Japan; for example, the expiratory and inspiratory positive airway pressures are lower in clinical practice than they were in the SERVE-HF study. There is a possibility that excessive positive airway pressure may have increased the risk of cardiovascular mortality because the pressure decreased the cardiac output, leading to increased cardiac events, including arrhythmia.

A few studies have shown the effects of ASV on arrhythmia in HF patients. Piccini et al. conducted a sub-analysis of the Cardiovascular Improvements with Minute Ventilation-Targeted ASV Therapy in Heart Failure (CAT-HF) study and reported that the treatment of SDB with ASV led to a reduction in AF compared with optimal medical therapy alone, without inducing an increase in VT or ventricular fibrillation events among patients with HF and SDB (13). In a sub-analysis of a randomized trial, Priefert et al. reported that ASV therapy may reduce nocturnal ventricular extrasystole, couplets, and non-sustained VT among heart failure-reduced ejection fraction (HFrEF) patients with SDB (14). The present study showed a beneficial effect of ASV therapy (i.e., the prevention of the incidence of arrhythmias, including PAF and VT) using the data of patients

**Table 2. Odds Ratios of ASV for Arrhythmia Events, Including PAF and VT, in HF Patients.**

| | Number of events | Unadjusted OR (95% CI) | Model 1[a] OR (95% CI) | Model 2[b] OR (95% CI) |
|---|---|---|---|---|
| **Arrhythmia events** | | | | |
| No ASV (n=66) | 40 | ref | ref | ref |
| ASV (n=75) | 27 | 0.37 (0.18 to 0.72)* | 0.37 (0.17 to 0.79)* | 0.27 (0.11 to 0.63)* |
| **PAF** | | | | |
| No ASV (n=66) | 29 | ref | ref | ref |
| ASV (n=75) | 17 | 0.37 (0.18 to 0.77)* | 0.31 (0.14 to 0.69)* | 0.27 (0.12 to 0.64)* |
| **VT** | | | | |
| No ASV (n=66) | 20 | ref | ref | ref |
| ASV (n=75) | 12 | 0.44 (0.19 to 0.98)** | 0.54 (0.22 to 1.34) | 0.33 (0.11 to 1.01) |

[a]adjusted for age, sex, and body mass index.

[b]adjusted for New York Heart Association class, systolic blood pressure, heart rate, hypertension, diabetes, dyslipidemia, smoking, estimated glomerular filtration rate, left ventricle ejection fraction, and anti-arrhythmia drug use

*p<0.01, **p<0.05

ASV: adaptive servo-ventilation, HF: heart failure, OR: odds ratio, PAF: paroxysmal atrial fibrillation, VT: ventricular tachycardia

**Table 3. Changes in Parameters from Baseline to 1-year Follow-up.**

| Parameters | ASV (n=75) | Non-ASV (n=66) | p value |
|---|---|---|---|
| **BNP (pg/mL)** | | | |
| Baseline | 995.31 (812.67) | 879.85 (696.24) | 0.37 |
| 1-year follow-up | 644.87 (535.08) | 659.66 (528.33) | 0.87 |
| **LVEF (%)** | | | |
| Baseline | 37.93 (14.80) | 41.18 (14.88) | 0.2 |
| 1-year follow-up | 38.89 (14.04) | 42.11 (14.27) | 0.18 |
| **eGFR (mL/min/1.73 cm$^2$)** | | | |
| Baseline | 50.07 (24.37) | 49.10 (23.78) | 0.81 |
| 1-year follow-up | 52.66 (24.78) | 46.81 (18.34) | 0.12 |

ASV: adaptive servo-ventilation, BNP: brain natriuretic peptide, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction

with HF due to IHD. Although there was no statistically significant association between ASV therapy and a reduced incidence of VT, the ASV group tended to have a lower OR for VT than the Non-ASV group (OR, 0.33; 95% CI, 0.11-1.01). The reduced number of events of VT compared to PAF might be responsible, at least in part, for the lack of a significant association between ASV therapy and VT events.

There are several potential explanations for the preventive effect of ASV therapy on the incidence of arrhythmias. The positive airway pressure of ASV is considered to improve congestion and reduce dyspnea in the acute phase, leading to the suppression of tachypnea and tachycardia via the slowing of respiratory rates and the stabilization of respiratory patterns in patients with HF. In addition, ASV therapy has been reported to stabilize the heart rate and suppress cardiac sympathetic nerve activity in the chronic phase by improving SDB (15). Using $^{123}$I-metaiodobenzylguanidine imaging, several studies showed that ASV therapy improved cardiac sympathetic nerve activity (16, 17). ASV therapy might prevent arrhythmias by partially mediating cardiac sympathetic nerve activity regulation. In contrast, the SERVE-HF study showed that arrhythmia events occurred in the ASV group to a great extent than in the control group. However, more patients in the ASV arm were receiving antiarrhythmic agents than in the control arm (22.4% vs. 18.0% ) and had presumably already exhibited an arrhythmia, indicating that patients with HFrEF and sleep apnea in the ASV arm are already at an increased risk of VT.

Few other studies on ASV therapy have focused on arrhythmias and IHD. Patients with HF due to IHD sometimes show complications and develop a critical condition upon experiencing arrhythmias. Preventing arrhythmias is necessary for such patients in order to improve the prognosis of HF. Furthermore, percutaneous coronary intervention (PCI) is often performed in patients with IHD. After performing PCI, patients are prescribed long-term dual antiplatelet therapies to prevent cardiovascular events. Patients with AF must take both antiplatelet and anticoagulation therapies after PCI. The combination of antiplatelet therapy and anticoagulation therapy is known to be associated with significant major bleeding risks (18). Thus, preventing arrhythmias, including AF, in patients with HF due to IHD may be very important for improving the outcomes of these patients. The results of the present study demonstrating the prevention of

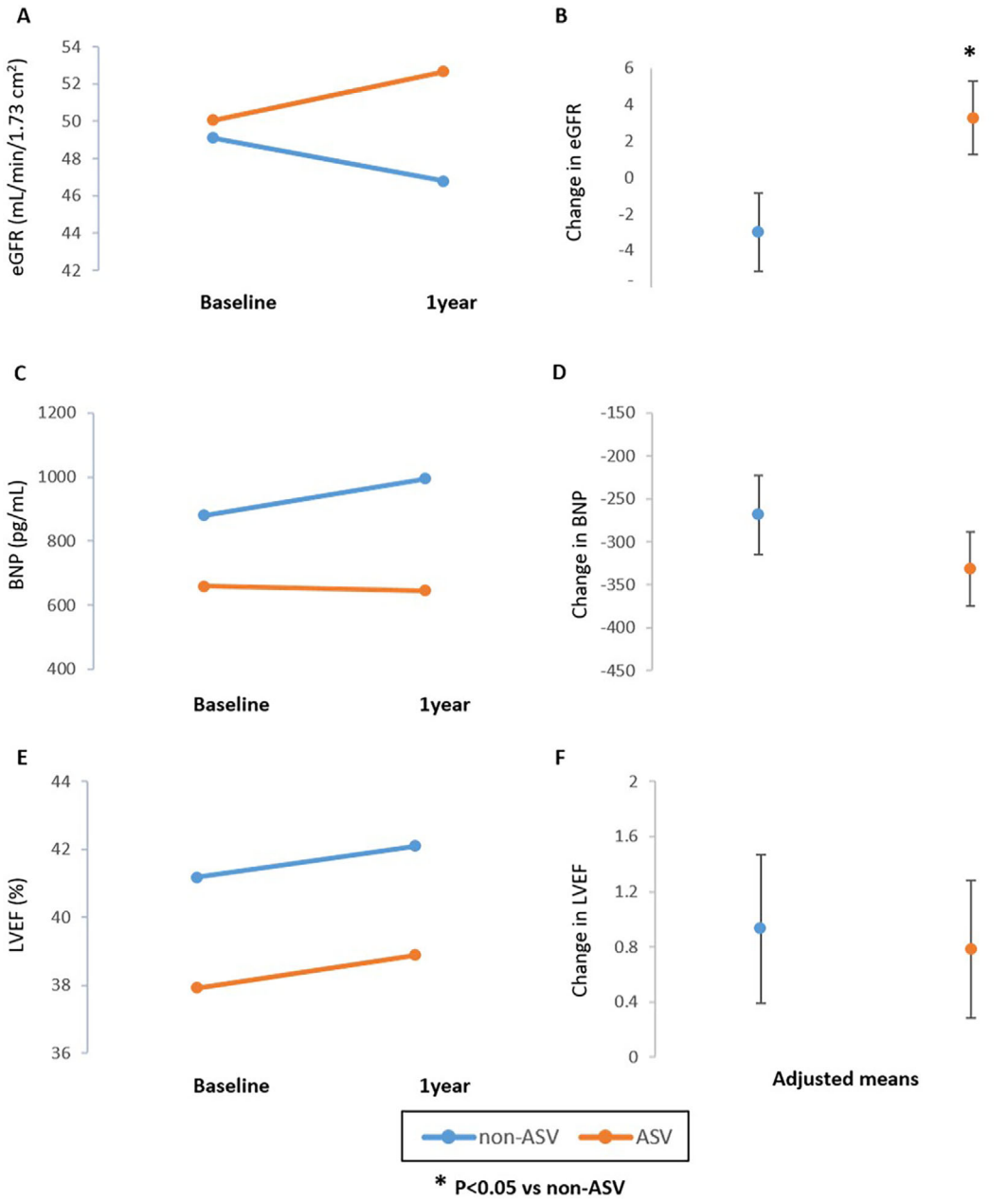


**Figure 2.** **Changes in clinical parameters over the one-year follow-up in the ASV and Non-ASV groups. The left panel (A: estimated GFR; C: BNP; E: LVEF) shows each parameter (mean value) at both baseline and one year later. The right panel (B: estimated GFR; D: BNP; F: LVEF) shows the adjusted mean for change in each parameter calculated using linear regression models. ASV: adaptive servo-ventilation, BNP: brain natriuretic peptide, GFR: glomerular filtration rate, LVEF: left ventricular ejection fraction**

incident AF by ASV therapy may influence the management of patients with HF due to IHD in the future.

The present study also confirmed that ASV therapy improved the eGFR in patients with HF, which corresponds with the findings of previous studies mainly conducted in Japan indicating that ASV improves renal function in HF patients (19, 20). HF leads to kidney dysfunction due to a reduced cardiac output and venous congestion (21). This is known as cardio-renal syndrome and refers to the worsening of HF associated with renal dysfunction. There are several potential reasons for the observed improvement in the renal function after ASV therapy. First, ASV improves the hypoxia that otherwise worsens the renal function (22). Second, ASV therapy increases the cardiac output and stroke volume in HF, accompanied by a reduction in systemic vascular resistance. The increases in the cardiac output due to ASV therapy may increase the renal blood flow and improve the renal function. In addition, ASV may decrease the sympathetic nerve activity, which plays an important role in the progression of renal dysfunction. Furthermore, a reduced renal function has been reported as a risk factor for the incidence of arrhythmia (23). The improvement in the renal

function might be one of the mechanisms involved in the reduction in the incident arrhythmias elicited by ASV therapy in the present study. We also noted no significant differences between the ASV and Non-ASV groups with respect to the BNP level and LVEF, although these variables were improved at one year compared with the baseline value in both groups. This result is consistent with the findings of a previous study that assessed the effect of ASV therapy on the cardiac function and LV remodeling in Japan (24).

### Limitations

Several limitations associated with the present study warrant mention. First, selection and information bias cannot be ruled out, as the present study was not a double-blind or randomized controlled trial but a retrospective study. In addition, the implementation of ASV therapy was decided subjectively by the attending physician based on the condition of each patient in the acute phase, regardless of the presence of SDB. Although we performed a multivariable regression model to improve the comparability between the ASV and the Non-ASV groups, some residual confounding factors might exist. Further randomized studies with larger sample sizes are necessary to establish the effectiveness of ASV therapy in patients with HF due to IHD. Second, we had no sleep study data because ASV therapy was initiated in the acute phase of HF, before performing the sleep study. We were unable to assess the impact of the presence or severity of SDB on the association of ASV therapy with the incidence of arrhythmia. Third, the follow-up term is still short in the present study. The average follow-up periods of most studies, including the SERVE-HF trial, are over one year. Therefore, we need to assess the long-term efficiency of ASV therapy in HF patients. Fourth, we might have an inflated type 1 error because of multiple testing.

## Conclusion

The present study showed that ASV therapy significantly decreased the incidence of PAF and VT with an improvement in the renal function of patients with HF due to IHD. These findings indicate that ASV therapy has preventive effects on arrhythmias, including PAF and VT, in patients with HF due to IHD.

**The authors state that they have no Conflict of Interest (COI).**

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