Adaptive Servo-Ventilation Treatment Increases Stroke Volume in Stable Systolic Heart Failure Patients With Low Tricuspid Annular Plane Systolic Excursion

Toshihiro Iwasaku, MD, Tomotaka Ando, MD, Akiyo Eguchi, MD, Yoshitaka Okuhara, MD, Yoshiro Naito, MD, Toshiaki Mano, MD, Tohru Masuyama, MD, and Shinichi Hirotani, MD

Summary

We hypothesized that the effects of adaptive servo-ventilation (ASV) therapy were influenced by right-sided heart performance. This study aimed to clarify the interaction between the effects of ASV and right-sided heart performance in patients with stable heart failure (HF) with reduced ejection fraction (HFrEF).

Twenty-six stable HF inpatients (left ventricular ejection fraction < 0.45, without moderate to severe mitral regurgitation (MR) were analyzed. Echocardiography was performed before and after 30 minutes of ASV. ASV increased stroke volume index (SVI) in 14 patients (30.0 ± 11.9 to 41.1 ± 16.1 mL/m²) and reduced SVI in 12 patients (36.0 ± 10.1 to 31.9 ± 12.2 mL/m²). Multivariate linear regression analysis revealed that tricuspid annular plane systolic excursion (TAPSE) before ASV was an independent association factor for (SV during ASV - SV before ASV)/LVEDV × 100 (%ΔSV/LVEDV). ROC analysis of TAPSE for %ΔSV/LVEDV > 0 showed that the cut-off point was 16.5 mm. All patients were divided into 2 groups according to the TAPSE value. Although no significant differences were found in the baseline characteristics and blood tests, there were significant differences in tricuspid lateral annular systolic velocity, TAPSE, right atrial area, and right ventricular (RV) area before ASV between patients with TAPSE ≤ 16.5 mm and those with TAPSE > 16.5 mm. Interestingly, ASV reduced RV area and increased TAPSE in patients with TAPSE ≤ 16.5 mm, while it reduced TAPSE in those > 16.5 mm.

ASV therapy has the potential to increase SVI in stable HFrEF patients with low TAPSE. (Int Heart J 2017; 58: 393-399)

Key words: Stable heart failure, Right-sided heart performance

Heart failure (HF) is a highly prevalent disorder that continues to be associated with repeated hospitalizations, high morbidity, and high mortality.1) Recently, respiratory management in HF patients has attracted attention. Noninvasive positive pressure ventilation (NIPPV) has been shown to reduce the need for intubation and mortality in patients with acute cardiogenic pulmonary edema.2) Previous studies have suggested that the curative effects of NIPPV are not only for patients with acute pulmonary edema, but also for stable HF patients.3) NIPPV improves gas exchange, counterbalances hydrostatic forces leading to pulmonary edema, and maintains airway patency.4) Positive end-expiratory pressure (PEEP) ameliorates the hemodynamic state in HF patients through the following mechanisms; reduction of left ventricular (LV) afterload,5) reduction of LV preload,6) decrease in work of breathing, and reversal of hypoxia-related pulmonary vaso-constriction.7) However, the mechanisms by which PEEP improves the respiratory status in HF patients have not been fully elucidated. Notably, interactions between the efficacy of PEEP therapy and right-sided heart performance in HF are largely unknown.

Adaptive-servo ventilation (ASV) is used as a positive airway pressure (PAP) device to treat HF. ASV devices are designed to efficiently suppress Cheyne-Stokes respiration with central sleep apnea (CSR/CSA) through a synchronized ventilator support using expiratory positive airway pressure (EPAP) and a pressure support system.8) Recent reports have shown that ASV treatment has favorable effects in HF patients regardless of the severity of their sleep-disordered breathing (SDB).9) Furthermore, it has been reported that ASV therapy improves HF status via an increase in cardiac output (CO).10) Although both continuous positive airway pressure (CPAP) and ASV are treatment devices which provide PAP, CPAP is a device for patients with obstructive sleep apnea, and ASV is a device for patients with HF regardless of the presence of CSR/CSA. We hypothesized that hemodynamic ameliorating effects due to

From the Division of Cardiovascular Medicine, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan.
This study was supported by a researcher’s grant from the Hyogo College of Medicine to Toshihiro Iwasaku and Shinichi Hirotani.
Address for correspondence: Shinichi Hirotani, MD, Division of Cardiovascular Medicine, Department of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa, Nishinomiya, Hyogo 663-8501, Japan; E-mail: hirotani@hyo-med.ac.jp
Received for publication July 15, 2016. Revised and accepted September 14, 2016.
Released in advance online on J-STAGE May 8, 2017.
All rights reserved by the International Heart Journal Association.
ASV treatment are determined by right-sided heart performance in HF patients. The aim of this study was to clarify the relationship between right-sided heart performance and hemodynamic changes through short-duration ASV treatment in stable HF patients.

**METHODS**

**Patients:** This was a prospective single-center trial. Thirty patients with HF with reduced ejection fraction (HFrEF) were enrolled. They were admitted to Hyogo College of Medicine College Hospital for acute decompensated HF between March 2012 and June 2016. This study complies with the Declaration of Helsinki and our Institutional Ethics Committee approved the study protocol. Informed consent from all participants was obtained. After receiving stable oral medication and complete resolution of systemic edema, transthoracic echocardiographic examination and a concise HF function test were performed in the patients. HF patients with New York Heart Association class II-III and left ventricular ejection fraction (LVEF) < 45% were included. HF patients were excluded if they had moderate to severe mitral regurgitation (MR) in order to eliminate beneficial effects of ASV on MR. In the end, data from 26 HF patients were analyzed.

**Study protocol:** Blood tests and upright chest roentgenograms (X-rays) were performed on the morning of the study day. Patients underwent transthoracic echocardiographic examination, received ASV therapy while they were awake in the echo laboratory for 30 minutes in a supine position, and then underwent transthoracic echocardiographic examination during ASV therapy (Figure 1). Recordings were performed at end-expiration with the exception of inferior vena cava diameter.

**Blood tests:** Plasma brain natriuretic peptide (BNP), estimated glomerular filtration rate (eGFR), and total bilirubin (T-bil) were measured.

**Chest roentgenography:** Chest X-ray films were taken during maximal inspiration in the standing position. The cardiothoracic ratio (CTR) was calculated as the ratio of the maximal transverse diameter of the cardiac silhouette to the distance between the internal margins of the ribs at the level of the right hemidiaphragm.

**Echocardiography:** Echocardiographic examinations were performed using a phased-array system with a 2.5-MHz transducer according to a standardized protocol. Left ventricular diastolic dimension was measured at the long axis. Left ventricular end-diastolic volume (LVEDV) was assessed by calculating volumes using the biplane method of disks summation technique. LVEF was assessed using Simpson’s rule and stroke volume (SV) was calculated as LV outflow tract area × velocity time integral of the LV outflow velocity. Pulsed-wave Doppler was performed in the apical 4-chamber view to obtain mitral inflow velocities to assess peak E (early diastolic) velocity and deceleration time of early filling (DcT). Left atrial volume (LAV) was measured using the biplane method of disks (modified Simpson’s rule) using apical 4-chamber and apical 2-chamber views at ventricular end-systole (maximum left atrial size). The tricuspid regurgitation peak gradient (TRPG) was calculated using the simplified Bernoulli equation. Tricuspid annular plane systolic excursion (TAPSE) was acquired by placing an M-mode cursor through the tricuspid annulus and measuring the amount of longitudinal motion of the annulus at peak systole. To determine tissue Doppler-derived early diastolic mitral interventricular septal annular velocity (e’) and tricuspid lateral annular systolic velocity (S’), an apical 4-chamber window was used with a tissue Doppler mode region of interest highlighting the interventricular septal wall and the right ventricular (RV) free wall. The right atrial (RA) area was measured in the 4-chamber view at end-diastolic RV diastole. The rate of pressure rise in the RV (dP/dt) was calculated by measuring the time required for the TRPG to increase in velocity from 1 to 2 cm/s. All measures of cardiac performances were averaged over 3 cardiac cycles (5 cycles for atrial fibrillation (AF)).

**ASV:** We used Auto Set CS (ResMed, Sydney, Australia) via the oral-nasal airway without oxygenation for this study. The default ASV setting was: EPAP 5 cm H2O; minimum pressure support (PS) 3 cm H2O; and maximum PS 10 cm H2O.

**Response to ASV:** SVI change was evaluated using %ASVI/LVEDVI. SVI during ASV – SVI before ASV adjusted by LVEDVI before ASV, which was defined by the formula: (SVI during ASV – SVI before ASV)/LVEDVI before ASV × 100 (%).

**Statistical analysis:** Continuous variables are expressed as the mean ± SD if normally distributed or as the median (interquartile range [IQR]) if skewed. Categorical variables were compared using the chi-square test. Parameters were analyzed using the unpaired t-test and a correlation coefficient was calculated to determine the strength of the association between two variables. The paired t-test was used to analyze the changes in parametric data before and during ASV treatment. Univariate and multivariate analyses were performed to assess the association between %ASVI/LVEDV and the patient baseline data. Receiver operator characteristic (ROC) analysis was also performed. A value of *P* < 0.05 was considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), a modified version of R commander (version 1.6-3).
RESULTS

Thirty patients with stable HFrEF were enrolled. Of these, 4 were excluded because of MR (moderate MR; n = 2, severe MR; n = 2). Thus, 26 patients were included in the analyses. The baseline characteristics and echocardiographic parameters of the patients are shown in Table I.

ASV therapy increased stroke volume index (SVI) in 14 patients (30.5 ± 12.6 to 44.0 ± 12.7 mL/m²; P = 0.0004) and reduced it in 12 patients (36.0 ± 10.1 to 31.6 ± 10.7 mL/m²; P = 0.005).

Univariate analysis was performed to identify the factors that are significantly correlated with SVI change (%ΔSVI/LVEDVI). We found that heart rate (HR), RV area, S’, and TAPSE were significantly correlated. Multivariate analysis was then performed for variables, such as HR, RV area, and TAPSE, that were significantly associated with %ΔSVI/LVEDVI to identify independent association variables. S’ was excluded from the analysis because S’ and TAPSE are parameters for the systolic function of RV free wall, and there was a significant association. TAPSE was identified as the independent correlation factor (Table II). A scatter (XY) plot has points that showed the relationship between TAPSE and %ΔSVI/LVEDVI (Figure 2).

To identify the cut-off value for %ΔSVI/LVEDVI increase (≥ 0), ROC analysis for TAPSE was performed. The analysis revealed that the cut-off point was 16.5 mm with specificity of 0.833 and sensitivity of 0.929 (Figure 3).

The baseline characteristics of the HF patients with TAPSE ≤ 16.5 mm and those with TAPSE > 16.5 mm are presented in Table III. There were no significant differences in the baseline characteristics of the HF patients.

Effects of ASV on BP, HR, and respiratory rate (RR) in the patients with TAPSE ≤ 16.5 mm and TAPSE > 16.5 mm are shown in Table IV. All patients were awake and did not have apnea or hypopnea during the study. Therefore, the beneficial effects of ASV on hemodynamics could not be attributed to an improvement of SDB. Before ASV, there were significant differences in S’, and TAPSE, RA area, and RV area between the patients with TAPSE ≤ 16.5 mm and those with TAPSE > 16.5 mm (S’: P = 0.042; TAPSE: P < 0.0001; RA area: P = 0.020; RV area: P = 0.003). In patients with TAPSE > 16.5 mm, ASV significantly reduced HR, RR, TRPG, and TAPSE. In contrast, in patients with TAPSE ≤ 16.5 mm, ASV significantly reduced E wave velocity and RV area and increased DcT and TAPSE (Table IV).

Table I. Baseline Characteristics and Echocardiographic Data

| Variable                  | Number | Age (years) | Male gender, n (%) | BSA (m²) | Systolic BP (mmHg) | HR (minute) | RR (minute) | Rhythm, n (%) | Sinus rhythm | AF rhythm |
|---------------------------|--------|-------------|--------------------|----------|-------------------|-------------|-------------|---------------|--------------|-----------|
|                           | 26     | 64 ± 12     | 22 (85)            | 1.69 ± 0.25 | 114 ± 20          | 64 ± 14     | 12 ± 2      | 18 (69)       | 8 (31)       |

| HF etiology, n (%) | Ischemic       | Hypertension | DCM        | NYHA class, n (%) | III | IV |
|-------------------|----------------|-------------|------------|-------------------|-----|----|
|                   | 14 (54)        | 10 (38)     | 2 (8)      | 20 (77)           | 6 (23) |

| Medication, n (%) | ACE-I/ARB | β-Blocker | Diuretics | Blood test |
|-------------------|-----------|-----------|-----------|------------|
|                   | 25 (96)   | 25 (96)   | 18 (69)   |            |

| Chest X-ray (postero-anterior) | CTR (%) | 56 ± 7 |
|-------------------------------|---------|--------|

| Echocardiographic data | Left side of the heart | Right side of the heart |
|-----------------------|------------------------|-------------------------|
|                       | LVEDVI (mL/m²) | LVEF (%) | LA VI (mL/m²) | E wave (cm/s) | E/e' | TRPG (mmHg) |
|                       | 111 ± 41 | 27 ± 10 | 64 ± 22 | 85.6 ± 31.0 | 4.6 ± 1.9 | 27 ± 8 |

|                       | DcT (msec) | TRPG (mmHg) |
|                       | 177 ± 68 | 27 ± 8 |

|                       | 8.1 ± 2.6 | 15.4 ± 0.9 |

|                       | 15.4 ± 0.9 | 24 ± 7 |

|                       | 64 ± 22 | 17 ± 4 |

|                       | 64 ± 22 | 17 ± 4 |

Data are presented as the mean ± SD or median [IQR]. SVI indicates stroke volume; BSA, body surface area; BP, blood pressure; HR, heart rate; AF, atrial fibrillation; HF, heart failure; DCM, dilated cardiomyopathy; NYHA, New York Heart Association; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; T-bil, total bilirubin; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; CTR, cardiothoracic ratio; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; DcT, deceleration time; TRPG, tricuspid regurgitation pressure gradient; S’, tricuspid lateral annular systolic velocity; TAPSE, tricuspid annular plane systolic excursion; RA, right atrium; RV, right ventricle; and IVC, inferior vena cava.

Table II. Baseline Characteristics and Echocardiographic Data

| Variable                  | Description |
|---------------------------|-------------|
|                           |             |

| RV dP/dt (mmHg/s) | 315 ± 75 |

| RA area (cm²) | 22 ± 6 |

| RV area (cm²) | 24 ± 7 |

| IVC (Expiratory phase) (mm) | 17 ± 4 |

| IVC (Inspiratory phase) (mm) | 10 ± 5 |

| Number 26 | Age (years) 64 ± 12 | Male gender, n (%) 22 (85) | BSA (m²) 1.69 ± 0.25 | Systolic BP (mmHg) 114 ± 20 | HR (minute) 64 ± 14 | RR (minute) 12 ± 2 | Rhythm, n (%) 18 (69) | Sinus rhythm 8 (31) |

| HF etiology, n (%) Ischemic 14 (54) Hypertension 10 (38) DCM 2 (8) Medication, n (%) ACE-I/ARB 25 (96) β-Blocker 25 (96) Diuretics 18 (69) Blood test T-bil (mg/dL) 0.8 ± 0.4 eGFR (mL/minute/1.73 m²) 50 ± 22 BNP 486 [328-729] Chest X-ray (postero-anterior) CTR (%) 56 ± 7 Echocardiographic data Left side of the heart LVEDVI (mL/m²) 111 ± 41 LVEF (%) 27 ± 10 LA VI (mL/m²) 64 ± 22 E wave (cm/s) 85.6 ± 31.0 DcT (msec) 177 ± 68 E/e’ 4.6 ± 1.9 E/e’ 20 ± 8 TRPG (mmHg) 27 ± 8 Right side of the heart S’ (cm/s) 8.1 ± 2.6 TAPSE (mm) 15.4 ± 0.9 RV dP/dt (mmHg/s) 315 ± 75 RA area (cm²) 22 ± 6 RV area (cm²) 24 ± 7 IVC (Expiratory phase) (mm) 17 ± 4 IVC (Inspiratory phase) (mm) 10 ± 5

Discussion

The primary findings of this study are that baseline TAPSE was an independent association factor for SVI change, and the cut-off value for %ΔSVI/LVEDVI was 16.5 mm. As the baseline RA area and RV area were larger in patients with TAPSE < 16.5 mm, low TAPSE was likely to indicate concomitance with RV dysfunction. ASV significantly increased SVI and TAPSE and significantly reduced RV area in patients with TAPSE < 16.5 mm. Therefore, it is safe to conclude that ASV increased SV in patients with RV dysfunction. The effects of ASV treatment seem to depend not only on left-sided heart performance, but also on right-sided heart performance in stable HFrEF patients. Notably, these results appeared to be independent of the severity of SDB because this study was performed while patients were awake.

It has been reported that ASV therapy ameliorates LV function in HF patients with LV dysfunction, such as higher...
Another group reported that predictors of increased SVI during ASV in HF patients included preserved right ventricular function, normal resting BP, non-ischemic HF etiology, mitral regurgitation, and increased left ventricular filling pressures.

Our finding that ASV treatment increased SV in HF patients with low TAPSE appears to contradict their report. However, there are some discrepancies in the study population and design. The average TAPSE in the present study was 15 ± 5 mm, whereas that in the study of Spiesshofer, et al. was 19 ± 6 mm. It remains possible that the right heart function of this study population was more severely impaired compared with that of Spiesshofer, et al. In addition, the TAPSE of the non-increase group in this study population was comparable with that of the small-change group. Regarding study design, the timing of examining the SV changes was different: in this study, the timing was the first introduction period, while in the Spiesshofer study it was during the stable maintenance period.

The mechanism by which ASV treatment increased SV in the HF patients with RV dysfunction was not fully clarified in the present study since the changes of the parameters across ASV treatment were significant but subtle. However, we believe the mechanism by which ASV treatment increased SV in ADHF patients with RV dysfunction may be as follows: in patients with severe RV dysfunction, ASV treatment reduced RV volume and increased TAPSE due to a reduction of preload. RV volume reduction at the same time reduced LV, RV, and pericardium constraint, improving LV diastolic performance, such as a reduction in E wave velocity and prolongation of DcT, and increasing LV volume. These allowed increasing SV.

The results in the present study may suggest that right-sided and left-sided heart performance are interrelated in HF. Under closed-chest circumstances, the pericardium, lungs, chest wall, and RV constrain the LV. Therefore, the LV end-diastolic pressure (LVEDP) is greatly affected by the pericardial pressure and the RV end-diastolic pressure. It is known that, in HF pa-

| Table II. Univariate and Multivariate Linear Regression Analysis of Association between %ΔSVI/LVEDVI by ASV and Baseline Characteristics and Echocardiographic Data in HF Patients |
|---------------------------------|------------|-----------------|-----|-----------------|------------|-----------------|
|                                | r          | 95%CI            | P   | r              | 95%CI      | P   |
| DcT (ms)                        | -0.028     | -0.418 0.372     | 0.896 |                |            |     |
| E wave (m/s)                    | -0.023     | -0.407 0.368     | 0.912 |                |            |     |
| E/e'                            | 0.366      | -0.025 0.660     | 0.066 |                |            |     |
| HR (minute)                     | 0.429      | 0.050 0.700      | 0.029 | 0.151          | -0.269     | 0.571 0.463 |
| LAVI (mL/m²)                    | -0.005     | -0.392 0.383     | 0.980 |                |            |     |
| LVEDVI (mL/m²)                  | -0.179     | -0.530 0.224     | 0.381 |                |            |     |
| LVEF (%)                        | -0.325     | -0.633 0.071     | 0.105 |                |            |     |
| RA area (cm²)                   | 0.409      | -0.004 0.703     | 0.053 |                |            |     |
| RV dP/dt                        | -0.125     | -0.495 0.284     | 0.553 |                |            |     |
| RV area (cm²)                   | 0.600      | 0.268 0.804      | 0.002 | 0.315          | -0.6302    | 1.204 0.500 |
| S' (cm/s)                       | -0.484     | -0.734 -0.119    | 0.001 |                |            |     |
| TRPG (mmHg)                     | 0.197      | -0.206 0.543     | 0.335 |                |            |     |
| TAPSE (mm)                      | -0.780     | -0.897 -0.563    | < 0.001 | -2.704       | -4.312    | -1.096 0.002 |

P value of 0.05 was considered significant. r indicates regression coefficient. Other abbreviations as in Table I.
Patients with high pulmonary capillary wedge pressure (PCWP), PEEP increases the cardiac output, whereas PEEP decreases the SV in healthy subjects. PEER therapies have the potential to ameliorate LV filling through relieving the constraints around the LV. Previously, we examined the effects of administration of nitroprusside at the dosage at which systemic blood pressure was not reduced in patients with severe dilated cardiomyopathy. The dosage of nitroprusside increased cardiac output, whereas it reduced LVEDP. Recently, Ormerod, et al have also reported that intravenous nitrate sodium infusion increases SV, and that the changes in SV are correlated with the increase in estimated trans-septal gradient. The right ventricle enlargement, pericardium, and volume overload can cause constraint of the LV, raise LVEDP but reduce LV end-diastolic volume, and worsen LV filling. Such an interaction is normally negligible, but it is accentuated in HF patients, that is, patients with volume overload and pulmonary hypertension.

### Table III. Baseline Characteristics of HF Patients With TAPSE ≤ 16.5 mm and Those With TAPSE > 16.5 mm

| TAPSE ≤ 16.5 mm | TAPSE > 16.5 mm | P  |
|-----------------|-----------------|----|
| Number          | 14              | 12 |    |
| Age (years)     | 65 ± 11         | 63 ± 14 | 0.665 |
| Male gender, n (%) | 12 (86)        | 9 (75) | 0.490 |
| BSA (m²)        | 1.72 ± 0.18     | 1.65 ± 0.31 | 0.440 |
| Systolic BP (mmHg) | 115 ± 21       | 114 ± 20 | 0.953 |
| RR (minute)     | 68 ± 17         | 59 ± 9  | 0.125 |
| Rhythm, n (%)   | 12 ± 2          | 13 ± 2  | 0.181 |
| Sinus rhythm    | 11 (79)         | 7 (58)  | 0.265 |
| AF              | 3 (21)          | 5 (42)  | 0.099 |
| Ischemic        | 5 (36)          | 9 (75)  | 0.175 |
| Hypertension    | 8 (57)          | 2 (17)  | 0.000 |
| DCM             | 1 (7)           | 1 (8)   |    |
| NYHA class, n (%) | 10 (73)        | 10 (83) | 0.535 |
| III             | 4 (27)          | 2 (17)  |    |
| Medication, n (%) | 11 (93)        | 12 (100) | 0.345 |
| ACE-I/ARB       | 14 (100)        | 11 (92) | 0.271 |
| β-Blocker       | 8 (57)          | 10 (83) | 0.149 |
| Blood test      |                |        |    |
| Tbil (mg/dL)    | 0.90 ± 0.46     | 0.62 ± 0.15 | 0.044 |
| eGFR (mL/minute/1.73m²) | 54 ± 20   | 46 ± 24  | 0.376 |
| BNP             | 452 [359-659]   | 488 [308-1380] | 0.238 |
| Chest X-ray     |                |        |    |
| CTR (%)         | 59 ± 6          | 54 ± 7  | 0.075 |

P value of 0.05 was considered significant. Abbreviations as in Table I.

### Table IV. Effects of ASV on Echocardiographic Parameters

| TAPSE ≤ 16.5 mm | TAPSE > 16.5 mm | P  |
|-----------------|-----------------|----|
| Number          | 14              | 12 |    |
| Systolic BP (mmHg) | 115 ± 21       | 114 ± 20 | 0.293 |
| SVI (mL/m²)     | 30.0 ± 11.9     | 36.6 ± 11.8 | 0.184 |
| LVEDVI (mL/m²)  | 114 ± 53        | 107 ± 23  | 0.773 |
| LVEF (%)        | 25.6 ± 11.8     | 30.8 ± 8.5 | 0.102 |
| E wave (cm/s)   | 84.8 ± 54.0     | 86.5 ± 23.9 | 0.095 |
| DcT (msec)      | 172 ± 67        | 185 ± 64  | 0.243 |
| TRPG (mmHg)     | 29.5 ± 9.4      | 36.0 ± 5.1 | 0.011 |
| RA area (cm²)   | 24.6 ± 6.4      | 19.0 ± 3.3 | 0.708 |
| RV area (cm²)   | 29.0 ± 7.4      | 20.1 ± 5.4 | 0.581 |
| S′ (cm/s)       | 7.1 ± 1.8       | 9.2 ± 3.0  | 0.391 |
| TAPSE (mm)      | 11.9 ± 3.2      | 19.6 ± 2.8 | 0.002 |
| IVC (Expiratory phase) (mm) | 18.0 ± 4.8 | 16.3 ± 3.7 | 0.329 |
| IVC (Inspiratory phase) (mm) | 10.9 ± 5.1 | 7.9 ± 3.6 | 0.100 |

P value of 0.05 was considered significant. Significant difference between patients with TAPSE ≤ 16.5 mm and TAPSE > 16.5 mm before ASV. Abbreviations as in Table I.
needed to clarify the changes in right-sided heart volume and systolic function across ASV treatment.

The finding that the plasma T-bil level was larger in patients with TAPSE ≤ 16.5 mm compared with those in patients with TAPSE > 16.5 mm may be because they had more severe liver congestion on admission compared to the patients with TAPSE ≤ 16.5 mm. Taken together, ASV treatment might work well for HFrEF patients with RV dysfunction despite the standard treatments for HF, such as angiotensin-converting enzyme inhibitors, β-adrenergic receptor blockers, and diuretics.

In the present study, while no patients with TAPSE > 16.5 mm passed away, 3 with TAPSE ≤ 16.5 mm died from worsening HF within 2 years. It remains unclear whether ASV treatment improves the prognosis of such HFrEF patients with RV dysfunction because most patients in this study refused the introduction of ASV treatment because of its associated high out-of-pocket medical cost. Further studies are needed to evaluate the effects of ASV treatment on the long-term prognosis in HFrEF patients from the standpoint of with/without severe RV dysfunction.

PEEP therapy increased the CO in stable HF patients with high pulmonary capillary wedge pressure (PCWP) before PEEP therapy. However, our results did not show any significant differences in E wave velocity and TRPG at baseline, which echocardiographically reflect LVEDP or PCWP, between patients with TAPSE > 16.5 mm and those ≤ 16.5 mm. There is a possibility that PCWP measured via a catheter and PCWP estimated by E wave velocity and TRPG differ under pericardial constraint conditions. In constrictive pericarditis, in which heart chamber pressure becomes elevated due to the pericardial constraint, the diastolic pressures of LA and LV are equalized. Furthermore, Yamada, et al and Haruki, et al reported that the severity of MR is one of the factors which determines ASV efficacy. In the present study, only stable HFrEF patients without moderate to severe MR were enrolled in order to exclude the ASV effects on MR and perform accurate assessment of the hemodynamic state by echocardiography. Thus, the methodology of this study and the selection of patients might be one of the reasons why our results were distinct from the results of the previous study. Prospective multicenter randomized trials have revealed that the effects of ASV therapy in chronic HF patients are limited. A randomized controlled study of adaptive-servo ventilation in patients with congestive heart failure (SAVOIR-C) revealed that the addition of ASV treatment to the medical therapy was not superior to only medical therapy in terms of the LVEF-improving effects. Another multinational, multicenter, randomized controlled Phase III trial (SERVE-HF) did not show a benefit in mortality of ASV therapy in patients with symptomatic HF complicated with CSA in addition to optimized medical care. Although the CANPAP trial did not show any superiority of CPAP in HF patients complicated with central sleep apnea, subanalysis of the trial implied that CPAP may have beneficial effects on patients whose apnea-hypopnea index (AHI) decreased to less than 15 per hour. The SERVE-HF trial was conducted to clarify if higher AHI reduction to less than 10 per hour had any beneficial effects on HF. To achieve an AHI less than 10 per hour, the device-measured mean median values of EPAP were 5.7 cm H2O and those of inspiratory PAP were 9.7 mm H2O at 12 months. These high PAPs may reduce cardiac output, and as a result, aggravate HF mortality. Methods to optimize the PAP setting other than reducing AHI are needed. SV increase by PAP using echocardiography may be a method to optimize the PAP setting. Therefore, it is very important to identify HF patients who can derive benefits from ASV treatment and the setting which is best suited for each HF patient.

In conclusion, the results of the present study suggest that ASV therapy was effective at increasing SV in stable HFrEF patients with low TAPSE. Further study is needed to clarify the relationship between the beneficial effects of ASV and right-sided heart function in HF patients.

Limitations: There are several limitations in the present study. First, this is a single-center study with a small sample size. Second, we examined the effects of only 30 minutes of ASV treatment. Short-term benefits are not necessarily associated with long-term benefits. Third, we conducted this study with respect to only one ASV setting (default setting: EPEP 5 cm H2O PS 3–10 cm H2O). Although inspiratory PAP was not recorded in all patients, inspiratory PAP was recorded in 5 of the 26 patients and it was less than 5 cm H2O. This reminds us that we are unclear about how ASV treatment works at other settings. Fourth, we did not assess the severity of SDB. It is possible that the severity of SDB is associated with RV dysfunction because both SDB and RV dysfunction have a poor prognosis. Further studies are needed to confirm the association between right-sided heart dysfunction and the effect of ASV therapy, as well as the short-term and long-term benefits.

**DISCLOSURE**

There is no conflict of interest with any financial organization.

**REFERENCES**

1. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham study. J Am Coll Cardiol 1993; 22: 6A-13A.
2. Peters J, Ihle P. Coronary and systemic vascular response to inspiratory resistive breathing. J Appl Physiol 1992; 72: 905-13.
3. Borghi-Silva A, Carraçosca C, Oliveira CC, et al. Effects of respiratory muscle unloading on leg muscle oxygenation and blood volume during high-intensity exercise in chronic heart failure. Am J Physiol Heart Circ Physiol 2008; 294: H2465-72.
4. Manzano F, Fernández-Mondéjar E, Colmenero M, et al. Positive end-expiratory pressure reduces incidence of ventilator-associated pneumonia in nonhypoxic patients. Crit Care Med 2008; 36: 2225-31.
5. Fessler HE, Brower RG, Wise RA, Pernmutt S. Mechanism of reduced tidal volume afterload by systemic and diastolic positive pleural pressure. J Appl Physiol 1988; 65: 1244-50.
6. Grace MP, Greibourn DM. Cardiac performance in response to PEEP in patients with cardiac dysfunction. Crit Care Med 1982; 10: 358-60.
7. Peters J, Ihle P. Coronary and systemic vascular response to inspiratory resistive breathing. J Appl Physiol 1992; 72: 905-13.
8. Kasi T, Usui Y, Yoshioka T, et al. 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. Circ Heart Fail 2010; 3: 140-8.
9. Momomura S, Seino Y, Kihara Y, Adachi H, Yasumura Y, Yokoyama H. Adaptive servo-ventilation therapy using an innovative ventilator for patients with chronic heart failure: A real-world, multicenter, retrospective, observational study (SAVIOR-R). Heart Vessels 2015; 30: 805-17.

10. Haruki N, Takeuchi M, Kaku K, et al. Comparison of acute and chronic impact of adaptive servo-ventilation on left chamber geometry and function in patients with chronic heart failure. Eur J Heart Fail 2011; 13: 1140-6.

11. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010; 23: 685-713.

12. Kanda Y. Investigation of the freely available easy-to-use software ‘EZIR’ for medical statistics. Bone Marrow Transplant 2013; 48: 452-8.

13. Asakawa N, Sakakibara M, Noguchi K, et al. Adaptive servo-ventilation has more favorable acute effects on hemodynamics than continuous positive airway pressure in patients with heart failure. Int Heart J 2015; 56: 527-32.

14. Spießhöfer J, Fox H, Lehmann R, et al. Heterogenous haemodynamic effects of adaptive servoventilation therapy in sleeping patients with heart failure and Cheyne-Stokes respiration compared to healthy volunteers. Heart Vessels 2016; 31: 1117-30.

15. Yamada S, Sakakibara M, Yokota T, et al. Acute hemodynamic effects of adaptive servo-ventilation therapy for patients with chronic heart failure in a confirmatory, multicenter, randomized, controlled study. Circ J 2013; 77: 1214-20.

16. Bradley TD, Holloway RM, McLaughlin PR, Ross BL, Walters J, Liu PP. Cardiac output response to continuous positive airway pressure in congestive heart failure. Am Rev Respir Dis 1992; 145: 377-82.

17. Jardin F, Faricot JC, Boisante L, Curien N, Margairaz A, Bourdarias JP. Influence of positive end-expiratory pressure on left ventricular performance. N Engl J Med 1981; 304: 387-92.

18. Masuyama T, St Goar FG, Alderman EL, Popp RL. Effects of nitroprusside on transmural flow velocity patterns in extreme heart failure: a combined hemodynamic and Doppler echocardiographic study of varying loading conditions. J Am Coll Cardiol 1990; 16: 1175-85.

19. Ormerod JO, Arif S, Mukadam M, et al. Short-term intravenous sodium nitrite infusion improves cardiac and pulmonary hemodynamics in heart failure patients. Circ Heart Fail 2015; 8: 565-71.

20. Atherton JJ, Moore TD, Lele SS, et al. Diastolic ventricular interaction in chronic heart failure. Lancet 1997; 349: 1720-4.

21. Moore TD, Fremeaux MP, Sas R, et al. Ventricular interaction and external constraint account for decreased stroke work during volume loading in chf. Am J Physiol Heart Circ Physiol 2001; 281: H2385-91.

22. Yamada S, Sakakibara M, Yokota T, et al. Acute hemodynamic effects of adaptive servo-ventilation in patients with heart failure. Circ J 2013; 77: 1214-20.

23. Momomura S, Seino Y, Kihara Y, et al. Adaptive servo-ventilation therapy for patients with chronic heart failure in a confirmatory, multicenter, randomized, controlled study. Circ J 2015; 79: 981-90.

24. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med 2015; 373: 1095-105.

25. Arzt M, Floras JS, Logan AG, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CNPAP). Circulation 2007; 115: 3173-80.