Adaptive Servo-Ventilation Has More Favorable Acute Effects on Hemodynamics Than Continuous Positive Airway Pressure in Patients With Heart Failure

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Summary

Adaptive servo-ventilation (ASV) has been attracting attention as a novel respiratory support therapy for heart failure (HF). However, the acute hemodynamic effects have not been compared between ASV and continuous positive airway pressure (CPAP) in HF patients.

We studied 12 consecutive patients with stable chronic HF. Hemodynamic measurement was performed by right heart catheterization before and after CPAP 5 cmH₂O, CPAP 10 cmH₂O, and ASV for 15 minutes each.

Heart rate, blood pressure, pulmonary capillary wedge pressure (PCWP), and stroke volume index (SVI) were not changed by any intervention. Right atrial pressure significantly increased after CPAP 10 cmH₂O (3.6 ± 3.3 to 6.7 ± 1.6 mmHg, P = 0.005) and ASV (4.1 ± 2.6 to 6.8 ± 1.5 mmHg, P = 0.026). Cardiac index was significantly decreased by CPAP 10 cmH₂O (2.3 ± 0.4 to 1.9 ± 0.3 L/minute/m², P = 0.048), but was not changed by ASV (2.3 ± 0.4 to 2.0 ± 0.3 L/minute/m², P = 0.299). There was a significant positive correlation between baseline PCWP and % of baseline SVI by CPAP 10 cmH₂O (r = 0.705, P < 0.001) and ASV (r = 0.750, P < 0.001). ASV and CPAP 10 cmH₂O had significantly greater slopes of this correlation than CPAP 5 cmH₂O, suggesting that patients with higher PCWP had a greater increase in SVI by ASV and CPAP 10 cmH₂O. The relationship between baseline PCWP and % of baseline SVI by ASV was shifted upwards compared to CPAP 10 cmH₂O. Furthermore, based on the results of a questionnaire, patients accepted CPAP 5 cmH₂O and ASV more favorably compared to CPAP 10 cmH₂O.

ASV had more beneficial effects on acute hemodynamics and acceptance than CPAP in HF patients. (Int Heart J 2015; 56: 527-532)

Key words: Noninvasive positive-pressure ventilation, Right heart catheterization, Respiratory support therapy, Left ventricular dysfunction, Non-pharmacological therapy

Patients with chronic heart failure (HF) commonly have sleep-disordered breathing (SDB) including central sleep apnea (CSA) with Cheyne-Stokes respiration (CSR). CSA with CSR has been shown to be associated with poor prognosis in HF patients due to overactivation of the sympathetic nervous system. Continuous positive airway pressure (CPAP) is a noninvasive positive-pressure ventilation (NPPV) device which can effectively treat CSA and obstructive sleep apnea (OSA). CPAP can not only decrease the apnea-hypopnea index but also increase cardiac output (CO) and stroke volume (SV) in HF patients with SDB. It has more favorable effects on hemodynamics in patients with HF and higher pulmonary capillary wedge pressure (PCWP). However, a randomized clinical trial, the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure study, showed that CPAP could not significantly decrease the rate of mortality or heart transplantation in patients with HF and CSR-CSA.

Adaptive servo-ventilation (ASV) has been attracting attention as a new treatment device for CSR-CSA in HF. ASV has several novel functions that could automatically adjust the setting of positive inspiratory pressure according to the analysis of the patient’s spontaneous breathing pattern, which could stabilize the respiratory condition and favorably regulate sympathetic nerve activity, and improve acceptance for use of this device. Therefore, ASV could also improve cardiac dysfunction and the long-term prognosis in HF patients regarding...
CPAP has been shown not to have significant acute effects on CO and SV despite a significant improvement in lung compliance, lung resistance, and airway resistance in patients with acute HF.\(^\text{13-15}\) In contrast, ASV has been reported to have acute beneficial effects on hemodynamics in HF patients.\(^\text{17}\) We have recently demonstrated that ASV can provide acute hemodynamic improvement by increasing stroke volume index (SVI) in HF patients with higher PCWP and greater mitral regurgitation.\(^\text{18}\) However, the acute effects of hemodynamics have not been compared between ASV and CPAP in HF patients. We thus aimed to measure the hemodynamic parameters by right heart catheterization and then compared them during CPAP with air pressure of 5 cmH\(_2\)O and 10 cmH\(_2\)O versus ASV.

**METHODS**

**Study patients:** The present study was a prospective, single-center, intervention trial that included 12 consecutive patients with stable chronic HF who underwent right heart catheterization (RHC) between November 2010 and December 2012 at Hokkaido University Hospital. HF was defined as New York Heart Association (NYHA) functional class II -IV, prior hospitalization due to worsening HF within 1 year, left ventricular ejection fraction (LVEF) lower than 45% by echocardiography, and a plasma brain-type natriuretic peptide (BNP) level higher than 100 pg/mL. We excluded patients with uncontrolled decompensated HF, respiratory failure, severe pulmonary disease, neurological or muscular disease, severe tricuspid valve regurgitation, and congenital heart disease such as atrial or ventricular septal defect. All patients received optimal medical therapy to stabilize HF. The study protocol was approved by the Ethics Committee of Hokkaido University Hospital, and complied with the Declaration of Helsinki. All patients gave written informed consent.

**Study protocol:** Patient hemodynamics were assessed by measuring PCWP, pulmonary artery systolic pressure (PASP), right atrial pressure (RAP), cardiac index (CI), and SVI by RHC with a 7 French Swan-Ganz catheter (Edwards LifeSciences, CA, USA) while awake. CI was measured using the thermo dilution method. Hemodynamic recordings were performed at the deepest expiration within 20 seconds without holding the breath. In each patient, pressure recordings and CI measurement were performed during CPAP with air pressure of 5 cmH\(_2\)O, CPAP 10 cmH\(_2\)O, and ASV for 15 minutes each (Figure 1). Intervals of 5 minutes were set between CPAP and ASV, and also after ASV to confirm the hemodynamics returned to the baseline values. The hemodynamic changes by CPAP 5 cmH\(_2\)O and 10 cmH\(_2\)O were compared to baseline 1, and those by ASV were compared to baseline 2 and the final measurement.

**Intervention:** Both CPAP and ASV were provided by using an Auto Set CS (Teijin Pharma, Tokyo). During CPAP, expiratory positive airway pressure (EPAP) was fixed at 5 cmH\(_2\)O or 10 cmH\(_2\)O. ASV was applied using a favorable fitting nasal mask (Mirage Activa LT, Teijin Pharma, Tokyo) in the default settings; EPAP 5 cmH\(_2\)O, and inspiratory positive airway pressure (IPAP) 3-10 cmH\(_2\)O, without oxygenation. The principle of operation of ASV was described in a previous study.\(^\text{19}\) IPAP was servo-controlled at 0.3 cmH\(_2\)O per L/minute per second automatically based on an analysis of the peak flow, average respiratory rate, and minute ventilation. If the patient’s central respiratory effort ceased, IPAP would increase from the minimum of 3 cmH\(_2\)O up to the maximum of 10 cmH\(_2\)O. Our preliminary studies in 6 patients demonstrated that the median airway pressure measured by Res-Scan\(^\text{TM}\) software (ResMed, Sydney, Australia) was 6.32 ± 0.26 cmH\(_2\)O during ASV, which was significantly higher than that of CPAP 5 cmH\(_2\)O (P < 0.001), but lower than that of CPAP 10 cmH\(_2\)O (P < 0.001) (Figure 2).

**Assessment of patient acceptance for device use:** Patient acceptance for each device was assessed by a questionnaire; 3 points for the most comfortable, 2 points for moderately comfortable, and 1 point for uncomfortable setting.

**Statistical analysis:** Continuous variables are expressed as the mean ± standard deviation. Hemodynamic parameters at baseline 1, during CPAP 5 cmH\(_2\)O, CPAP 10 cmH\(_2\)O, baseline 2, ASV, and final measurements were compared with a one-factor repeated-measures analysis of variance (ANOVA). Post-hoc comparisons were performed by Tukey’s honestly significant difference test. The correlation between baseline PCWP and % of baseline SVI was assessed by Pearson correlation analysis. The analysis of covariance (ANCOVA) with subjects as a random-effects analysis was used to assess whether the slopes of regression lines between baseline PCWP and % of baseline SVI were different for each intervention. Assessment of patient acceptance in each setting was compared by the Steel-Dwass test. For all analyses, a P value < 0.05 was con-

![Figure 1](image)
RESULTS

Patient characteristics: The demographic and clinical characteristics of the study patients are summarized in Table I. The underlying causes of HF were dilated cardiomyopathy in 4 (33%), ischemic cardiomyopathy in 3 (25%), hypertrophic cardiomyopathy in 3 (25%), and others in 2 (17%). Eight (67%) patients were in sinus rhythm, 3 (25%) had biventricular pacing, and 1 (8%) had atrial fibrillation. NYHA functional class was II in 4 (33%), III in 5 (42%), and IV in 3 (25%) patients. Plasma BNP was 585.2 ± 465.6 pg/mL. LVEF was 30.5 ± 10.2% by echocardiography. Medical treatment included angiotensin converting enzyme inhibitors or angiotensin II receptor blockers in 12 (100%), beta blockers in 11 (92%), and diuretics in 8 (67%) patients.

Baseline and changes of hemodynamic parameters: Hemodynamic parameters are presented in Table II. Heart rate, systolic blood pressure, PCWP, PASP, and SVI did not change during either intervention compared to baseline. RAP increased significantly during CPAP 10 cmH₂O (3.6 ± 3.3 to 6.7 ± 1.6 mmHg, \( P = 0.005 \)) and ASV (4.1 ± 2.6 to 6.8 ± 1.5 mmHg, \( P = 0.026 \)). CI decreased significantly during CPAP 10 cmH₂O (2.3 ± 0.4 to 1.9 ± 0.3 L/minute/m², \( P = 0.048 \)). There were no statistically significant differences in either hemodynamic parameter between the baseline 1, baseline 2, and final measure-
The present study demonstrated that SVI and % of baseline SVI were similar among CPAP 5 cmH2O, CPAP 10 cmH2O, and ASV. However, there was a significant positive correlation between PCWP and % of baseline SVI in CPAP 10 cmH2O and ASV. The extent of an increase in SVI was significantly greater in CPAP 10 cmH2O or ASV than in CPAP 5 cmH2O. Moreover, ASV had a significantly greater increase in SVI at the same level of PCWP than CPAP 5 cmH2O or CPAP 10 cmH2O. CI was significantly decreased by CPAP 10 cmH2O despite having a lower airway pressure than CPAP 10 cmH2O. CI was significantly decreased by CPAP 10 cmH2O, but not by ASV, which indicated that high-level positive airway pressure deteriorates the hemodynamic condition due to an excessive increase in intrathoracic pressure and a reduction in venous return. This finding is partially consistent with the study by Yoshiida, et al., who reported that CI was decreased in only CPAP 12 cmH2O but did not change in CPAP 4 and 8 cmH2O, and furthermore, CI was higher in Bi-PAP (EPAP 4 cmH2O + IPAP 9 cmH2O) than in CPAP 4 cmH2O in 18 HF patients. ASV is partially similar to Bi-PAP in terms of increasing the patient’s acceptance and desire for continued use of the device. Another study demonstrated that Bi-PAP with forced ventilation could have reduced the opportunity for tracheal intubation and mechanical ventilation in patients with acute cardiogenic pulmonary edema. However, a big concern has been that Bi-PAP with forced ventilation could have reduced the patient’s acceptance and desire for continued use of the device. Another study demonstrated that Bi-PAP increased the frequency and severity of CSA due to instability of the respiratory pattern and elevation of the apneic threshold.

In the present study, patients with higher PCWP had a greater increase in SVI by ASV. ASV could reduce preload...
and also functional mitral regurgitation (MR) by changing the morphology of the heart, which can lead to an increase in forward SV in HF patients with higher PCWP. These findings were consistent with our previous study in which ASV reduced SVI in control subjects without HF, whereas it increased in HF patients with high PCWP (≥12 mmHg). Furthermore, MR and the left ventricular sphericity index could predict such acute hemodynamic improvement by ASV. SV are largely dependent on preload, and receiving CPAP or ASV (EPAP) causes a reduction of SV by the Frank-Starling mechanism due to the decrease in venous return and left ventricular filling. NPPV with high positive airway pressure may even worsen the hemodynamic conditions in HF patients with low or normal PCWP. In the present study, CI did not change by using ASV with the default setting, whereas it was significantly decreased by CPAP 10 cmH2O. Therefore, we believe that ASV may maintain favorable hemodynamics by autonomic regulation of IPAP even in HF patients without pulmonary congestion.

SV is affected by afterload as well as preload, especially in the failing heart. In HF patients with CSA, the sympathetic nervous system was activated by hypoxia and hypercapnia related to apnea, which increased peripheral vascular resistance and afterload. Short-term ASV could reduce the variation of tidal volume and decrease muscle sympathetic nerve activity in HF patients, but CPAP could not. Therefore, the beneficial acute hemodynamic effects by ASV in the present study might be also due to the reduction of afterload by inhibiting sympathetic nerve activity in HF patients. However, their study focused on the sympathetic inhibitory effect of ASV in comparison with CPAP, and it was still unclear whether ASV was better or not than CPAP in terms of the hemodynamic effect.

ASV has an additional benefit in HF patients, with the exception of hemodynamics, because ASV and CPAP 5 cmH2O had patient acceptance for use of the device that was superior to that of CPAP 10 cmH2O. This finding is in agreement with a previous study in which operating time as an index of acceptance was significantly longer in ASV than in CPAP.

The reason ASV may have a superior adherence might be lower airway pressure. ASV could automatically regulate IPAP between 3-10 cmH2O depending on the patient’s respiratory condition and provide EPAP 5 cmH2O in the default setting. As a consequence, maximum airway pressure of ASV can be as high as 15 cmH2O (EPAP 5 cmH2O + IPAP 10 cmH2O). However, the actual median airway pressure during ASV was significantly lower than CPAP 10 cmH2O (Figure 2).

According to the present guidelines, CPAP is the first option of respiratory support therapy for acute HF. However, we demonstrated more beneficial acute hemodynamic effects using ASV in HF patients, especially in those with higher PCWP. Therefore, we believe ASV can be used in patients with acute decompensated HF. However, the efficacy of ASV in acute HF as an alternative treatment to CPAP needs to be confirmed in randomized controlled trials.

There are several limitations to the present study. First, the patients were kept awake during the study because ASV and CPAP were often used while they were awake to treat HF. However, the hemodynamic changes during ASV and CPAP might differ between awake and asleep conditions. Second, the duration of each intervention was too short to detect hemodynamic changes. In fact, CPAP and ASV were performed for 30 minutes in two previous studies. However, our previous study demonstrated that 15 minutes was long enough to achieve the efficacy of ASV in HF patients. Third, the order of interventions was fixed as CPAP 5 cmH2O, CPAP 10 cmH2O, and ASV. Therefore, the prior intervention might have affected the subsequent results. However, in the present study, we allowed time for recovery between CPAP and ASV, and further confirmed that hemodynamic parameters returned to their baseline values (Table II). Fourth, this study was designed to assess the short-term effects of hemodynamic changes between CPAP and ASV. Therefore, the hemodynamic effects under chronic treatment might differ from the present results. Finally, the sample size was small and the study was performed at a single-center. Therefore, multicenter and randomized controlled trials are needed to investigate whether the present findings can be extrapolated to general HF patients.

In conclusion, ASV had acute beneficial effects on hemodynamics and favorable device acceptance compared to CPAP in patients with HF.

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