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Original article

# Beneficial effects of adaptive servo-ventilation therapy on albuminuria in patients with heart failure

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ABSTRACT

*Background:* Short-duration adaptive servo-ventilation (ASV) therapy can be effective for heart failure (HF) patients. Albuminuria is recognized as a prognostic marker for HF. We investigated whether short-duration and short-term ASV therapy reduced albuminuria in HF patients.

*Methods and results:* Twenty-one consecutive HF patients were divided into two groups: those who tolerated ASV therapy (ASV group, $n = 14$) and those who did not (non-ASV group, $n = 7$). ASV therapy was administered to enrolled patients for 1 week for 2 h per day (1 h in the morning and 1 h in the afternoon). The urinary albumin to creatinine ratio (UACR), urinary 24 h norepinephrine (NE) excretion, high-sensitivity C-reactive protein (hs-CRP), and plasma brain natriuretic peptide (BNP) levels were measured before and 1 week after ASV therapy. In the ASV group, but not the non-ASV group, the UACR significantly decreased, together with a decrease in urinary NE and hs-CRP levels. There were significant correlations between the changes in UACR and hs-CRP and between the changes in urinary NE and hs-CRP. Multiple linear regression analyses indicated that ASV use was the strongest predictor of decreased UACR.

*Conclusion:* Albuminuria, urinary NE, and hs-CRP levels reduced in HF patients who could receive short-duration and short-term ASV therapy. Anti-inflammatory effects of ASV therapy may partly mediate the reduction of albuminuria.



## Introduction

Various cardiovascular pathologies are closely associated with albuminuria, which contributes to the progression of heart failure (HF). These include activation of the renin–angiotensin system (RAS) [1], impaired glomerular blood flow [2], systemic endothelial dysfunction, and vascular inflammation [3]. Microalbuminuria is a risk and prognostic factor for chronic HF [4,5], as well as renal failure. In the clinic, the urinary albumin to creatinine ratio (UACR) is used as a simple and convenient index to evaluate albuminuria excretion.

We previously showed that adaptive servo-ventilation (ASV) therapy improved cardiac function and prognosis in HF patients, and the effects were apparent in HF patients regardless of sleep-disordered breathing [6]. We further showed that cardiac contractile dysfunction improved even in patients who used ASV for a short duration [7]. It is likely that mechanisms underlying HF improvement with ASV therapy involve reductions in sympathetic nerve activity as well as hemodynamic assistance. Elevated sympathetic nerve activity activates the RAS [8], which can cause vascular inflammation and remodeling, where albuminuria was observed. Moreover, we previously found that ASV therapy improved renal function through a reduction of inflammatory responses [9]. Based on these findings, we hypothesize that short-duration ASV therapy may reduce albuminuria in patients with HF.

## Methods

### Study design

We enrolled 21 consecutive HF patients for ASV therapy from November 2011 to May 2012 who met the following indications: (1) diagnosed with New York Heart Association (NYHA) class II or III stable HF, (2) had left ventricular ejection fraction (LVEF) <55%, and (3) could receive optimized medical treatment for HF. Patients

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were excluded if they had already experienced another positive airway pressure therapy, could not accept conventional drug therapy, or were admitted 6 months prior to ASV therapy. The study design is summarized in Fig. 1. Enrolled patients were divided into two groups based on the results of an ASV mask-fitting test and a 20 min hemodynamic check during ASV therapy: patients who tolerated ASV therapy (ASV group, $n = 14$) and those who did not (non-ASV group, $n = 7$). The day after the fitting tests, patients underwent ASV therapy for 2 h per day: 1 h in the morning from 10 to 11 AM and 1 h in the afternoon from 2 to 3 PM. Physical examination, echocardiographic parameters, plasma brain natriuretic peptide (BNP) levels, high sensitivity C-reactive protein (hs-CRP) levels, 24-h urinary norepinephrine (NE) excretion levels, 24-h creatinine clearance (CCr), and UACR were measured before and 1 week after ASV treatment in the two groups. We evaluated the effects of ASV therapy on albuminuria in stable chronic HF patients. Therefore, at the time of the operation of ASV therapy, patients who had just recovered from acute HF or decompensated HF were excluded from the study. Prescriptions were not changed during the week of ASV therapy. All participants provided informed consent prior to enrollment in the study. This study was approved by the clinical research and ethics committee of the University of Akita.

*Laboratory measurements*

Plasma BNP and hs-CRP levels were analyzed from blood samples using standard methods. Albuminuria was analyzed using a spot urine sample. Urinary NE excretion and CCr levels were measured from 24-h urine samples.

*Echocardiography*

Two-dimensional, M-mode, Doppler echocardiography (iE33; Philips Medical Systems, Andover, MA, USA) was used to evaluate various cardiac parameters in the patients. The LVEF, LV end-systolic volume (LVESV), and LV end-diastolic volume (LVEDV) were estimated from the apical two- and four-chamber views using the modified biplanar Simpson's rule. The sonographers were blinded to the study protocol and were not involved in treating the enrolled patients.

*ASV therapy*

ASV therapy (AutoSet CS®; ResMed, Sydney, Australia) was initiated in 21 consecutive patients with HF. During the first 20 min of ASV treatment, heart rate (HR), oxygen saturation ($SaO_2$), and blood pressure were monitored every 5 min. ASV therapy was initiated by experienced physicians who were familiar with the ASV device. An expiratory positive airway pressure of 5 cm $H_2O$ and inspiratory pressure support between 3 and 10 cm $H_2O$ were used. A follow-up assessment was conducted 1 week later. Compliance data were downloaded from the ASV devices and checked 1 week after ASV therapy. In addition, physicians who were familiar with ASV therapy observed and monitored patients every 20 min during the therapy. Enrolled patients were instructed to use the ASV device in bed while resting in a supine position, whether or not they were sleeping.

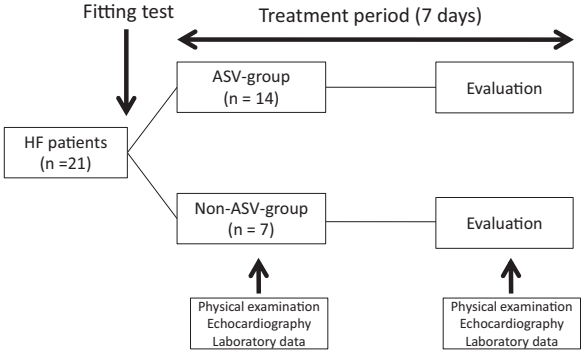


**Fig. 1.** Flow diagram of the study design. HF, heart failure; ASV, adaptive servo-ventilation.

*Statistical analysis*

Continuous variables are expressed as means ± standard deviation (SD) except for UACR and BNP data. For continuous and normally distributed data, Student's *t*-test for comparison between groups or paired *t*-test for paired sample were used, as appropriate. For non-normally distributed data, a Wilcoxon signed-rank test was used for paired sample, and the Mann–Whitney *U* test was used when comparing 2 groups. The data of plasma BNP levels and UACR were natural log-transformed. Categorical variables were compared using $\chi^2$ analysis and Yate's correction. Correlations were analyzed using Pearson's correlation coefficient. All parameters with $p < 0.10$ on univariate analysis, baseline ln BNP and age were entered into the multivariate analysis. A *p*-value of $<0.05$ indicated statistical significance. All analyses were performed using the Statistical Package for the Social Science Windows ver. 16.0 (SPSS, Chicago, IL, USA).

## Results

Baseline characteristics of the enrolled HF patients are shown in Table 1. No significant differences in age, gender, body mass index (BMI), blood pressure, pharmacological data, echocardiographic parameters, or laboratory data were found between the two groups. A total of 14 patients used the ASV device for 2 h during the day (ASV group), while 7 patients could not tolerate ASV therapy (non-ASV group) due to mask intolerance ($n = 5$) or subjective intolerance of positive airway pressure ($n = 2$). No significant complications were observed during the 1 week of therapy.

Table 2 shows the changes in physical, echocardiographic, and laboratory data for each group. Echocardiography data including LVEF and LVEDV were not changed in either group. There was a significant decrease in plasma BNP in the ASV group [−36.8 ± 25.9% (583.4 ± 292.9 to 414.6 ± 584.1 pg/mL)] compared to the non-ASV group [2.9 ± 39.4% (328.7 ± 209.4 to 311.2 ± 202.6 pg/mL), $p = 0.011$]. However, there were no differences in the physical findings between the groups, including HR, blood pressure, and BMI.

Fig. 2A depicts the relative change in UACR in patients before and 1 week after ASV therapy. There are significant differences between the groups [ASV group: −19.6 ± 30.0% (31.5 ± 10.3 to 23.7 ± 10.2 mg/gCr); non-ASV group: 24.8 ± 27.1% (32.1 ± 14.2 to 40.2 ± 17.9 mg/gCr); $p = 0.003$]. The relative changes in 24-h urinary NE excretion levels are shown in Fig. 2B. Urinary NE excretion significantly decreased in the ASV group [−28.1 ± 22.8% (219.1 ± 76.6 to 139.9 ± 63.2 μg/day)] compared to the non-ASV group [1.4 ± 29.5% (204.0 ± 107.2 to 203.6 ± 114.1 μg/day), $p = 0.037$]. Fig. 2C shows the change in hs-CRP after therapy. It also changed significantly more in the ASV group [−33.4 ± 24.9% (0.29 ± 0.28 to 0.22 ± 0.25 mg/dL)] than in the non-ASV group [6.8 ± 45.3% (0.28 ± 0.33 to 0.25 ± 0.31 mg/dL), $p = 0.044$]. Fig. 2D shows the relative change in 24-h CCr after therapy. It was −5.5 ± 13.1% (63.8 ± 28.4 to 59.7 ± 26.9 mL/min) in the ASV group and −0.2 ± 17.7% (58.5 ± 26.1 to 61.4 ± 34.7 mL/min) in the non-ASV group, although the differences were not statistically significant ($p = 0.263$).