Effect of Short-Duration Adaptive Servo-Ventilation Therapy on Cardiac Function in Patients With Heart Failure

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Background: The aim of this study was to investigate whether short-duration adaptive servo-ventilation (ASV) therapy improves cardiac function in heart failure (HF) patients.

Methods and Results: Consecutive HF patients (n=86) were divided into 3 groups: group A, ASV for a mean of ≥ 4 h; group B, ASV for ≥ 1 to < 4 h per day; and group C, no ASV or ASV < 1 h. The frequency of ASV use did not significantly differ between groups A ($79.3 \pm 19.2\%$) and B ($70.9 \pm 17.4\%$). After 6 months, a significant increase in left ventricular ejection fraction (LVEF), significant decrease in plasma brain natriuretic peptide (BNP) and decrease in LV end-diastolic volume (LVEDV) were observed in groups A (LVEF, $5.0 \pm 8.1\%$; BNP, $-24.9 \pm 33.7\%$; LVEDV, $-6.2 \pm 10.1\%$) and B (LVEF, $3.5 \pm 5.5\%$; BNP, $-16.5 \pm 24.6\%$; LVEDV, $-5.1 \pm 8.2\%$) as compared with group C (LVEF, $-1.5 \pm 6.0\%$, $P=0.004$, $P=0.017$; BNP, $2.8 \pm 10.2\%$, $P=0.002$, $P=0.017$; LVEDV, $0.8 \pm 9.1\%$, $P=0.031$, $P=0.043$). Significant correlation was seen between the total ASV time and changes of LVEF ($r=0.369$, $P=0.002$), BNP ($r=-0.445$, $P<0.001$), and LVEDV ($r=-0.374$, $P=0.001$). Admission rate was lower in groups A (4.1%) and B (7.1%) than in group C (25%, log-rank test; $P=0.042$, $P=0.045$). Multivariate analysis showed that the frequency of ASV use was a strong parameter for the improvement of LVEF (coefficient=0.284, standard error=0.035, $P=0.019$).

Conclusions: Even a short-duration of ASV therapy may improve cardiac function in HF patients. (*Circ J* 2012; 76: 2606–2613)

Key Words: Adaptive servo-ventilation; Cardiac function; Heart failure; Short-duration

Adaptive servo-ventilation (ASV) was initially developed to treat sleep-disordered breathing (SDB), but it is an effective therapeutic option for patients with heart failure (HF).¹ ASV therapy is commonly used throughout the night for HF patients who suffer from SDB² because it prevents the hypoxic stress, oxidative stress, metabolic dysregulation and elevated sympathetic nerve activity (SNA) caused by SDB.¹ Although our previous study was retrospective and could not provide a definite conclusion, nighttime ASV therapy for ≥ 4 h improved cardiac function, renal function,³ and prognosis in HF patients.^{1,4} Moreover, ASV therapy has been shown to be effective in HF patients regardless of the severity of SDB.⁴

Decreased lung inflation caused by abnormal breathing can reduce pulmonary vagal afferent activity, thus enhancing SNA,⁵ which is associated with malignant arrhythmias, hematologic abnormalities,⁶ decreased cardiac pump function, and a poor prognosis in HF patients. ASV therapy provides hemodynam-

ic support to suppress this vicious cycle and improve cardiac function in HF patients.⁴

Nevertheless, a relatively large number of HF patients are unable to wear an ASV device,^{1,4} so a novel therapeutic approach that avoids the problems associated with ASV intolerance is desirable. HF patients frequently show abnormal breathing patterns, such as rapid, shallow breathing and periodic breathing, even during the day.⁷ A recent study reported that short-duration ASV therapy immediately reduced SNA in HF patients by stopping abnormal breathing patterns.⁸ Either the prevention of abnormal breathing or the hemodynamic support by ASV therapy may contribute to an increase in left ventricular ejection fraction (LVEF), decreased concentration of plasma brain natriuretic peptide (BNP) and a reduced rate of hospital admissions in HF patients.

Therefore, even a short-duration of ASV therapy may assist HF patients who cannot tolerate long-duration ASV therapy. The present study aimed to clarify whether short-duration ASV

Received March 12, 2012; revised manuscript received June 22, 2012; accepted July 4, 2012; released online July 31, 2012 Time for primary review: 23 days

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All authors declare no conflicts of interest.

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ISSN-1346-9843 doi:10.1253/circj.CJ-12-0328

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Table 1. Baseline Characteristics of the HF Subjects

	Group A (n=24)	Group B (n=42)	Group C (n=20)	P value
Age (years)	66.9±11.4	66.4±12.0	70.7±6.4	0.481
Male	22 (91.7)	34 (80.9)	16 (80.0)	0.460
BMI (kg/m ²)	24.0±2.1	23.4±4.3	23.3±2.1	0.135
NYHA class II	19 (79.2)	27 (64.3)	12 (60.0)	0.333
Hypertension	20 (83.3)	31 (73.8)	17 (85.0)	0.498
Diabetes mellitus	8 (33.3)	9 (21.4)	5 (25.0)	0.565
Dyslipidemia	10 (41.7)	15 (35.7)	7 (35.0)	0.867
Underlying heart disease				
Ischemic heart disease	5 (20.8)	16 (38.1)	7 (35.0)	0.342
Valvular heart disease	5 (20.8)	13 (30.9)	4 (20.0)	0.536
Cardiomyopathy	6 (25.0)	14 (33.3)	4 (20.0)	0.513
Heart rhythm disorder				
Atrial fibrillation	10 (41.7)	11 (26.2)	8 (40.0)	0.351
Pacemaker	5 (20.8)	12 (28.6)	5 (25.0)	0.785
Blood pressure				
Systolic (mmHg)	115.8±15.8	116.2±17.0	111.6±19.9	0.753
Diastolic (mmHg)	63.7±11.1	61.0±11.4	63.7±11.2	0.618
Heart rate (beats/min)	66.5±8.6	65.1±6.6	69.1±7.0	0.109
Medication				
ACEI/ARB	22 (91.7)	41 (97.6)	18 (90.0)	0.402
β -blocker	19 (79.2)	39 (92.9)	17 (85.0)	0.262
Aldosterone antagonist	16 (66.6)	33 (78.6)	12 (60.0)	0.278
Diuretic	17 (87.5)	39 (92.9)	17 (85.0)	0.595
Calcium antagonist	13 (54.2)	17 (40.5)	10 (50.0)	0.528
Statin	12 (50.0)	21 (50.0)	8 (40.0)	0.735
Echocardiography data				
LVEF (%)	41.2±8.8	40.2±9.8	42.4±9.4	0.717
LVEDV (ml)	157.1±34.0	160.5±44.8	158.1±34.8	0.830
LVESV (ml)	93.5±30.6	98.6±46.1	92.6±33.2	0.945
Laboratory data				
Plasma BNP (pg/ml)	215.1±141.5	314.0±171.7	285.9±186.8	0.091
hs-CRP (mg/dl)	0.21±0.15	0.17±0.14	0.22±0.16	0.324
eGFR (ml·min ⁻¹ ·1.73m ⁻²)	57.6±20.6	52.2±18.1	60.6±24.9	0.424
Polysomnography data				
AHI (n/h)	30.2±13.7	26.4±13.9	24.1±12.3	0.224
AI (n/h)	12.3±10.9	11.9±11.5	9.5±7.4	0.871
Central type (n/h)	4.2±4.7	5.7±6.2	4.6±5.3	0.615
Obstructive type (n/h)	6.1±8.7	3.8±4.6	3.6±6.2	0.658
HI (n/h)	18.0±12.1	14.9±8.4	14.5±8.1	0.654
Mean SaO ₂ (%)	94.5±1.8	93.5±2.3	93.8±2.7	0.128
Arousal index (n/h)	28.5±11.5	32.6±12.0	28.9±10.4	0.372
Total sleep time (h)	5.3±1.1	5.5±0.8	5.2±1.1	0.251

Data are mean±SD or n (%).

HF, heart failure; BMI, body mass index; NYHA, New York Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; BNP, brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; AHI, apnea-hypopnea index; AI, apnea index; HI, hypopnea index.

therapy can improve cardiac function in HF patients.

Methods

Study Design

Between January 2009 and June 2011, 86 consecutive patients diagnosed with New York Heart Association (NYHA) class II or III HF, LVEF <55% and admitted to hospital for acute HF

in the 6 months before ASV therapy initiation were enrolled. The patients were retrospectively divided into 3 groups according to their use of ASV during a 6-month period: group A, ASV for ≥4h per day; group B, ASV ≥1h and <4h per day; and group C, no ASV or ASV <1h. Echocardiographic parameters, concentrations of plasma BNP and high-sensitivity C-reactive protein (hs-CRP), and the estimated glomerular filtration rate (eGFR) were measured before and after 6 months of

Table 2. Characteristics of ASV Device Use by HF Patients						
	Group A	Group B	Group C	P value		
				A vs. B	A vs. C	B vs. C
Frequency of ASV use, %	79.3±19.2	70.9±17.4	4.8±8.6	0.115	<0.001	<0.001
ASV use time, h/day	6.7±1.8	2.2±0.9	0.1±0.2	<0.001	<0.001	<0.001

Group A: ASV use ≥4 h/day; Group B: 1 h/day≤ASV use<4 h/day; Group C: ASV use <1 h/day or discontinue. ASV, adaptive servo-ventilation; HF, heart failure.

ASV treatment in all 3 groups, as reported previously.³ Patients who had recovered from acute HF or decompensated HF were excluded from the study. If enrolled patients experienced a decrease in blood pressure (BP; systolic BP <100 mmHg) or increased BP (systolic BP >140 mmHg), calcium antagonists or diuretics were decreased or increased by increments of half the previous dosage. Additionally, if HF patients experienced a minimum of 3 kg increase or decrease in body weight, diuretics were decreased or added, respectively, by half-increments.³ The doses of angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker or β -blocker were not changed during the follow-up, taking into account their cardioprotective effects.

Polysomnography

Enrolled patients underwent overnight polysomnography monitoring using the ProFusion PSG® Sleep Diagnostic System (Compumedics, Vic., Australia), which continuously acquires the data of an electroencephalogram, electrooculogram, oxygen saturation (SaO₂), airflow, snoring, and thoracoabdominal motion. Apnea was defined as an absence of inspiration for ≥10 s, and obstructive apnea was distinguished from the central type by analyzing chest and abdominal motions. Hypopnea was defined as ≥30% reduction in monitored airflow accompanied by a decrease in SaO₂ of ≥4%. Arousal responses were defined according to the recommendations of the American Sleep Disorders Association. Apnea-hypopnea index (AHI) was defined as the number of apnea and hypopnea episodes per hour during sleep. AHI ≥5/h was defined as SDB. A diagnosis of moderate-to-severe SDB was assigned an AHI of ≥15/h, and non-SDB to mild SDB was assigned an AHI of <15/h. Central sleep apnea was defined as AHI >5/h with >50% of

the events labeled as the central type rather than the obstructive type of apnea.⁹

Echocardiography

Two-dimensional, M-mode, Doppler echocardiography (iE33; Philips Medical Systems, Andover, MA, USA) was used to evaluate various cardiac parameters. The LVEF, LV end-systolic volume, and LV end-diastolic volume (LVEDV) were estimated from the apical 2- and 4-chamber views using the modified biplanar Simpson’s rule. The sonographers were blinded to the study protocol and were not involved in treating the patients.

ASV Therapy

ASV therapy (AutoSet CS®; ResMed, Sydney, NSW, Australia) was initiated in the 86 consecutive HF patients. The first 3 days of the treatment period were used as the mask-fitting period. During the first 20 min of ASV treatment, each patient’s heart rate (HR), SaO₂, and BP were monitored every 5 min. A follow-up assessment was conducted 6 months later. ASV therapy was initiated by experienced physicians who were familiar with the device. An expiratory positive airway pressure of 5 cmH₂O and inspiratory pressure support between 3 and 10 mH₂O were used. Compliance data were downloaded monthly from the ASV devices and checked at the outpatient clinic. Based on these data, the patients were divided into the 3 groups already described. Some patients refused ASV therapy or could not tolerate ASV therapy for ≥1 h because of the positive airway pressure or mask discomfort. These patients were defined as unable to tolerate ASV therapy. The requirements for HF patients undergoing ASV therapy were as follows: (1) frequency of device use, >2 weeks per month; (2) mean

Figure 2. (A) Change in LVEF, (B) plasma BNP concentration and (C) LVEDV during the 6-month follow-up period. Group A: patients using ASV therapy for ≥ 4 h/day; Group B: patients using the ASV device for ≥ 1 to < 4 h during the day. Group C: patients who refused ASV therapy or who could not use the ASV device for ≥ 1 h. ASV, adaptive servo-ventilation; BNP, brain natriuretic peptide. LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume.

duration of ASV therapy per day, ≥ 1 h; (3) ASV not discontinued for > 3 days; and (4) daytime use in bed while supine, regardless of the presence or absence of sleep. Based on the data downloaded from the ASV device, the frequency of ASV use (%), mean use time (h/day), and total use time (frequency of ASV use [%]/100 $\times$ mean use time [h/day] $\times$ 180 days) were calculated.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ SD. Student's t-test was used to compare the 2 groups. Analysis of variance (ANOVA) was used when comparisons involved more than 2 groups. When group differences were found, 1-way ANOVA was followed by Scheffé's method to test for significant differences among the means in all groups. Categorical variables were compared using chi-squared analysis and Yate's correction, as necessary. The time to a cardiac event was estimated

Figure 3. Kaplan-Meier survival curve in groups A, B, and C during 6-month follow-up period. Group A: patients using ASV therapy for ≥ 4 h/day; Group B: patients using the ASV device for ≥ 1 to <4 h during the day. Group C: patients who refused ASV therapy or who could not use the ASV device for ≥ 1 h. ASV, adaptive servo-ventilation.

using the Kaplan-Meier method, with comparisons made using the log-rank test. Correlations were analyzed using Pearson's correlation coefficient. Multiple linear regression analysis was used to identify the influential parameters for the LVEF changes. All parameters with $P < 0.10$ on univariate analysis were entered into the multivariate analysis as previously reported.⁶ $P < 0.05$ was deemed to indicate statistical significance. All analyses were performed using SPSS for Windows Windows ver. 16.0 (SPSS, Chicago, IL, USA).

Results

The baseline characteristics of the enrolled HF patients are listed in **Table 1**. No significant differences in age, sex ratio, body mass index, BP, HR, pharmacological data, echocardiographic parameters, laboratory data or polysomnography data were found among the 3 groups. A total of 24 patients used the ASV device for a mean of ≥ 4 h during the day (group A), 42 patients had a mean ASV duration of ≥ 1 h to <4 h per day (group B), and 20 patients could not tolerate ASV therapy (group C). The AHI score was 30.2 ± 13.7 in group A, 26.3 ± 13.9 in group B, and 24.1 ± 12.3 in group C. There were no significant differences among the 3 groups ($P = 0.224$). No significant differences were seen between the AHI scores of group A and that of nighttime users in group B (30.2 ± 13.7 vs. 25.1 ± 13.9 , $P = 0.263$, respectively).

The study design is depicted in **Figure 1**. All patients in group A used ASV therapy for ≥ 4 h during the night. Of the 42 patients in group B, 15 (35.7%) used ASV therapy during the night, 13 (31.0%) used it during the day, and 14 patients (33.3%) used the ASV device during both nighttime and daytime. All patients in group B used the ASV device for ≥ 1 to 4h/day during the follow-up period. Of the 20 patients in group C, 5 could not tolerate ASV therapy for ≥ 1 h/day during the 6-month period and 15 patients declined the therapy because of mask intolerance ($n = 9$) or subjective intolerance of positive airway pressure ($n = 6$). The HF patients in groups A and B continued ASV therapy throughout the 6-month period. No deaths occurred during the 6-month follow-up period.

The characteristics of ASV device use during the study period are shown in **Table 2**. The frequency of ASV use over the 6-month period was $79.3 \pm 19.2\%$, $70.9 \pm 17.4\%$, and $4.8 \pm 8.6\%$ in groups A, B, and C, respectively. A significant difference was observed between groups A and C ($P < 0.001$) and between groups B and C ($P < 0.001$), but no significant difference was found between groups A and B ($P = 0.115$). The duration of daily ASV use was 6.7 ± 1.8 h, 2.2 ± 0.9 h, and 0.1 ± 0.2 h in groups A, B, and C, respectively. The duration was significantly different between groups A and B ($P < 0.001$), A and C ($P < 0.001$), and B and C ($P < 0.001$).

Figure 2A shows the change in LVEF after 6 months of ASV therapy. The change in groups A ($5.0 \pm 8.1\%$) and B ($3.5 \pm 5.5\%$) was significantly different from the change in group C ($-1.5 \pm 6.0\%$; $P = 0.004$, $P = 0.017$, respectively). The change in LVEF was not significantly different between groups A and B ($P = 0.646$).

Changes in BNP concentration after 6 months of ASV therapy are shown in **Figure 2B**. BNP decreased significantly in groups A ($-24.9 \pm 33.7\%$ [215.1 ± 141.5 to 157.0 ± 126.5 pg/ml]) and B ($-16.5 \pm 24.6\%$ [314.0 ± 171.7 to 247.9 ± 136.1 pg/ml]) as compared with group C ($2.8 \pm 10.2\%$ [285.9 ± 186.8 to 285.5 ± 178.0 pg/ml]; $P = 0.002$, $P = 0.017$, respectively). The change in BNP concentration did not differ significantly between groups A and B ($P = 0.401$).

Figure 2C shows the change in LVEDV after 6 months of ASV therapy. It was significantly reduced in groups A ($-6.2 \pm 10.1\%$) and B ($-5.1 \pm 8.2\%$) as compared with group C ($0.8 \pm 9.1\%$; $P = 0.031$, $P = 0.043$, respectively). The change in LVEDV was not significantly different between groups A and B ($P = 0.887$).

The hs-CRP concentrations decreased significantly in group A ($-62.4 \pm 27.6\%$) and B ($-46.2 \pm 36.4\%$) when compared with group C ($8.5 \pm 28.3\%$; $P < 0.001$, $P < 0.001$, respectively). A significant increase in the eGFR was shown in groups A ($6.7 \pm 16.9\%$) and B ($6.0 \pm 16.5\%$) as compared with group C ($-11.5 \pm 12.0\%$; $P = 0.001$, $P = 0.001$, respectively).

The hospital admission rate during the 6-month follow-up period was 4.1% in group A, 7.1% in group B and 25% in

Figure 4. Correlations between total time of ASV use and changes in LVEF (A), plasma BNP concentration (B), and LVEDV (C) in HF patients with ASV therapy. Yellow circle: group A. Orange circle: group B. Blue circle: group C. ASV, adaptive servo-ventilation; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; LVEDV, left ventricular end-diastolic volume; HF, heart failure.

group C. Kaplan-Meier survival analysis showed that the event-free rate at 6 months was greater in groups A and B, when compared with groups C (P=0.042, P=0.045, log-rank test; Figure 3).

Figure 4 shows the correlations between total ASV use time and changes in LVEF, plasma BNP concentration and LVEDV in patients with ASV therapy (group A, group B, and 5 patients of group C). Significant correlations were found between total ASV use time and changes in LVEF (r=0.369, P=0.002, Figure 4A), plasma BNP concentration (r=-0.445, P<0.001, Figure 4B), and LVEDV (r=-0.374, P=0.001, Figure 4C).

The improvement in LVEF (44.4±8.4 to 46.6±8.0%, P<0.001), plasma BNP concentration (267.6±163.1 to 223.0±130.0pg/ml, P=0.011), and LVEDV (143.5±24.7 to 133.4±

Table 3. Multiple Linear Regression Analyses for Change in LVEF of HF Patients			
	Change in LVEF		
	Coefficient	SE	P value
Frequency of ASV use	0.284	0.035	0.019
ASV use time	0.118	0.305	0.338
Change in hs-CRP	-0.236	0.022	0.053
Change in eGFR	0.218	0.044	0.074

R²=0.267, P<0.001.
SE, standard error. Other abbreviations as in Tables 1,2.

25.7 ml, $P=0.002$) also occurred in nighttime ASV users in group B ($n=15$). Moreover, among the daytime users of ASV in group B ($n=13$), LVEF was significantly increased (38.8 ± 10.8 to $40.0 \pm 11.2\%$, $P=0.041$), while plasma BNP concentration (321.8 ± 167.9 to 223.6 ± 145.3 pg/ml, $P=0.014$) and LVEDV (159.7 ± 40.6 to 153.6 ± 45.3 ml, $P=0.044$) were significantly decreased. The changes in LVEF, plasma BNP concentration and LVEDV were not statistically significant between daytime and nighttime users of ASV in group B.

In the multiple linear regression analyses including the duration of ASV use, the frequency of ASV use, changes in hs-CRP concentration and changes in eGFR, the frequency of ASV use (coefficient=0.284, SE=0.035, $P=0.019$) was significantly associated with changes in LVEF (Table 3).

Discussion

The present study made several major insights into the effects of short-duration ASV therapy on cardiac function in HF patients. Short-duration ASV therapy improved cardiac function and reduced both the plasma BNP concentration and LVEDV, together with a decrease in hs-CRP concentration and an increase in the eGFR. Total time of ASV use significantly correlated with improvement of cardiac function. Multiple linear regression analyses shows that the frequency of ASV use was a strongly influential factor in the improvement of cardiac function. This is the first report to show that short-duration ASV therapy can be a novel therapeutic approach for HF patients who cannot tolerate long-duration ASV therapy.

CPAP therapy could provide many beneficial effects for HF patients, but it occasionally has adverse hemodynamic effects in such patients because of the continuous increase in intrathoracic pressure.¹⁰ ASV therapy emerged as a novel non-pharmacological treatment for HF patients and has been shown to improve HF coexistent with SDB with no hemodynamic disadvantages.^{1,3,11} Previously, we showed that ASV treatment for ≥ 4 h during the night improved cardiac function and the prognosis in HF patients with no clinical adverse effects.^{1,4} These beneficial effects of ASV therapy may be attributable to not only the prevention of hypoxic stress, oxidative stress, and metabolic dysregulation but also to its property of low-grade expiratory positive airway pressure during respiration, where automatic self-adjustment to the patient's breathing efforts is applied. Nevertheless, discomfort from the mask or the positive airway pressure associated with ASV therapy may present serious problems for patient compliance. In our previous study, 37 (42%) of 88 consecutive HF patients could not continue ASV therapy because of mask discomfort and were defined as patients who could not tolerate ASV therapy.^{1,4} Initially, ASV therapy was developed as a therapeutic option for eliminating SDB, such as central sleep apnea.^{2,11} It was commonly believed that patients should undergo ASV therapy during sleep for as long as possible. Recently, it was reported that HF patients frequently develop a rapid, shallow breathing pattern or periodic breathing patterns during the daytime.⁷ This abnormal breathing reduces pulmonary vagal afferents activity, thus enhancing SNA,^{5,8} which is closely associated with reduced cardiac function and the prognosis of HF patients.¹² The abnormal breathing patterns could be an important therapeutic target for ASV therapy, because the therapy can produce regular, slow breathing in HF patients by maintaining the patient's minute ventilation, and immediately reducing SNA.⁸ In the present study, moderate-to-severe SDB was observed in patients in all groups, implying that the HF patients who were enrolled in this study had abnormal breathing patterns. How-

ever, it was not clear whether ASV therapy provides beneficial effects for HF patients who cannot use the ASV device for ≥ 4 h/day. Moreover, it is unknown how long or how often an ASV device must be used each day to produce beneficial effects in HF patients. The present study was designed to test the hypothesis that short-duration ASV therapy could improve cardiac function in HF patients.

In the present study, we found that 23% of the HF patients either could not continue or declined ASV therapy, 28% could use ASV treatment only during the night, and 49% of the patients underwent the complete short-duration ASV therapy. As a result, more patients in the current study than in our previous study were able to continue ASV therapy and showed increased cardiac contractile function, decreased plasma BNP concentrations, and reduced LVEDV. We believe that short-duration ASV therapy will improve the compliance of HF patients with this therapeutic approach and thus increase the number of patients who benefit from ASV treatment.

The present study showed that long-duration nighttime, as well as short-duration, ASV therapy improved cardiac function in HF patients. These results imply that the low-grade expiratory positive airway pressure and pressure support of ASV prevents an increase in preload, even while the HF patient is supine, without causing hemodynamic problems.⁴ In this study, cardiac function in both daytime and nighttime short-duration ASV users significantly improved, supporting the idea that the hemodynamic assistance of ASV therapy is an important mechanism for the refinement of cardiac function. The lung inflation and expansion that occurs during ASV therapy decreases SNA and improves HF.^{5,8} However, the underlying mechanisms mediating the beneficial effects of short-duration ASV therapy in HF patients are not clear. It may be that short-duration ASV therapy reduces preload or that SNA has a carryover effect that triggers an improvement in cardiac function and establishment of a new hemodynamic balance. Short-duration use of the ASV device may cause slight changes in circulatory system function that result in hemodynamic stabilization in HF patients. In the present study, the frequency of ASV device use per month was relatively high in groups A and B; thus, according to the multiple regression analyses, it may be that the frequency, as well as the duration, of ASV therapy is a critical factor for the improvement of cardiac function. These results imply that it is important to extend total ASV use time by increasing the frequency of ASV device use or the duration of ASV use per day for an improvement in the cardiac function of HF patients.

Although changes in several parameters related to cardiac function were not statistically different between groups A and B, the changes tended to be greater in those undergoing long-duration ASV use than in those who underwent short-duration ASV use, suggesting that nighttime long-duration ASV treatment may be more beneficial than short-duration ASV use. A possible explanation is that long-duration ASV use prevents more adverse effects related to SDB,¹³ hemodynamic deterioration¹⁴ and abnormal breathing⁸ than does short-duration ASV therapy. However, our results indicate that short-duration ASV therapy is more beneficial than no ASV therapy in HF patients. Thus, we believe that short-duration ASV therapy is an alternative approach for HF patients who are unable to tolerate nighttime long-duration ASV therapy.

Study Limitations

Both the present and previous study were based on a retrospective approach, whereby these studies can not give definite conclusions related to the effects of ASV on HF. Moreover,

this approach has the risk of leading to inappropriate use of the ASV device. Although short-duration ASV therapy was shown in this study to be a possible alternative approach for patients who can not tolerate conventional ASV use, further prospective studies are needed to establish the beneficial effects of short-duration ASV treatment for HF. Patients who were enrolled in this study had relatively mild systolic dysfunction because we used the same methodological approach as in our previous study.⁴ Further studies will be needed to clarify the effect of ASV therapy on severe HF patients whose LVEF is <40%.

In conclusion, short-duration ASV therapy improved cardiac function in HF patients. This novel ASV therapy may be an important alternative therapeutic approach for HF patients who are unable to tolerate long-duration ASV therapy.

Disclosures

The authors declare no conflict of interest.

References

1. Koyama T, Watanabe H, Kobukai Y, Makabe S, Munehisa Y, Iino K, et al. Beneficial effects of adaptive servo-ventilation in patients with chronic heart failure. *Circ J* 2010; **74**: 2118–2124.
2. Teschler H, Döhring J, Wang YM, Berthon-Jones M. Adaptive pressure support servo-ventilation: A novel treatment for Cheyne-Stokes respiration in heart failure. *Am J Respir Crit Care Med* 2001; **164**: 614–619.
3. Koyama T, Watanabe H, Terada S, Makabe S, Igarashi G, Nobori K, et al. Adaptive servo-ventilation improves renal function in patients with heart failure. *Respir Med* 2011; **105**: 1946–1953.
4. Koyama T, Watanabe H, Igarashi G, Terada S, Makabe S, Ito H. Short-term prognosis of adaptive servo-ventilation therapy in patients with heart failure. *Circ J* 2011; **75**: 710–712.
5. Goso Y, Asanoi H, Ishise H, Kameyama T, Hirai T, Nozawa T, et al. Respiratory modulation of muscle sympathetic nerve activity in patients with chronic heart failure. *Circulation* 2001; **104**: 418–423.
6. Terada S, Koyama T, Watanabe H, Makabe S, Igarashi G, Seki K, et al. Abnormal coagulation and platelet profile in patients with obstructive sleep apnea syndrome. *Int J Cardiol* 2011; **146**: 423–425.
7. La Rovere MT, Pinna GD, Maestri R, Robbi E, Mortara A, Fanfulla F, et al. Clinical relevance of short-term day-time breathing disorders in chronic heart failure patients. *Eur J Heart Fail* 2007; **9**: 949–954.
8. Harada D, Joho S, Oda Y, Hirai T, Asanoi H, Inoue H. Short term effect of adaptive servo-ventilation on muscle sympathetic nerve activity in patients with heart failure. *Auton Neurosci* 2011; **161**: 95–102.
9. Koshino Y, Satoh M, Katayose Y, Yasuda K, Tanigawa T, Takeyasu N, et al. Association of sleep-disordered breathing and ventricular arrhythmias in patients without heart failure. *Am J Cardiol* 2008; **101**: 882–886.
10. Arzt M, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D, 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 (CANPAP). *Circulation* 2007; **115**: 3173–3180.
11. Oldenburg O, Schmidt A, Lamp B, Bitter T, Muntean BG, Langer C, et al. Adaptive servo ventilation improves cardiac function in patients with chronic heart failure and Cheyne-Stokes respiration. *Eur J Heart Fail* 2008; **10**: 581–586.
12. Hiasa G, Hamada M, Saeki H, Ogimoto A, Ohtsuka T, Hara Y, et al. Cardiac sympathetic nerve activity can detect congestive heart failure sensitively in patients with hypertrophic cardiomyopathy. *Chest* 2004; **126**: 679–686.
13. Hastings PC, Vazir A, Meadows GE, Dayer M, Poole-Wilson PA, McIntyre HF, et al. Adaptive servo-ventilation in heart failure patients with sleep apnea: A real world study. *Int J Cardiol* 2010; **139**: 17–24.
14. Haruki N, Takeuchi M, Kaku K, Yoshitani H, Kuwaki H, Tamura M, 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**: 1140–1146.