Effectiveness of Adaptive Servo-Ventilation for Treating Heart Failure Regardless of the Severity of Sleep-Disordered Breathing

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Background: It is unclear whether adaptive servo-ventilation (ASV) is effective for all patients with heart failure (HF). The aim of the present study was therefore to investigate the effectiveness of ASV for all patients with HF.

Methods and Results: Sixty-one patients with HF were recommended for ASV treatment, regardless of sleep-disordered breathing (SDB) severity and type. On the basis of the apnea–hypopnea index (AHI) results, patients were classified into 3 groups: 28 patients with AHI ≥ 40 /h were designated as group A; 20 patients with AHI ≥ 20 /h and < 40 /h were designated as group B; and 13 patients with AHI < 20 /h were designated as group C. After ASV treatment, brain natriuretic peptide (BNP) levels and left ventricular ejection fraction (LVEF) were improved almost equally in the 3 groups (changes in BNP level: group A, -313 ± 480 pg/ml; group B, -401 ± 801 pg/ml; group C, -225 ± 240 pg/ml; $P=0.69$; changes in LVEF: group A, $8.5 \pm 11.3\%$; group B, $10.5 \pm 9.6\%$; group C, $2.4 \pm 12.4\%$; $P=0.17$).

Conclusions: ASV treatment for patients with mild SDB resulted in almost equal improvements in BNP levels and LVEF compared to that in patients with moderate and severe SDB, demonstrating that ASV is effective for all patients with HF. (*Circ J* 2011; **75**: 1164–1169)

Key Words: Adaptive servo-ventilation; Heart failure; Sleep-disordered breathing

Adaptive servo-ventilation (ASV) is used for treating patients with Cheyne–Stokes respiration (CSR) and provides suitable ventilatory support using expiratory positive airway pressure and a pressure support system.¹ Multiple studies have reported that ASV has been successfully used for treating central sleep apnea and CSR in patients with heart failure (HF).^{2–5} Furthermore, ASV improves cardiac function including exercise tolerance.⁶

Sleep-disordered breathing (SDB) is closely related not only to HF but also to cardiovascular disease, including hypertension, fatal arrhythmias, and coronary artery disease.^{7–12} Furthermore, SDB is a strong risk factor for fatal cardiovascular events and mortality.^{13,14} Therefore, SDB must be treated to stabilize the underlying cardiovascular disease. Most patients with cardiovascular disease suffer not only from central sleep apnea but also from other types of SDB including obstructive sleep apnea and hypopnea.^{7,8,15,16} ASV is effective for treating not only central sleep apnea and CSR but also other types of SDB including obstructive sleep apnea and complex sleep apnea syndrome,^{17–19} and has the added advantage of providing expiratory positive airway pressure and a pressure support system. Continuous positive airway pressure (CPAP) is effective when used as a treatment for

HF.^{20–22} For these reasons, the question of whether ASV is an effective option for patients with HF, regardless of SDB severity and type, must be evaluated. The aim of the present study was therefore to investigate the effectiveness of ASV as a treatment for HF in patients with mild SDB compared to those with moderate and severe SDB.

Methods

Study Design and Ethics Considerations

This was a single-center, prospective, observational study. Sixty-one patients with HF who presented to Isesaki Municipal Hospital with grade II–IV symptoms, as defined by the New York Heart Association classification for HF stages, participated in the study. After medical treatment was optimized, full-night polysomnography was performed, and ASV treatment was recommended regardless of SDB severity and type. Patients were followed up at outpatient visits for 6 months, and all procedures were performed at the medical center at Isesaki Municipal Hospital. This study was conducted in accordance with the recommendations of the Declaration of Helsinki (1975), and the protocol was approved by the medical center's Institutional Review Board. Informed consent was

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Table 1. Subject Characteristics

	Group A (n=28)	Group B (n=20)	Group C (n=13)	P value
Age (years)	71±10	71±10	68±10	0.75
Male, n (%)	20 (71)	13 (65)	8 (62)	0.62
Body mass index (kg/m²)	25.2±4.6	23.2±4.2	23.6±8.6	0.50
Drug therapy, n (%)				
β-blocker	5 (18)	1 (5)	2 (15)	0.36
ARBs or ACE inhibitors	12 (43)	9 (45)	8 (62)	0.59
NYHA classification III or IV	21 (75)	13 (65)	11 (85)	0.44
Underlying disease, n (%)				
ICM	14 (50)	9 (45)	5 (39)	0.78
Valvular heart disease	1 (4)	4 (20)	3 (23)	0.09
DCM or HCM	11 (39)	5 (25)	3 (23)	0.45
Others	2 (7)	2 (10)	2 (15)	0.73
Coronary risk factors, n (%)				
Hypertension	23 (82)	19 (95)	13 (100)	0.08
Dyslipidemia	19 (68)	11 (55)	8 (62)	0.66
Diabetes mellitus	14 (50)	12 (60)	4 (31)	0.25
Smoking	7 (25)	6 (30)	2 (15)	0.58

Data given as mean±SD or n (%).

ARB, angiotensin II receptor blocker; ACE, angiotensin I-converting enzyme; NYHA, New York Heart Association; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy.

provided by each patient before participating in the study.

Sleep Evaluation and Treatment Devices

During the sleep evaluation, all patients who underwent full-night polysomnography were assessed using a digital polygraph (P-Series Plus; Compumedics, Abbotsford, Vic., Australia). The assessment included electroencephalography, an electro-oculogram, a chin electromyogram, and chest and abdominal movements using 2 inductive respiratory bands. Airflow was assessed using a thermistor. Arterial oxygen saturation (SaO₂) was measured continuously at a sampling frequency of 1 s using a pulse oximeter with a finger probe (Nonin 8000J adult flex sensor; Nonin Medical, Plymouth, MN, USA). Sleep staging and arousal were scored according to standard methods.^{23,24} Apnea was defined as the complete cessation of airflow lasting ≥10 s. Hypopnea was defined as a decrease in airflow of ≥50% for ≥10 s accompanied by desaturation (3% decrease in SaO₂) and/or an electroencephalographic arousal response. The apnea–hypopnea index (AHI) was defined as the total number of apnea and hypopnea episodes per hour of sleep.

ASV (AutoSet-CS; ResMed, Sydney, NSW, Australia) was administered using a full facemask (ResMed). It consisted of expiratory positive airway pressure at 4 cmH₂O and a suitable minimum–maximum inspiratory support, which fell in the recommended minimum manufacturer setting range of 3–8 cmH₂O. The backup respiratory rate was 15 breaths/min.

Data Collection

Two-dimensional transthoracic echocardiography was performed before ASV. The left ventricular end-diastolic and end-systolic dimensions were measured on M-mode echocardiography, and the left ventricular ejection fraction (LVEF) was calculated using Teichholz's method. Venous blood samples were obtained after an overnight fast, and the brain natriuretic peptide (BNP) level was determined. Arterial blood samples were obtained for blood gas analysis when the patients were supine and were not receiving supplemen-

tal oxygen. Dyslipidemia was defined as the current use of cholesterol-lowering drugs, triglyceride level ≥150 mg/dl, low-density lipoprotein cholesterol ≥140 mg/dl, and/or high-density lipoprotein cholesterol <40 mg/dl. Hypertension was defined as the current use of anti-hypertensive drugs or blood pressure ≥140/90 mmHg. Diabetes mellitus was defined as current use of insulin or anti-diabetic drugs, fasting blood glucose ≥126 mg/dl, and/or hemoglobin A_{1c} ≥6.5%. After discharge, clinical data including BNP and echocardiography were obtained again for all patients at 6 months.

Statistical Analysis

Continuous data are expressed as mean±SD and compared among the 3 groups using 1-way analysis of variance followed by Tukey's test. Categorical data are reported as counts (expressed as percentages) and compared using chi-square test. The significance level was set at 5%, and all analyses were performed using JMP 6.0 (SAS Institute, Cary, NC, USA).

Results

The study group consisted of 61 patients with HF (age, 70±10 years). All patients were treated with ASV after medical treatment was optimized in the acute phase. The patients were classified into 3 groups based on the AHI level. A group of 28 patients with an AHI ≥40/h was designated as group A, 20 patients with an AHI ≥20/h and <40/h was designated as group B, and 13 patients with an AHI <20/h was designated as group C (Table 1). No significant differences were observed between the 3 groups with respect to age, sex, body mass index, drug therapy, or history of coronary risk factors, including a history of hypertension, dyslipidemia, diabetes mellitus, or smoking. Baseline LVEF before ASV was equally low for all the 3 groups (group A, 43.9±18.0%; group B, 43.9±17.2%; group C, 46.2±16.7%; P=0.91). On blood biochemistry, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and fasting blood sugar

Table 2. Clinical Findings

	Group A (n=28)	Group B (n=20)	Group C (n=13)	P value
LVEF (%)	43.9±18.0	43.9±17.2	46.2±16.7	0.91
Baseline heart rate (/min)	70.5±12.5	70.1±11.6	76.5±20.3	0.41
Blood pressure (mmHg)				
Systolic	124±22	130±18	117±19	0.20
Diastolic	70±13	70±9	64±10	0.25
Triglyceride (mg/dl)	129±102	88±38	109±61	0.22
HDL cholesterol (mg/dl)	51±16	56±18	46±10	0.20
LDL cholesterol (mg/dl)	110±37	101±29	112±36	0.59
Fasting glucose (mg/dl)	130±65	122±30	100±39	0.23
Brain natriuretic peptide (pg/ml)	488±341	590±730	379±214	0.48
HOMA-IR	4.3±4.6	2.6±2.7	4.6±9.4	0.67
Arterial CO ₂ tension (mmHg)	37.2±4.7	37.7±4.4	35.3±3.3	0.28
Arterial O ₂ tension (mmHg)	85.0±17.7	85.5±16.3	95.1±24.0	0.25
Estimated GFR (ml·min ⁻¹ ·1.73 m ⁻²)	49.2±23.8	52.7±15.3	50.0±19.5	0.84

Data given as mean ± SD or no. subjects.

LVEF, left ventricular ejection fraction; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; GFR, glomerular filtration rate.

Table 3. Sleep Assessment

	Group A (n=28)	Group B (n=20)	Group C (n=13)	P value
Total sleep time (min)	278±129	285±159	296±186	0.94
Sleep efficiency (%)	41.9±17.8	43.6±19.9	50.7±26.5	0.46
Apnea hypopnea index (/h)	62.9±16.2	30.7±5.6	8.9±7.1	<0.0001
Central apnea index (/h)	13.6±16.1	8.5±9.9	0.9±2.0	0.035
Obstructive apnea index (/h)	14.1±20.9	3.6±4.2	1.2±2.1	0.011
Apnea index (/h)	33.4±27.5	14.6±11.3	2.1±3.1	<0.0001
Baseline oxygen saturation level (%)	95.8±1.4	95.9±2.1	95.8±2.6	0.98
Minimum oxygen saturation level (%)	81.0±6.4	83.6±5.1	88.1±4.3	0.0026
Cumulative percentage time at a pulse-oximetric oxygen saturation <90% (%)	6.0±7.2	5.3±13.5	3.6±6.7	0.78
Oxygen desaturation index at the 4% level (/h)	34.1±13.7	24.2±12.2	8.7±7.0	<0.0001

Data given as mean ± SD.

were not significantly different between the 3 groups. Blood gas analysis also showed no significant differences between the 3 groups. The baseline BNP level was equally high for all the 3 groups (group A, 488±341 pg/ml; group B, 590±730 pg/ml; group C, 379±214 pg/ml; $P=0.48$; **Table 2**).

On full-night polysomnography the AHI was significantly greater in group A than in the other groups (group A, 62.9±16.2/h; group B, 30.7±5.6/h; group C, 8.9±7.1/h; $P<0.0001$). The central sleep apnea index was significantly greater in group A than in group C (group A, 13.6±16.1/h; group B, 8.5±9.9/h; group C, 0.9±2.0/h; $P=0.035$). The obstructive sleep apnea index was significantly greater in group A than in the other 2 groups (group A, 14.1±20.9/h; group B, 3.6±4.2/h; group C, 1.2±2.1/h; $P=0.011$). **Table 3** summarizes several parameters analyzed during polysomnography.

No significant difference was observed with respect to the average time used for ASV treatment in the 3 groups (group A, 5.6±2.7/h; group B, 7.1±2.9/h; group C, 7.1±2.4/h; $P=0.14$).

BNP level was improved almost equally in the 3 groups after ASV treatment (changes in BNP level: group A, -313±480 pg/ml; group B, -401±801 pg/ml; group C, -225±240 pg/ml; $P=0.69$; **Figure 1A**), and LVEF was also im-

proved almost equally in the 3 groups (changes in LVEF level: group A, 8.5±11.3%; group B, 10.5±9.6%; group C, 2.4±12.4%; $P=0.17$; **Figure 1B**). **Figure 2** summarizes the parameters analyzed during the polysomnography before and after ASV treatment. In particular, AHI improved significantly in the 3 groups after ASV (group A, 19.9±13.0/h; group B, 11.8±14.4/h; group C, 2.4±2.9/h).

Discussion

We examined the ASV treatment data of patients with HF to determine whether ASV is effective for patients with mild SDB compared to those with moderate and severe SDB. The results show that ASV was effective for treating HF in patients with mild SDB and improved physical condition, indicating that patients with mild SDB should also be treated with ASV in addition to patients with moderate and severe SDB.

Until recently, the results of several studies suggested that CPAP is effective for treating not only obstructive sleep apnea but also HF.^{20–22} In contrast, ASV is effective for treating central sleep apnea and CSR in patients with coexisting HF,^{2–5} and is also effective for treating other types of SDB including obstructive sleep apnea and complex sleep apnea syndrome

Figure 1. (A) Brain natriuretic peptide levels and (B) left ventricular ejection fraction before and after adaptive servo-ventilation (ASV) treatment.

by providing suitable ventilatory support using expiratory positive airway pressure and a pressure support system.^{17–19} The question of whether ASV is effective for treating HF, however, regardless of SDB severity and type, remained unclear. Although evidence exists that most patients with HF suffer from SDB including central and obstructive sleep apnea,^{16,25,26} comparing patients with SDB to those without

SDB is difficult. For this reason we limited the study population to patients with HF who suffered from mild, moderate, or severe SDB, in order to assess the effectiveness of ASV treatment.

We found that ASV treatment for patients with mild SDB resulted in an almost equal improvement in BNP levels compared to those for patients with moderate and severe SDB.

Figure 2. (A) Apnea–hypopnea index, (B) central apnea index, and (C) obstructive apnea index as measured by polysomnography before and after adaptive servo-ventilation (ASV) treatment.

Patients with mild SDB had almost equal improvements in LVEF compared to patients with moderate and severe SDB. After ASV treatment, several SDB parameters including AHI, central apnea index, and obstructive apnea index improved. In particular, AHI improved significantly in the 3 groups, thus indicating that ASV is effective in treating HF regardless of SDB severity and type. ASV for the treatment of HF comprehensively provides better performance in patients with moderate and severe SDB, but the effectiveness of ASV for treating HF is also good in patients with mild SDB.

The present study had some limitations. First, it was a single-center study, and selection bias was a major concern. To minimize potential selection bias, we struggled to include all patients who presented to the hospital with grade II–IV symptoms, as defined by the New York Heart Association classification for the stages of HF. It was difficult, however, to use ASV in all patients with HF. Second, the most important limitation in this study was the small number of patients. Although the BNP level and LVEF were improved almost equally in the 3 groups after ASV treatment, the standard deviations were relatively large, and the LVEF improvement in the mild SDB group was relatively modest. Finally, some patients had already taken β -blockers before the study. No significant difference was observed among the 3 groups with respect to β -blocker treatment, but it might have created a bias.

We found that ASV was beneficial for treating HF, regardless of SDB severity and type. We believe that ASV treatment will be recognized in the future as an effective option for treating pure HF, similar to CPAP treatment.

In conclusion, we found that ASV treatment for patients with mild SDB resulted in almost equal improvements in BNP levels and LVEF compared to those for patients with moderate and severe SDB, thus demonstrating that ASV is an effective option for treating HF regardless of SDB severity and type.

Disclosure

Conflict of Interest: None declared.

References

1. Teschler H, Dohring 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.
2. Kasai T, Narui K, Dohi T, Takaya H, Yanagisawa N, Dungan G, et al. First experience of using new adaptive servo-ventilation device for Cheyne-Stokes respiration with central sleep apnea among Japanese patients with congestive heart failure: Report of 4 clinical cases. *Circ J* 2006; **70**: 1148–1154.
3. Arzt M, Wensel R, Montalvan S, Schichtl T, Schroll S, Budweiser S, et al. Effects of dynamic bilevel positive airway pressure support on central sleep apnea in men with heart failure. *Chest* 2008; **134**: 61–66.
4. Pepperell JCT, Maskell NA, Jones DR, Langford-Wiley BA, Crosthwaite N, Stradling JA, et al. A randomized controlled trial of adaptive ventilation for Cheyne-Stokes breathing in heart failure. *Am J Respir Crit Care Med* 2003; **168**: 1109–1114.
5. 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.
6. 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.
7. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J Respir Crit Care Med* 1999; **160**: 1101–1106.
8. Javaheri S, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure: Types and their prevalences, consequences, and presentations. *Circulation* 1998; **97**: 2154–2159.
9. Moruzzi P, Sarzi-Braga S, Rossi M, Contini M. Sleep apnea in ischemic heart disease: Differences between acute and chronic coronary syndromes. *Heart* 1999; **82**: 343–347.
10. Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Predictors of all-cause mortality in clinical ambulatory monitoring: Unique aspects of blood pressure during sleep. *Hypertension* 2007; **49**: 1235–1241.
11. Serizawa N, Yumino D, Kajimoto K, Tagawa Y, Takagi A, Shoda M, et al. Impact of sleep-disordered breathing on life-threatening ventricular arrhythmia in heart failure patients with implantable cardioverter-defibrillator. *Am J Cardiol* 2008; **102**: 1064–1068.
12. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: An American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. *J Am Coll Cardiol* 2008; **52**: 686–717.
13. Takama N, Kurabayashi M. Influence of untreated sleep-disordered breathing on the long-term prognosis of patients with cardiovascular disease. *Am J Cardiol* 2009; **103**: 730–734.
14. Wang H, Parker JD, Newton GE, Floras JS, Mak S, Chiu KL, et al. Influence of obstructive sleep apnea on mortality in patients with heart failure. *J Am Coll Cardiol* 2007; **49**: 1625–1631.
15. Takama N, Kurabayashi M. Possibility of close relationship between sleep disorder breathing and acute coronary syndrome. *J Cardiol* 2007; **49**: 171–177.
16. Kato M, Adachi T, Koshino Y, Somers VK. Obstructive sleep apnea and cardiovascular disease. *Circ J* 2009; **73**: 1363–1370.
17. Allam JS, Olson EJ, Gay PC, Morgenthaler TI. Efficacy of adaptive servo-ventilation in treatment of complex and central sleep apnea syndromes. *Chest* 2007; **132**: 1839–1846.
18. Khayat RN, Abraham WT, Patt B, Roy M, Hua K, Jarjoura D. Cardiac effects of continuous and bilevel positive airway pressure for patients with heart failure and obstructive sleep apnea: A pilot study. *Chest* 2008; **134**: 1162–1168.
19. 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.
20. Sin DD, Logan AG, Fitzgerald FS, Liu PP, Bradley TD. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. *Circulation* 2000; **102**: 61–66.
21. Egea CJ, Aizpuru F, Pinto JA, Ayuela JM, Ballester E, Zamarró NC, et al. Cardiac function after CPAP therapy in patients with chronic heart failure and sleep apnea: A multicenter study. *Sleep Med* 2008; **9**: 660–666.
22. 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.
23. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles, Brain Information Service/Brain Research Institute, UCLA, 1968.
24. EEG arousals: Scoring rules and examples: A preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep* 1992; **15**: 174–184.
25. Kapur V, Strohl KP, Redline S, Iber C, O'Connor G, Nieto J. Underdiagnosis of sleep apnea syndrome in U.S. communities. *Sleep Breath* 2002; **6**: 49–54.
26. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* 1997; **20**: 705–706.