‘A Single Night’ Beneficial Effects of Adaptive Servo-Ventilation on Cardiac Overload, Sympathetic Nervous Activity, and Myocardial Damage in Patients With Chronic Heart Failure and Sleep-Disordered Breathing

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Background: Sleep-disordered breathing (SDB), including Cheyne-Stokes respiration with central sleep apnea (CSR-CSA), causes a deterioration in the prognosis of patients with chronic heart failure (CHF). Adaptive servo-ventilation (ASV) and oxygen therapy (O₂) are useful for improving the CSR-CSA of CHF. The purpose of the present study was to examine the short-term effects of ASV and O₂ on suppressing SDB (CSR-CSA dominant) in CHF, and the accompanying neurohumoral abnormalities (cardiac overload, sympathetic nervous activation, and myocardial damage).

Methods and Results: Forty-two patients with CHF and SDB (mean LVEF 34.6%, apnea hypopnea index (AHI) 39.0/h, central apnea index (CAI) 17.6/h, obstructive apnea index (OAI) 2.6/h) were enrolled. We performed polysomnography (baseline, O₂, and ASV) for 3 consecutive days, and we measured levels of atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), noradrenalin, urinary catecholamines, and high-sensitivity troponin T. Both O₂ and ASV reduced the AHI, CAI, arousal index, mean heart rate during sleep, and the levels of noradrenalin, urinary catecholamines, and high-sensitivity troponin T. However, only ASV, not O₂, decreased the levels of ANP and BNP.

Conclusions: ASV reduces cardiac overload, attenuates sympathetic nervous activity and ongoing myocardial damage effectively in CHF patients with SDB, and for patients who cannot use ASV, O₂ is an alternative therapy. (Circ J 2012; 76: 2153–2158)

Key Words: Adaptive servo-ventilation; B-type natriuretic peptide; High-sensitivity troponin T; Oxygen therapy; Sympathetic nervous activity

Sleep-disordered breathing (SDB), including Cheyne-Stokes respiration with central sleep apnea (CSR-CSA), is associated with adverse outcomes in patients with chronic heart failure (CHF). Approximately half of CHF patients reportedly have SDB, which consists of obstructive sleep apnea (OSA) and CSR-CSA. OSA is thought to be caused by upper airway obstruction during sleep, whereas instability of respiratory control is the major cause of CSR-CSA. SDB, either OSA or CSR-CSA, results in multiple pathological consequences such as an imbalance in myocardial oxygen delivery/consumption, activation of sympathetic nervous system and other neurohumoral factors, and increased right and left ventricular afterload. Oxygen therapy (O₂) improves exercise capacity and attenuates cardiac sympathetic nervous activity in patients with CHF and CSR-CSA. Adaptive servo-ventilation (ASV) is a ventilator support system specifically designed to normalize ventilation in patients with CSR-CSA. Moreover, ASV has an automatic airway tracing feedback function, and several advantages of ASV have been reported over continuous positive airway pressure (CPAP), bi-level PAP, and O₂. ASV
can regulate airway ventilation volume according to demand, based on the variable tidal volume throughout the period of CSR-CSA. In addition, ASV automatically provides positive pressure ventilation during apnea when necessary.

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Treating SDB may improve cardiac function in patients with CHF. CPAP reportedly suppresses the abnormal breathing pattern, attenuates sympathetic nervous activity, and improves the left ventricular ejection fraction (LVEF) in CHF patients with either OSA or CSR-CSA. Furthermore, there are several reports about mid-term (several months) effects of ASV on cardiac function, and we have reported that ASV improves the long-term prognosis in patients with CHF and CSR-CSA. However, the short-term (a single night) effects, and the mechanisms of O₂ and ASV on cardiac function in patients with CHF and CSR-CSA, are not fully understood.

Sympathetic nervous activation, ongoing myocardial damage, and inflammation play critical roles in the progression of CHF and are associated with adverse prognosis. Levels of plasma norepinephrine, serum troponin T, C-reactive protein (CRP) and C-reactive protein (CRP) are useful prognostic markers in patients with CHF. However, the acute effects of O₂ and ASV on atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), plasma norepinephrine, serum troponin T, and CRP levels have not been rigorously examined.

ASV is more useful for improving CSR-CSA than O₂, as previously reported, but compliance with long-term use of ASV is not enough. On the other hand, O₂ therapy has better compliance than ASV. Therefore, the primary purpose of the present study was to review the short-term (a single night) multiple effects of suppressing SDB (CSR-CSA dominant) and neurohumoral abnormalities of ASV compared with O₂. The secondary purpose was to determine which of ASV or O₂ was more effective for CHF with SDB in a single night. We compared the short-term (a single night) multiple effects of ASV and O₂ on cardiac function, sympathetic nervous activity, ongoing myocardial damage, and inflammation in CHF patients with SDB (CSR-CSA dominant).

**Methods**

**Study Subjects and Study Protocol**

This study enrolled 42 consecutive patients with CHF and SDB (CSR-CSA dominant) who were referred for overnight polysomnography (PSG) at Fukushima Medical University. The inclusion criteria were (1) the presence of symptomatic CHF, which was defined as the New York Heart Association (NYHA) class ≥II, (2) LVEF <50%, (3) enforcement of standard pharmacotherapy (including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers and diuretics), (4) stable clinical status, which was defined as receiving optimal medical therapy and without worsening of CHF at least 3 months prior to study enrollment, and (5) diagnosed as having moderate-severe SDB, and CSR-CSA dominant, which was defined as an apnea hypopnea index (AHI) ≥15/h with a majority of central sleep apnea events. The exclusion criteria was defined as an apnea hypopnea index (AHI) ≥15/h with a majority of central sleep apnea events. The exclusion criteria was (1) age <20 or >80 years, (2) resynchronization therapy within 6 months prior to study enrollment, (3) the presence of severe chronic pulmonary disease, (4) on dialysis, (5) a history of stroke with neurological deficit, (6) psychotic disorders, (7) pharyngeal disease, and (8) acute coronary syndrome and acute decompensated heart failure.

This study used an acute prospective random crossover design. We examined 3 consecutive days because of the exclusion of a change in HF condition and treatment. We performed polysomnography for 3 sequential night (baseline, O₂, and ASV): baseline PSG done on the first night, and then subjects were tested on 2 treatment nights in random order: O₂ and ASV. The 42 patients were divided into 2 groups and randomly assigned to either baseline, O₂, and ASV (n=21) or baseline, ASV, and O₂ (n=21). In addition, we measured levels of ANP, BNP, plasma noradrenaline, high-sensitivity troponin T, high-sensitivity C-reactive protein (hsCRP) each morning, and 24 h accumulated urinary catecholamines. Written informed consent was given by all study subjects. The study protocol was approved by the Ethical Committee of Fukushima Medical University.

**Polysomnography**

All subjects underwent overnight complete polysomnography with the use of standard techniques and scoring criteria for sleep stages and arousals from sleep as previously reported. Briefly, the polysomnography was performed using a computerized system (Alice 5, Philips Respironics, Murrysville, PA, USA) that consisted of monitoring of the electroencephalogram, electro-oculogram, submental electromyogram, electrocardiogram, thoracoabdominal motion, oronasal airflow by an airflow pressure transducer, and arterial oxyhemoglobin saturation (SPO₂) by pulse oximetry. Apnea was defined as an absence of airflow for >10 s. Hypopnea was defined as a >30% reduction in monitored airflow accompanied by a decrease in SPO₂ >4%. An AHI ≥15/h was defined as moderate–severe SDB. A diagnosis of moderate–severe CSR-CSA was assigned at an AHI ≥15/h with a majority of CSA events. The major polysomnographic parameters investigated were AHI, central apnea index (CAI), obstructive apnea index (OAI), hypopnea index (HI), arousal index, 3% oxidative desaturation index (3%ODI), lowest pulse oxyhemoglobin saturation (lowest SPO₂), elevated pulse oxyhemoglobin saturation (mean SPO₂), %time <SPO₂ 90%/total sleep time (CT90), %time <SPO₂ 95%/total sleep time (CT95), slow wave sleep (SWS) (stage III+IV/total sleep time (%)), REM sleep (rapid eye movement (REM) sleep/total sleep time (%)), and sleep efficacy (total sleep time/time in bed (%)), as previously reported.

**Echocardiography**

Echocardiography was performed blindly only at baseline daytime using the standard techniques by an experienced echocardiographer. Two-dimensional echocardiographic images were acquired from the parasternal long and short axes, apical long axis, and apical 4-chamber views. Echocardiographic parameters investigated were left ventricular end-diastolic volume index (LVEDVI), left ventricular end-systolic volume index (LVESVI), LVEF, left atrial volume index (LAVI), estimated right ventricular systolic pressure (RVSP), and the ratio of early transmitial flow velocity to mitral annular velocity (E/E’). The LVEDVI, LVESVI, LVEF and LAVI were calculated using a modification of Simpson’s method. E/E’ was calculated by transmitial Doppler flow and tissue Doppler imaging. All recordings were performed on the ultrasound system (ACUSON Sequoia, Siemens Medical Solutions USA, Inc, Mountain View, CA, USA).

**Measurement of ANP, BNP, Plasma Noradrenaline, High-Sensitivity Troponin T, hsCRP, and Urinary Catecholamines**

The patients underwent polysomnography for 3 consecutive
days. After waking up each morning, we asked the patients to rest for at least 30 min before we took blood samples to measure levels of plasma ANP, plasma BNP, plasma noradrenalin, serum high-sensitive troponin T, and serum hsCRP. The 24-h urinary catecholamines, such as metanephrine and normetanephrine, were measured.

**Oxygen Therapy**

Patients were administered oxygen at a rate of 3 L/min through a nasal cannula during sleep as previously described.\(^5,7\)

**Adaptive Servo-Ventilation (ASV)**

We used ASV (VPAP Adapt SV/Auto Set CS, ResMed, Sydney, NSW, Australia). Patients underwent a titration of the device overnight while attended by the polysomnographer. The aim was to reduce the AHII to <10/h using a minimum of positive airway pressure. In summary, we set expiratory positive airway pressure (EEP) to cause the disappearance of OSA, and next set minimum and maximum pressure support (PS) to cause the disappearance CSR-CSA. All patients were able to tolerate ASV until the next morning.

**Statistical Analysis**

Data are presented as mean±SD. ANP and BNP are presented as median and interquartile range. The data measured repeatedly at baseline, on O\(_2\), and on ASV, such as the polysomnographic data and blood examinations, were analyzed by 1-way repeated-measures analysis of variance (ANOVA) followed by Bonferroni post-hoc test. ANP and BNP were analyzed by repeated-measures analysis of variance (ANOVA) followed by Bonferroni post-hoc test. All analyses were performed using a statistical software package (StatView version 5.0, SAS Institute, Abacus Concepts, Berkeley, CA, USA).

**Results**

**Clinical Characteristics of Study Subjects**

Clinical characteristics are shown in Table 1. Males accounted for 88%, and the major etiology of CHF was cardiomyopathy (69%); 7 patients underwent cardiac resynchronization therapy. Median BNP was 245.8 pg/ml, and mean LVEF was 34.6%.

The results of the polysomnographic recordings (baseline) are shown in Table 2. Mean AHII was 39.0/h, mean CAI was 17.6/h, OAI was 2.6/h and mean lowest SPO\(_2\) was 79.1%. These data suggest that these patients had severe SDB (CSR-CSA dominant).

**Effects of O\(_2\) and ASV on Polysomnographic Data and Vital Signs**

We set the EEP to eliminate OSA, and then set the minimum and maximum PS to eliminate CSR-CSA by attended manual titration. Consequently, mean EEP was 6.0±2.0 cmH\(_2\)O (range 4–10), mean minimum PS was 3.6±2.4 cmH\(_2\)O (range 3–6), mean maximum PS was 8.5±4.1 cmH\(_2\)O (range 6–12) and the respiratory rate was set to automatic in the present study. All patients were successfully titrated on ASV.

Table 2 shows the polysomnographic data of the patients at baseline, on O\(_2\), and on ASV. Both O\(_2\) and ASV significantly improved the polysomnographic data in terms of AHII, CAI, HI, arousal index, %ODI, lowest SPO\(_2\), mean SPO\(_2\), CT90, and CT95 (P<0.01 for each) compared to baseline. However, only ASV increased the SWS (P<0.05). In addition, AHII and OAI were significantly lower with ASV than with O\(_2\): (P<0.05). The mean SPO\(_2\) was significantly higher with O\(_2\) than with ASV (P<0.05). By the next morning, both O\(_2\) and ASV had reduced the mean heart rate during sleep (P<0.01), the heart rate during REM (P<0.01) and NREM sleep (P<0.01), and systolic and diastolic blood pressures (Table 2).

**Effects of O\(_2\) and ASV on Neuropeptides, Plasma Noradrenalin, High-Sensitivity Troponin T, hsCRP, and Urinary Catecholamines**

ASV reduced the levels of ANP (P<0.01), BNP (P<0.01), plas-
ma noradrenalin (P<0.01), urinary catecholamine excretion (P<0.01), and high-sensitive troponin T (P<0.05) compared to baseline (Table 2). O2 reduced plasma noradrenalin (P<0.05), urinary catecholamines (P<0.01), and high sensitivity troponin T (P<0.05), but not ANP and BNP. However, the hsCRP level did not change with either O2 or ASV.

### Discussion

#### Effects of O2 and ASV on Cardiac Overload in HF

Noninvasive ventilation increases cardiac output in HF patients whose pulmonary arterial wedge pressure is high.26,27 Infrathoracic positive pressure by noninvasive ventilation is thought to reduce cardiac preload and afterload,26 and decrease left ventricular volume, leading to an improvement in mitral regurgitation,16,27 but it is still uncertain whether short-term use of ASV is beneficial for cardiac overload in CHF patients with SDB. There are several reports about a reduction in the BNP level after several months of using ASV.17,25,29,30 In the present study, only ‘single night’ use of ASV directly decreased cardiac overload as demonstrated by significant decreases in the ANP and BNP levels in CHF patients with SDB. This effect by ASV seems to be driven by infrathoracic positive pressure. O2 does not have a direct effect of decreasing cardiac end-diastolic wall stress. To the best of our knowledge, this is the first reporting of acute reduction of cardiac overload in patients with CHF and SDB (CSR-CSA dominant) by the use of ASV in a single night.

#### Effects of O2 and ASV on Sympathetic Nervous Activity in HF

Sympathetic nervous activation plays a critical role in the progression of CHF and is associated with adverse clinical outcomes.18 Sympathetic nervous activity affects the mean heart rate during sleep, arousal index, plasma noradrenalin level, and high-sensitivity troponin T as a marker of ongoing myocardial damage and inflammation. Short-term use of ASV improves periodic breathing and attenuates sympathetic nervous activity which induces sympathetic nervous overactivation, such as muscle sympathetic nerve activity.

#### Effects of O2 and ASV on Myocardial Damage and Inflammation in HF

High-sensitivity troponin T as a marker of ongoing myocardial damage19,20 and hsCRP as a marker of inflammation21,22 are useful in understanding the clinical condition of CHF pa-

| Table 2. Comparisons of Data for Polysomnography and Blood and Urinary Examinations |
|-----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                  | Baseline        | O2              | ASV             | ANOVA P value   |
| AHI (times/h)                    | 39±17.3         | 22.3±13.4**     | 9.8±7.9**       | <0.01           |
| CAI (times/h)                    | 17.6±14.2       | 3.3±5.2**       | 1.1±1.6**       | <0.01           |
| OAI (times/h)                    | 2.6±4.5         | 6.0±8.8*        | 1.0±2.1*        | <0.01           |
| HI (times/h)                     | 18.0±12.1       | 8.8±4.4**       | 6.3±4.8**       | <0.01           |
| Arousal index                    | 25.9±9.0        | 18.6±7.5**      | 16.7±7.5**      | <0.01           |
| % ODI (times/h)                  | 27.5±16.2       | 6.8±15.6**      | 6.5±15.2**      | <0.01           |
| Lowest SPO2 (%)                 | 79.1±8.9        | 90.2±7.5**      | 89.2±5.8**      | <0.01           |
| Mean SPO2 (%)                   | 94.7±2.8        | 98.0±1.6**      | 96.7±1.6**      | <0.01           |
| CT90 (%)                        | 9.7±16.7        | 1.1±4.0**       | 0.8±2.8**       | <0.01           |
| CT95 (%)                        | 33.1±30.0       | 6.4±15.8**      | 9.5±21.8**      | <0.01           |
| SWS (%)                         | 2.1±3.5         | 3.0±4.3         | 4.4±8.1*        | 0.04            |
| REM sleep (%)                   | 18.3±6.5        | 18.2±6.1        | 16.5±5.2        | 0.20            |
| Sleep efficacy (%)              | 67.2±14.1       | 71.4±12.4       | 72.4±13.7       | 0.06            |
| Mean HR during sleep (beats/min) | 72.1±10.8       | 68.9±11.0**     | 67.4±9.8**      | <0.01           |
| Mean HR during REM (beats/min)  | 68.8±9.1        | 64.8±9.8**      | 64.8±9.8**      | <0.01           |
| Mean HR during NREM (beats/min) | 68.0±10.1       | 64.3±10.4**     | 63.9±9.1**      | <0.01           |
| SBP (mmHg)                      | 113.3±19.1      | 106.8±15.6*     | 103.6±13.9**    | 0.02            |
| DBP (mmHg)                      | 66.5±14.1       | 62.4±9.7*       | 61.8±8.1*       | 0.04            |
| ANP (pg/ml)                     | 165.5 (205.7)   | 152.4 (233.1)   | 122.0 (229.8)** | <0.01           |
| BNP (pg/ml)                     | 245.8 (517.5)   | 214.8 (477.8)   | 184.5 (491.1)** | <0.01           |
| Plasma noradrenalin (pg/ml)     | 848.8±471.1     | 765.4±401.8*    | 705.1±402.9*    | 0.02            |
| Urinary catecholamines (mg/day) | 0.450±0.161     | 0.382±0.131**   | 0.358±0.093**   | <0.01           |
| High-sensitive troponin T (ng/ml) | 0.042±0.034   | 0.028±0.018*     | 0.026±0.017*     | 0.04            |
| High-sensitive CRP (mg/dl)      | 0.263±0.277     | 0.455±0.685     | 0.350±0.429     | 0.52            |

1 Data are presented as median (interquartile range). *P<0.05, **P<0.01 vs. baseline, #P<0.05 vs. O2.

AH, apnea hypopnea index; CAI, central apnea index; OAI, obstructive apnea index; HI, hypopnea index; ODI, oxidative desaturation index; Lowest SPO2, lowest oxyhemoglobin saturation; Mean SPO2, mean oxyhemoglobin saturation; CT90, %time <SPO2 90%/total sleep time; CT95, %time <SPO2 95%/total sleep time; SWS, slow wave sleep; REM, rapid eye movement; SBP, systolic blood pressure; DBP, diastolic blood pressure; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CRP, C-reactive protein.
O₂ and ASV for HF With CSR-CSA
O₂ improves exercise capacity and attenuates cardiac sympathetic nervous activity in patients with CHF and CSR-CSA. A large-scale randomized clinical trial, the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP), has shown that CPAP does not improve long-term transplant-free survival in CHF patients with CSR-CSA. However, in a CANPAP subanalysis, improvement of CSR-CSA (especially AHI <15) was important for cardiac function and prognosis in CHF patients. ASV has an automatic airway tracing feedback function and several advantages (eg, suppressing AHI in CSR-CSA) over CPAP, bi-level PAP, and O₂ have been reported. ASV has better compliance and improvement effect on CSR-CSA than CPAP, so the use of ASV may have resulted in good consequences for cardiac function and prognosis. In the present study, the indices of improved SDB (eg, AHI, O/A, SWS) by O₂ were inferior to those for ASV, but O₂ has good compliance, and we can expect long-term use of O₂. Both ASV and O₂ are important non-pharmacotherapies for HF patients with CSR-CSA.

Study Limitations
Firstly, a crossover design with 2 active treatment arms does not allow for comparison with true placebo and therefore does not account for time-dependent effects. The subjects did not have washout periods before undergoing ASV or O₂. The crossover design has limitations compared to an independent parallel group design. Secondly, polysomnography was done on consecutive days. We are unclear whether the interval between the tests was sufficient for the patient to return to the baseline condition. Thirdly, we used only a fixed O₂ flow of 3L/min, as previously described, and we did not examine the effects of another dose of O₂. Finally, acute effects do not necessarily predict long-term effects. However, an acute study has the merit of another dose of O₂. Additionally, the tests was sufficient for the patient to return to the baseline condition.

Conclusions
In this study, use of ASV led to more improvement in SDB (CSR-CSA dominant) than did O₂ therapy. To the best of our knowledge, the present study is the first to show an acute short-term (a single night) beneficial effect of ASV on multiple parameters such as ANP, BNP, noradrenaline, high-sensitive troponin T, and urinary catecholamine levels. These data suggest that short-term use of ASV has the multiple effect of not only improving SDB (CSR-CSA dominant) but also attenuating sympathetic nervous activity, reducing cardiac overload and myocardial damage. ASV might be a promising non-pharmacotherapy for CHF. On the other hand, although O₂ was inferior to ASV in terms of improving SDB, it has good compliance. For patients who cannot use ASV, O₂ to some extent is effective for CSR-CSA and suppressing sympathetic nervous activation and myocardial damage.

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