Differing Effects of Adaptive Servoventilation and Continuous Positive Airway Pressure on Muscle Sympathetic Nerve Activity in Patients With Heart Failure
Ryuichi Ushijima, MD; Shuji Joho, MD; Takashi Akabane, MD; Yoshitaka Oda, MD; Hiroshi Inoue, MD

Background: Long-term adaptive servoventilation (ASV) increases cardiac function more effectively than continuous positive airway pressure (CPAP), possibly via alleviation of sympathetic overactivation. The present study evaluated the effect of ASV and CPAP at comparable pressure on muscle sympathetic nerve activity (MSNA) in patients with heart failure (HF) and with or without periodic breathing (PB).

Methods and Results: A total of 57 patients with HF (ejection fraction <0.45) were randomized to receive CPAP (n=28) or ASV (n=29). Respiratory profiles and MSNA were continuously monitored before and during CPAP and ASV (30 min) at pressures of 6.5 and 6.6 cmH2O, respectively. The severity of respiratory instability was determined using the coefficient of variation of tidal volume (CV-TV). Although heart rate and blood pressure remained unchanged, only ASV improved CV-TV. MSNA decreased in the ASV (P<0.001), but not in the CPAP group. The change in CV-TV independently predicted changes in MSNA (P<0.001). Device type and PB significantly interacted with changes in MSNA (P<0.05) and ASV exerted sympathoinhibitory effects in patients with PB, whereas CPAP did not. A sympathoinhibitory effect in patients without PB was not evident in either treatment arm.

Conclusions: ASV probably exerts its sympathoinhibitory effects in patients with HF and PB through pressure support. (Circ J 2014; 78: 1387–1395)

Key Words: Autonomic nervous system; Chronic heart failure; Periodic breathing; Servoventilation; Sympathoinhibition

Breathing abnormalities are very frequently associated with chronic heart failure (HF) and their presence is an indicator of poor prognosis.1–5 Recent clinical studies have closely related breathing abnormalities to sympathetic overactivation in patients with HF.6–8 Attenuated sympathetic outflow entrainment mediated by pulmonary mechanoreceptors is considered to be a potent mechanism of sympathetic overactivation in these patients.9

Editorial p1323

Adaptive servoventilation (ASV) is a novel method of providing positive expiratory airway pressure and of adding varying pressure support (servoventilation function).10 Ventilation is servo-controlled with a high-gain integral controller to maintain minute ventilation. So far, long-term ASV has conferred the benefit of increased cardiac function determined by ejection fraction (EF) or brain natriuretic peptide (BNP) levels compared with continuous positive airway pressure (CPAP) alone.11–13 This advantage of ASV might be attributable to more effective alleviation of hypoxia and sympathetic overactivation induced by sleep apnea in addition to cardiac unloading by positive pressure.14

Short-term CPAP (end-expiratory pressure [EEP] 10cmH2O) in patients with HF modestly increases or does not change muscle sympathetic nerve activity (MSNA), which comprises vasoconstrictor impulses into vascular smooth muscle to regulate systemic blood pressure.7,15 By contrast, our preliminary study showed that short-term ASV (EEP 5 cmH2O + variable pressure support from 3 to 10 cmH2O) reduced MSNA in patients with HF and periodic breathing (PB).16 A higher level of CPAP (10 cmH2O) compared with ASV should suppress cardiac performance more in patients with HF who have less congestion,17 and result in an increase in MSNA. However, it remains unknown whether the effect of ASV on MSNA differs from that of CPAP at comparable pressure levels; whether suppressing PB is important to the sympathoinhibitory effect of these devices in patients with HF also remains unknown.

Therefore, the present randomized controlled study examined the hypothesis that ASV would improve respiratory instability more effectively and exert a greater sympathoinhibitory effect than CPAP.
**Methods**

**Patients**
Between June 2010 and April 2013, 111 consecutive patients with previous or current symptoms attributable to structural heart diseases (HF stage C, New York Heart Association functional class I–III, and left ventricular EF <0.45) were screened for the presence and type of sleep apnea. In total, 9 of 70 patients without obstructive sleep apnea met the exclusion criteria and 57 of the remaining 61 patients who had stable MSNA recordings were included in the present study (Figure 1). Patients with obstructive sleep apnea (obstructive apnea index >5.0/hr) were excluded because of their potential need for higher EEP during ASV or CPAP. Patients with moderate to severe valvular heart diseases, stroke, respiratory failure or pulmonary diseases, severe anemia (hemoglobin level <9.0 g/dl) and end-stage renal disease treated by hemodialysis were also excluded. The Institutional Ethics Board of Toyama University Hospital approved the study protocol, which complied with the Declaration of Helsinki. Written informed consent to participate was given by all patients.

**Echocardiography**
LVEF and left atrial dimension were determined using 2-dimensional echocardiography (Aplio SSA-770A, Toshiba, Tokyo, Japan). Left ventricular end-diastolic and end-systolic volumes were determined according to a modification of Simpson’s method.

**Specific Activity Scale**
We quantified daily activity using a specific activity scale\(^{18}\) that expresses maximal physical activity and the energy cost to the patient. By definition, 1 metabolic equivalent of the task (MET) is equivalent to a metabolic rate that consumes 3.5 ml oxygen/kg of body weight/min. The specific activity scale contains questions related to specific physical activities that a patient would routinely perform. Each patient was required to describe whether or not each type of activity could be performed without symptomatic limitations. A specific number of metabolic costs (specific activity scale) of self-perceived exercise tolerance was derived for each patient from a summary of their answers to a questionnaire.

**Cardiorespiratory Polygraphy**
Sleep was studied in-hospital to exclude patients with obstructive sleep apnea as described earlier. Briefly, the proportion of central and obstructive sleep apnea was determined by monitoring patients using a Somé cardiorespiratory monitoring device (Compumedics, Abbotsford, VIC, Australia).\(^{19}\) We analyzed nasal airflow, thoracic and abdominal effort, arterial

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**Figure 1.** Flow chart of study population. ASV, adaptive servoventilation; CPAP, continuous positive airway pressure; HF, heart failure; LVEF, left ventricular ejection fraction; OAI, obstructive apnea index.
Effects of ASV and CPAP on MSNA

Operation of ASV

The operating principle of ASV has been described. Briefly, ventilation was servo-controlled at 0.3 cmH₂O · L⁻¹ · min⁻¹ · s⁻¹ (pegged to 3–10 cmH₂O) to maintain minute ventilation. If all central respiratory efforts suddenly ceased, machine support (pressure swing amplitude) would increase from the minimum of 3 cmH₂O to the amount of pressure required to maintain minute ventilation at 90% of the average ventilation (up to a maximum of 10 cmH₂O reached within ≈12 s). Smaller or slower changes in effort would result in proportionally smaller or slower changes in the degree of support. When ventilation exceeded the 90% target in the steady state, pressure support remained at a minimum of 3 cmH₂O.

Protocol

After baseline cardiorespiratory polygraphy and the day before the study started, the participants were familiarized to positive pressure in the daytime with an Autoset CS (ResMed, Sydney, NSW, Australia) while acclimatizing patients to the ASV mode (Upper). End-expiratory pressure (EEP) for the CPAP group was fixed to the median airway pressure of the ASV mode determined as described above. Pressure setting for the ASV group was the same as that during acclimatization to the device (Lower). EIP, end-inspiratory pressure.

![Figure 2. Setting airway pressure for adaptive servoventilation (ASV) and continuous positive airway pressure (CPAP). Median airway pressure of ASV was automatically determined using Res-Scan™ software (ResMed, Sydney, NSW, Australia) while acclimatizing patients to the ASV mode (Upper). End-expiratory pressure (EEP) for the CPAP group was fixed to the median airway pressure of the ASV mode determined as described above. Pressure setting for the ASV group was the same as that during acclimatization to the device (Lower). EIP, end-inspiratory pressure.](image)
Therwil, Switzerland) were placed on supine patients as described. Integrated sympathetic nerve activities, analog blood pressure traces, and the ECG and respiratory signals were sampled at 2 kHz per channel and stored using an online data acquisition and analysis system (PowerLab 8SP, AD Instruments, Grand Junction, CO, USA).

Baseline data were recorded for 10 min and then the patient was randomized to receive ASV or CPAP with a coded envelope that was opened immediately before application of the device. Either ASV or CPAP was provided using an AutoSet CS ASV device (ResMed) as follows. For the CPAP group, EEP was fixed to the median airway pressure determined as described (Figure 2) and ASV was applied to the ASV group as practiced before the study (Figure 2). Either ASV or CPAP was applied for 30 min using the same mask (Ultra Mirage).

All participants remained conscious and alert throughout the study to avoid the effects of sleep on hemodynamic and other variables. Blood samples were withdrawn from the antecubital

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### Table 1. Characteristics of the Patients With Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>ASV (n=29)</th>
<th>CPAP (n=28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63±14</td>
<td>60±15</td>
<td>0.56</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>24/5</td>
<td>19/9</td>
<td>0.19</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.6±4.4</td>
<td>22.4±3.9</td>
<td>0.86</td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic/non-ischemic</td>
<td>9/20</td>
<td>7/21</td>
<td>0.62</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (21%)</td>
<td>6 (21%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (45%)</td>
<td>12 (43%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>14 (48%)</td>
<td>12 (43%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Specific activity scale (METs)</td>
<td>4.9±1.2</td>
<td>4.9±1.3</td>
<td>0.99</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAS inhibitors</td>
<td>27 (93%)</td>
<td>26 (93%)</td>
<td>0.97</td>
</tr>
<tr>
<td>β-blockers</td>
<td>22 (76%)</td>
<td>20 (71%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Loop-diuretics</td>
<td>23 (79%)</td>
<td>24 (86%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>17 (59%)</td>
<td>13 (46%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Statins</td>
<td>17 (59%)</td>
<td>11 (39%)</td>
<td>0.15</td>
</tr>
<tr>
<td>%VC</td>
<td>93±19</td>
<td>97±12</td>
<td>0.38</td>
</tr>
<tr>
<td>FEV₁,%</td>
<td>74±13</td>
<td>78±10</td>
<td>0.18</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>237±225</td>
<td>252±189</td>
<td>0.79</td>
</tr>
<tr>
<td>Left atrial dimension (mm)</td>
<td>45±9</td>
<td>43±8</td>
<td>0.49</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>31±8</td>
<td>31±9</td>
<td>0.88</td>
</tr>
<tr>
<td>pH</td>
<td>7.43±0.04</td>
<td>7.40±0.03</td>
<td>0.07</td>
</tr>
<tr>
<td>pO₂ (mmHg)</td>
<td>88±11</td>
<td>89±9</td>
<td>0.79</td>
</tr>
<tr>
<td>pCO₂ (mmHg)</td>
<td>37±6</td>
<td>37±8</td>
<td>0.99</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.3±2.3</td>
<td>13.5±2.3</td>
<td>0.68</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.0±0.3</td>
<td>1.0±0.4</td>
<td>0.80</td>
</tr>
<tr>
<td>Cardiorespiratory polygraphy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI (/h)</td>
<td>17±12</td>
<td>15±14</td>
<td>0.47</td>
</tr>
<tr>
<td>Central AI (/h)</td>
<td>7±8</td>
<td>6±10</td>
<td>0.65</td>
</tr>
<tr>
<td>Obstructive AI (/h)</td>
<td>2±2</td>
<td>2±2</td>
<td>0.65</td>
</tr>
<tr>
<td>Mixed AI (/h)</td>
<td>1±1</td>
<td>1±2</td>
<td>0.52</td>
</tr>
<tr>
<td>Hypopnea index (/h)</td>
<td>7±7</td>
<td>5±5</td>
<td>0.30</td>
</tr>
<tr>
<td>ODI4% (/h)</td>
<td>15±12</td>
<td>13±11</td>
<td>0.61</td>
</tr>
<tr>
<td>Minimal SpO₂ (%)</td>
<td>86.0±6.0</td>
<td>87.1±4.4</td>
<td>0.45</td>
</tr>
<tr>
<td>Mean SpO₂ (%)</td>
<td>95.7±1.4</td>
<td>95.9±1.4</td>
<td>0.52</td>
</tr>
<tr>
<td>Periodic breathing</td>
<td>12 (41%)</td>
<td>11 (39%)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD or number (%) of patients.

AHI, apnea hypopnea index; AI, apnea index; ASV, adaptive servoventilation; BNP, brain natriuretic peptide; CPAP, continuous positive airway pressure; FEV, forced expiratory volume; LVEF, left ventricular ejection fraction; ODI, oxygen desaturation index; RAS, renin-angiotensin system; SpO₂, oxygen saturation; VC, vital capacity.

NSW, Australia) set to default settings of expiratory pressure, 5cmH₂O; inspiratory pressure support, 3–10cmH₂O (Figure 2). Maximal pressure support and EEP were reduced to 8 and 4cmH₂O in 9 patients who could not tolerate pressures of 10 and 5cmH₂O, respectively. All patients could breathe consistently under the ASV mode for 30 min using an oronasal face mask (Ultra Mirage, ResMed). Actual median airway pressure during ASV was automatically determined at the end of the familiarization process using Res-Scan™ software (ResMed) (Figure 2).

The study started on the following morning at 2 h after the patients consumed a low-energy breakfast free of caffeine and medications for underlying diseases and HF. Microelectrodes for sympathetic nerve recordings, ECG electrodes, noninvasive tonometry (Jentow 7700, Colin, Komaki, Aichi, Japan), thoracic electrical impedance (Impedance plethysmograph, AI-600G, Nihon Kohden, Tokyo, Japan) and sensors for oxygen saturation measurements (V-sign™ Sensor, SenTec AG, Therwil, Switzerland) were placed on supine patients as described. Integrated sympathetic nerve activities, analog blood pressure traces, and the ECG and respiratory signals were sampled at 2kHz per channel and stored using an online data acquisition and analysis system (PowerLab 8SP, AD Instruments, Grand Junction, CO, USA).

Baseline data were recorded for 10 min and then the patient was randomized to receive ASV or CPAP with a coded envelope that was opened immediately before application of the device. Either ASV or CPAP was provided using an AutoSet CS ASV device (ResMed) as follows. For the CPAP group, EEP was fixed to the median airway pressure determined as described (Figure 2) and ASV was applied to the ASV group as practiced before the study (Figure 2). Either ASV or CPAP was applied for 30 min using the same mask (Ultra Mirage). All participants remained conscious and alert throughout the study to avoid the effects of sleep on hemodynamic and other variables. Blood samples were withdrawn from the antecubital
Effects of ASV and CPAP on MSNA

Determination of MSNA
Multiunit recordings of efferent postganglionic SNA to the skeletal muscle were obtained via a microelectrode inserted directly into the left peroneal nerve posterior to the fibular head. Nerve signals were amplified ×100,000, passed through a band-pass filter (500–5,000 Hz) and integrated with a custom nerve-traffic analysis system (Neuropack Σ MEB-5504, Nihon Kohden). Data were analyzed in a blinded manner by 2 of the authors (RU and YO) and MSNA was expressed as burst rate (bursts/min) and incidence (bursts/100 beats).

Measurement of Respiratory Rate and Tidal Volume by Electrical Impedance
Respiration was continuously and conveniently monitored as thoracic electrical impedance. We previously showed that the tidal volume derived from this method closely correlated with that derived from thermal dissipation (AE-300, Minato, Osaka, Japan) (R=0.98, P<0.001). PB was defined as a repeated oscillation of tidal volume with regularly recurring hypopnea and hypopnea (or apnea) and >25% variation in tidal volume. If PB accounted for >75% of the 10-min recording period at baseline, PB was diagnosed. The amplitude of the respiratory signal (tidal volume) was counted based on the electrical impedance signal. Respiratory instability was assessed as the coefficient of variation of the tidal volume (CV-TV) as described.

Statistical Analysis
Data are expressed as mean±standard deviation. Mean values for MSNA, heart rate, mean blood pressure, oxygen saturation and respiratory rate were determined for 5 min before and during the application of ASV or CPAP. The CV-TV was determined during the final 5 min of each study period. Variables between groups were compared using the χ² test or an unpaired t-test. Differences in variables between the 2 study periods were assessed using 2-way analysis of variance for repeated measures. The 2-way analysis of variance was applied to determine how 2 factors (device type [ASV or CPAP] and PB) affected changes in burst rate, burst incidence and CV-TV, and the Bonferroni-Dunn procedure was used for multiple comparisons.

Relationships between changes in burst rate or burst incidence and changes in heart rate, mean blood pressure, respiratory rate, oxygen saturation level and CV-TV were assessed using univariate analysis (n=57). Relationships between changes in MSNA and baseline clinical variables (EEP, median airway pressure, forced expiratory volume at 1s, LVEF, levels of BNP, pO₂, pCO₂, hemoglobin, serum creatinine, AHI and central apnea index) were also evaluated using univariate analysis. Variables with statistical significance in the univariate analysis (P<0.05) were included in a multivariate regression analysis. Statistical significance was established at P<0.05.

Data were statistically analyzed using JMP software, version 10.0 (SAS Institute Inc, Cary, NC, USA).

Results
Patients’ Characteristics and Baseline Parameters
Sleep apnea was documented in 40 (70%) of the 57 patients enrolled in the present study and 24 (42%) and 16 (28%) of them presented with dominant central apnea and dominant hypopnea, respectively. The severity of sleep apnea was mild,
Effect of ASV or CPAP on Hemodynamics, Respiration and MSNA

Actual median airway pressure was comparable between the ASV and CPAP groups (6.6±1.1 vs. 6.5±1.0 cmH2O, P=0.69). Figure 3 shows representative tracings of MSNA and respiration before and during ASV or CPAP. Heart rate and mean blood pressure did not significantly change in either group during the application of devices, whereas oxygen saturation levels increased from the baseline (Table 2). Although ASV reduced CV-TV, CPAP did not (interaction, P<0.001). Burst rate and burst incidence decreased significantly in the ASV group, but not in the CPAP group (interaction, P=0.003 and P<0.001, respectively).

Relationship Between Sympathoinhibitory Effect and Respiratory Stability

Changes in oxygen saturation, EEP and actual pressure did not correlate with those in MSNA (Table 3). In contrast, BNP level and changes in CV-TV significantly correlated with changes in burst incidence. Multivariate analysis revealed that the change in CV-TV was the only independent predictor of decreased burst incidence.

PB was diagnosed in 12 of 29 and 11 of 28 patients in the ASV and CPAP groups, respectively (Table 4). Device type and PB significantly interacted with the changes in burst rate and moderate and severe in 16 (40%), 15 (38%) and 9 (22%) of the 40 patients, respectively.

Table 1 shows the baseline characteristics of the participants (n=57). The etiology of heart disease was ischemic and non-ischemic in 16 and 41 patients, respectively. Age, sex, body mass index, BNP level, EF and sleep parameters including AHI, central apnea index, mixed apnea index and ODI 4% were similar between the 2 groups. Among the 57 patients, 23 (40%) had PB and the remaining 34 (60%) did not. The AHI was higher in patients with than without PB (P=0.012).

Effects of ASV or CPAP on Hemodynamics, Respiration and MSNA

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![Table 2. Comparisons of Hemodynamic Parameters, Respiratory Parameters and Muscle Sympathetic Nerve Activity Before and During Adaptive Servoventilation (ASV) and Continuous Positive Airway Pressure (CPAP) in Patients With Heart Failure](image)
Effects of ASV and CPAP on MSNA

The major findings of the present study are as follows. Unlike CPAP, short-term ASV reduced CV-TV and MSNA under comparable pressure. Notably, the sympathoinhibitory effect closely correlated with improved respiratory instability. In addition, device type and PB significantly interacted with changes in MSNA. The effect of ASV on respiratory stabilization and sympathoinhibition was greater than that of CPAP in patients with PB, whereas neither device exerted sympathoinhibitory effects in patients without PB. Thus, ASV exerts sympathoinhibitory effects in patients with HF and PB via respiratory stabilization.

**ASV Stabilizes Respiration in Patients With HF**

A previous study showed that CPAP reduces central sleep apnea in only half of patients with HF and central sleep apnea, and another found that CPAP does not remove central sleep apnea during non-REM sleep when the ratio of the apnea length to the ventilation length of central sleep apnea was >1. Thus, CPAP does not always decrease central sleep apnea or respiratory instability in the clinical setting.

Central sleep apnea was eliminated more effectively by ASV.

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**Discussion**

The major findings of the present study are as follows. Unlike CPAP, short-term ASV reduced CV-TV and MSNA under comparable pressure. Notably, the sympathoinhibitory effect closely correlated with improved respiratory instability. In addition, device type and PB significantly interacted with changes in MSNA. The effect of ASV on respiratory stabilization and sympathoinhibition was greater than that of CPAP in patients with PB, whereas neither device exerted sympathoinhibitory effects in patients without PB. Thus, ASV exerts sympathoinhibitory effects in patients with HF and PB via respiratory stabilization.

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**Table 4. Comparison of Changes in CV-TV and MSNA Among 4 Groups of Patients With Heart Failure**

<table>
<thead>
<tr>
<th>Study group</th>
<th>ΔCV-TV (%)</th>
<th>ΔBurst rate (%)</th>
<th>ΔBurst incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASV, PB (–) (n=17)</td>
<td>–5±59</td>
<td>–12±11</td>
<td>–10±11</td>
</tr>
<tr>
<td>ASV, PB (+) (n=12)</td>
<td>–47±21*</td>
<td>–24±16*</td>
<td>–24±14*</td>
</tr>
<tr>
<td>CPAP, PB (–) (n=17)</td>
<td>4±38†</td>
<td>–6±11 †</td>
<td>–3±12 †</td>
</tr>
<tr>
<td>CPAP, PB (+) (n=11)</td>
<td>11±25§</td>
<td>–3±11§</td>
<td>–2±11§</td>
</tr>
</tbody>
</table>

**ANOVA P value**

<table>
<thead>
<tr>
<th>Device (ASV/CPAP)</th>
<th>PB (+/–)</th>
<th>Interaction (device x PB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.004</td>
<td>0.126</td>
<td>0.033</td>
</tr>
<tr>
<td>0.001</td>
<td>0.137</td>
<td>0.043</td>
</tr>
<tr>
<td>&lt;0.001</td>
<td>0.056</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD. *P<0.05 vs ASV, PB (–); †P<0.05 vs ASV, PB (+); ‡P<0.001 vs ASV, PB (+); §P<0.01 vs ASV, PB (+); #P<0.001 vs ASV, PB (+).

ANOVA, analysis of variance; MSNA, muscle sympathetic nerve activity. Other abbreviation as in Table 2.
than by CPAP during sleep because ventilation was servo-controlled to maintain a moving target minute ventilation of 90% of the long-term average ventilation. Similarly, we found that ASV restored normal breathing while awake, whereas CPAP did not. Tidal volume was stabilized by the servo-ventilation function as indicated by the decreased CV-TV in the ASV group.

Mechanisms of Sympathoinhibitory Effect of ASV

The findings in the present CPAP group are consistent with those of previous reports indicating that the MSNA of patients with HF on short-term CPAP (5 and 10 cmH₂O) modestly increased or did not change. By contrast, short-term ASV reduced MSNA in patients with HF and PB. Because the positive pressure was comparable between CPAP and ASV (6.5 vs. 6.6 cmH₂O) in the present study, the effect elicited via aortic receptor unloading by positive pressure might have been similar between the 2 groups. In addition, the sympathoinhibitory effect did not significantly correlate with EEP in the present study. Therefore, the level of positive pressure was unlikely to have caused the differences in the effects of ASV and CPAP on MSNA.

The sympathoinhibitory effect also closely correlated with a reduction in CV-TV in the present study. Our preliminary study also found that changes in CV-TV and respiratory rate elicited by ASV were independent predictors of changes in MSNA. Respiratory rate correlated positively, whereas tidal volume correlated inversely, with MSNA in the patients with HF. Abnormal respiration such as rapid and shallow, or irregular breathing might be associated with a smaller tidal volume. In patients with Cheyne-Stokes respiration, MSNA is at the lowest at the end of hyperpnea and peaks at the end of apnea. Thus, the extent of lung inflation induced by respiration might be an important factor in determining tonic SNA in patients with HF. Smaller tidal volumes could be increased towards the normal level by ASV and tidal volume stabilization might result in sympathoinhibition among patients with HF. Stimulating pulmonary vagal afferents by mechanical ventilation might be a mechanism of reflexively reduced cardiac sympathetic outflow. Thus, the sympathoinhibitory effect caused by stabilizing tidal volume by servoventilation seems to override the modest sympathoexcitatory effect resulting from positive EEP, thus resulting in a mild decrease in MSNA for most patients with HF.

We found that MSNA remained unchanged in the CPAP group. Moreover, the sympathoinhibitory effect of the devices did not correlate with EEP. However, low-level CPAP might benefit MSNA by reducing pulmonary congestion, especially in patients with higher left atrial pressure. Because the left atrial dimension is an indicator of left atrial pressure, we divided the CPAP group into subgroups with a larger or smaller left atrium. We found that MSNA decreased in the group with the larger, but not the smaller left atrium (data not shown). Thus, relatively low-level CPAP might reduce MSNA only in patients with higher left atrial pressure.

Although oxygen saturation levels and MSNA significantly changed only in the ASV group, the changes in these 2 variables did not correlate. Thus, the sympathoinhibitory effects might not be elicited simply by improving oxygenation during ASV. In fact, simple oxygen inhalation did not result in sympathoinhibition among patients with HF.

Clinical Implications

Short-term (30 min) ASV applied at 5 cmH₂O EEP significantly increased cardiac output measured by echocardiography in patients with HF. Importantly, the increase in cardiac output inversely correlated with a decrease in systemic vascular resistance. Adding pressure support to CPAP (bi-level positive airway pressure) increased the cardiac index by 0.2 L·min⁻¹·m⁻² compared with CPAP alone. Importantly, bi-level positive airway pressure decreased systemic vascular resistance, whereas CPAP alone did not. These findings in the present and previous studies support the notion that ASV has both sympathoinhibitory and vasodilatory effects.

The sympathoinhibitory effect of ASV has clinical implications because sympathetic activation is associated with a poor prognosis for patients with HF. MSNA parallels renal and cardiac SNA, and it is an independent predictor of mortality in patients with HF. A sympathoinhibitory effect was also documented by measuring urinary catecholamine excretion after using ASV for 1 night.

We previously showed that long-term (3.5 months) ASV decreased MSNA and improved cardiac function in association with central sleep apnea suppression in patients with HF. The effectiveness of ASV for HF might be mediated, at least in part, by reducing SNA in patients with HF and both daytime and nighttime respiratory instability. These beneficial effects of even short-term ASV might contribute to improvements in cardiac function in patients with HF.

The long-term effects of ASV and CPAP on cardiac function have been compared in patients with HF. The results suggest that ASV confers the greater benefit of an increase in cardiac function. However, the mechanisms of this effect have not been thoroughly investigated. The present and a previous study found that a greater decrease in respiratory instability, MSNA, AHI and urinary norepinephrine levels was evoked by ASV, but not by CPAP and that these effects could contribute to the salutary effects of ASV on cardiac function compared with CPAP.

Study Limitations

First, we did not definitively determine whether the patients were awake or asleep during the application of ASV and CPAP. Because MSNA decreases during sleep, we could not completely exclude the possibility that falling asleep might also have caused the decrease in MSNA. Second, our study participants remained awake and PB is generally more prevalent during sleep. Thus, the sympathoinhibitory effect of ASV compared with CPAP might be more prominent while asleep than while awake. Third, the duration of ASV application (30 min) was too short to realistically represent overnight sleep. Fourth, we did not examine in detail the reaction between ventilation or cardiac function and positive airway pressure in different modes.

Despite these limitations, the present findings indicated that ASV reduced MSNA in patients with HF and PB, whereas CPAP did not. Such respiratory responses might influence the clinical effectiveness of ASV and CPAP. Further studies of a larger cohort of patients are required to draw definitive conclusions.

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Disclosures

None of the authors has a conflict of interest to disclose.

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