Adaptive Servo-Ventilation Therapy for Patients With Chronic Heart Failure in a Confirmatory, Multicenter, Randomized, Controlled Study

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Background: Adaptive servo-ventilation (ASV) therapy is expected to be novel nonpharmacotherapy with hemodynamic effects on patients with chronic heart failure (CHF), but sufficient evidence has not been obtained.

Methods and Results: A 24-week, open-label, randomized, controlled study was performed to confirm the cardiac function-improving effect of ASV therapy on CHF patients. At 39 institutions, 213 outpatients with CHF, whose left ventricular ejection fraction (LVEF) was <40% and who had mild to severe symptoms [New York Heart Association (NYHA) class: ≥II], were enrolled. After excluding 8 patients, 102 and 103 underwent ASV plus guideline-directed medical therapy (GDMT) [ASV group] and GDMT only [control group], respectively. The primary endpoint was LVEF, and the secondary endpoints were HF deterioration, B-type natriuretic peptide (BNP), and clinical composite response (CCR: NYHA class+HF deterioration). LVEF and BNP improved significantly at completion against the baseline values in the 2 groups. However, no significant difference was found between these groups. HF deterioration tended to be suppressed. The ASV group showed a significant improvement in CCR corroborated by significant improvements in NYHA class and ADL against the control group.

Conclusions: Under the present study's conditions, ASV therapy was not superior to GDMT in the cardiac function-improving effect but showed a clinical status-improving effect, thus indicating a given level of clinical benefit. (Circ J 2015; 79: 981 – 990)

Key Words: Adaptive servo-ventilation; Cardiac function; Chronic heart failure; Noninvasive positive pressure ventilation; Nonpharmacotherapy

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have suggested that ASV therapy, regardless of the severity of sleep-disordered breathing (SDB), can inhibit sympathetic nerve overactivity, improve left ventricle ejection fraction (LVEF), B-type natriuretic peptide (BNP) levels, and cardiovascular events, as well as clinical symptoms and exercise tolerance, and induce LV reverse remodeling.11–17

Patients with LV reverse remodeling have a very favorable prognosis as compared with patients who do not.18

The present study was conducted as a multicenter, randomized, controlled study in order to examine the superiority of the ASV group to the control group regarding the cardiac function-improving and LV remodeling-inducing effects of ASV therapy that SAVIOR-R14 had suggested.

Methods

Subjects and Study Design

The target number of patients for the present study was 200 in total as described in the protocol article of the present study.19

At 39 medical institutions in Japan (Appendix 1), 213 patients with CHF (age ≥20 years; GDMT; capable of using the ASV ventilator at home; New York Heart Association (NYHA) class ≥II; LVEF; <40%; mean age: 63.3 years; 165 males) were enrolled. The exclusion criteria are described in the protocol article.19

The Confirmatory, multicenter, randomized, controlled Study of Adaptive servo-Ventilation In patients with chronic heart failure.
The primary endpoint for efficacy was LVEF measured according to the biplane Simpson’s method, and the Central Adjudication Committee (Appendix 2) determined, in a blinded manner, the acceptability of LVEF measurements obtained at each participating medical institution in accordance with the specified procedures for echocardiography.

The secondary endpoints for efficacy were: (1) cardiac events (death from heart failure, sudden death, admission to the hospital because of disease progression, treatment modification for HF, and long-term (≥12 weeks) deterioration of symptoms) that the Central Adjudication Committee finally determined in a blinded manner; (2) plasma BNP levels measured at each participating medical institution; and a clinical composite response (CCR: categorized as worsened, unchanged, and improved) consisting of NYHA classes and clinical events.

The endpoint for safety was an adverse event. The endpoints, which were based on the case report form, were as follows with respect to the ASV group and the control group:

Patient background, QOL, activities of daily living (ADL), vital signs, physical findings, echocardiograms, chest X-ray, hematology results, sleep study outcomes (e.g., apnea-hypopnea)

Definitions and Endpoints
The definitions of and treatments for CHF followed the Guide-
A total of 213 patients with CHF were enrolled and then randomly assigned to either the ASV or control group. After excluding 8 patients, 102 patients in the ASV group and 103 patients in the control group received their allocated interventions (Figure 1). Patients were followed up for 24 weeks after the baseline.

Patient characteristics at baseline are shown in Table 1. The mean ages of the patients in the ASV group and the control group were 63.3 ± 13.0 years and 63.3 ± 13.9 years, respectively. Male patients accounted for 80.4% and 80.6% in the ASV group and the control group, respectively. The proportions of ischemic heart disease among the underlying heart diseases were 40.2% and 35.0% in the ASV group and the control group, respectively. The proportions of patients with NYHA classes II and III/IV heart failure were 55.9% and 44.1%, and 61.2% and 38.8% in the ASV group and the control group, respectively. A significant difference (P=0.013) was found between the groups regarding LVEF at baseline: 29.7 ± 7.7% in the ASV group and 27.2 ± 7.1% in the control group. However, no statistically significant difference was found between the groups for any of the other variables examined.

Echocardiography Baseline-completion changes in LVEF in the ASV and control groups are shown in Figure 2. LVEF in the ASV group and the control group increased significantly (P<0.001 each) from 29.6 ± 7.5% and 27.1 ± 6.9% to 35.2 ± 11.0% and 33.5 ± 10.7%, respectively. Namely, LVEF improved by 5.6 ± 9.0% and 6.4 ± 11.7% in the ASV group and the control group, respectively. Analysis of covariance revealed no significant difference between the groups (P=0.659), which did not demonstrate the additive effect of ASV therapy on LVEF.

Echocardiographic variables other than LVEF at baseline and completion are shown in Table 2. LV end-diastolic volume (LVEDV) at completion decreased in the ASV group and the control group, with a tendency (P=0.053) and a significant index (AHI) at baseline only), and ventilator usage. At each participating institution, AHI was determined by polysomnography or a portable monitoring device type 2 or 3 as per the published methodology and in accordance with the published definition. Electronic media were used to collect (1) echocardiograms, ventilator usage, and air flow of the sleep study in the ASV group, as well as (2) echocardiograms and air flow of the sleep study in the control group.

Daytime sleepiness was self-assessed according to the Epworth sleepiness scale. The attending physician assessed the ADL based on a 21-item questionnaire entered by the patient. Furthermore, the patient assessed QOL by him/herself via a 21-item questionnaire to evaluate the physical and mental dimensions.

Statistical Analysis LVEF, the primary endpoint, was analyzed using analysis of covariance. The cumulative incidences of cardiac events were analyzed using the Kaplan-Meier method and log-rank test. Intra- and intergroup differences for continuous variables were evaluated using paired t-test and unpaired t-test, respectively. Intra- and intergroup differences for BNP and categorical variables were analyzed using 1- and 2-sample Wilcoxon tests, respectively. Binary variables were analyzed using the Fisher’s exact probability test. Missing values were imputed using the Last-Observation-Carried-Forward approach. All analyses were conducted with the SAS Analysis System, version 9.2 (SAS Institute Inc, Cary, NC, USA), and a 2-tailed P value <0.05 was considered statistically significant.

Results

Patients
Patients were enrolled in the present study between December 2011 and May 2013 and underwent the predetermined examinations and assessments at baseline (8 weeks before enrollment to day of enrollment), as well as at weeks 12 and 24 of the study.
showing statistically significant decreases in the 2 groups (P<0.001 each). However, no statistically significant difference was found between the groups (P=0.575).

Cardiac Events
The Kaplan-Meier curves for event-free survival exhibited time-course declines in the 2 groups, and the extent of dissociation between the 2 curves tended to increase at approximately 2 months or more of follow-up (Figure 4). The total numbers of cardiac events in the ASV group and the control group were 14 and 21, respectively, with the following breakdowns: death from HF: 1 and 2; sudden death: 0 and 0; admission to hospital because of disease progression: 10 and 16; treatment modification for HF: 2 and 3; and long-term deterioration (≥12 weeks) of symptoms: 1 and 0. No statistically significant difference (P=0.283) was found between the groups with respect to these events. Furthermore, the numbers of noncardiac deaths in the ASV and control groups were 1 (hepatocyte carcinoma) and 1 (pneumonia), respectively.
ADL assessed with the specific activity scale improved significantly (P<0.001) in both the ASV group and the control group at completion in conjunction with improvements in NYHA class, with a significant intergroup difference (P=0.042).

In contrast, QOL assessed with the Minnesota Living with Heart Failure Questionnaire improved significantly (P<0.001) in the 2 groups at completion; however, QOL in the ASV group did not improve to such an extent to generate a significant intergroup difference (P=0.612).

Symptoms, ADL, and QOL
The proportions of CCR at completion in the ASV group and the control group are shown in Figure 5. The proportion of patients with improved CCR was significantly greater (P=0.002) in the ASV group than in the control group. At completion, NYHA class (a component of CCR) had improved significantly (P<0.001 and P=0.044) in the ASV group and the control group, respectively, with a significant intergroup difference (P=0.009).
ASV Home Therapy for CHF

Mandatory declarations

Miscellaneous

Vital signs (systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate), and X-ray (cardiothoracic ratio (CTR) and intensity of pulmonary congestion) exhibited no intergroup differences at completion, although significant changes at completion were found with respect to some variables (eg, BMI, SBP, DBP, and CTR).

Safety Assessment

The adverse events were as follows: in the ASV group, 29 episodes (diarrhea, worsened HF, ventricular tachycardia, conjunctivitis, anemia, hemorrhagic stroke, alcohol-induced

Table 3. Analysis of Variables Stratified by the AHI (<15/≥15/h), an Index of the Severity of Sleep-Disordered Breathing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stratified threshold</th>
<th>Group</th>
<th>n</th>
<th>Change from baseline to completion</th>
<th>Intragroup P value</th>
<th>Intergroup P value</th>
<th>P value on stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td>AHI &lt;15/h</td>
<td>ASV</td>
<td>20</td>
<td>Mean ± SD</td>
<td>3.32±4.99</td>
<td>0.008</td>
<td>0.385</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>21</td>
<td></td>
<td>Mean ± SD</td>
<td>5.18±8.23</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AHI ≥15/h</td>
<td>ASV</td>
<td>41</td>
<td>Mean ± SD</td>
<td>6.52±9.89</td>
<td>&lt;0.001</td>
<td>0.447</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>31</td>
<td></td>
<td>Mean ± SD</td>
<td>8.76±13.86</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Cardiac events with HF deterioration</td>
<td>AHI &lt;15/h</td>
<td>ASV</td>
<td>33</td>
<td>No. of patients with events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AHI ≥15/h</td>
<td>ASV</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>60</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>AHI &lt;15/h</td>
<td>ASV</td>
<td>30</td>
<td>Median [25–75 percentile range]</td>
<td>−61.6 [−149.8 to 72.9]</td>
<td>0.204</td>
<td>0.699</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>26</td>
<td></td>
<td>Median [25–75 percentile range]</td>
<td>−21.9 [−94.7 to 49.5]</td>
<td>0.235</td>
<td></td>
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<td></td>
<td>AHI ≥15/h</td>
<td>ASV</td>
<td>56</td>
<td>Median [25–75 percentile range]</td>
<td>−62.7 [−269.0 to 3.9]</td>
<td>&lt;0.001</td>
<td>0.632</td>
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<tr>
<td></td>
<td>Control</td>
<td>48</td>
<td></td>
<td>Median [25–75 percentile range]</td>
<td>−60.0 [−285.8 to 42.4]</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>Clinical composite response</td>
<td>AHI &lt;15/h</td>
<td>ASV</td>
<td>29</td>
<td>n (%) at completion</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Control</td>
<td>26</td>
<td></td>
<td>Improved</td>
<td>17 (58.6%)</td>
<td>7 (24.1%)</td>
<td>0.194</td>
</tr>
<tr>
<td></td>
<td>AHI ≥15/h</td>
<td>ASV</td>
<td>58</td>
<td>Unchanged</td>
<td>18 (32.7%)</td>
<td>18 (32.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>55</td>
<td></td>
<td>Worsened</td>
<td>13 (22.4%)</td>
<td>19 (34.5%)</td>
<td></td>
</tr>
</tbody>
</table>

†Intragroup differences were calculated using paired t-test or one-sample Wilcoxon test; ‡intergroup differences were calculated using Student’s t-test, log-rank test, or two-sample Wilcoxon test; §differences between two stratified ASV groups were calculated using Student’s t-test, log-rank test, or two-sample Wilcoxon test. CI, confidence interval; HF, heart failure. Other abbreviations as in Table 1.
hepatopathy, arthralgia, complete total occlusion, and influenza infection) in 18 patients, including 16 serious (ie, hepatocytic carcinoma, colon cancer, worsened HF, ventricular tachycardia, urinary infection, fever, fracture, and decreased renal function); in the control group, 41 episodes (ie, worsened HF, atrial fibrillation, ventricular tachycardia, cardiac resynchronization therapy, suspected thrombotic phlebitis of the legs, anemia, coronary atherosclerosis, dyspnea, fatigueability, weight gain, lightheadedness after standing, interstitial pneumonia, skin ulcer, and hematuria) in 29 patients, including 17 serious (ie, worsened HF, stomach cancer, bladder cancer, complete total occlusion, pneumonia, cholestocholitis, increased BNP, and sick sinus syndrome). None of these adverse events was considered by the attending physician to have causality with ASV therapy.

**Stratified Analysis**

The results from the analysis of variables (LVEF, cardiac events without HF deterioration, BNP, and CCR) that were stratified by AHI to assess the severity of SDB are shown in Table 3. The stratified analysis revealed no enhancement of the cardiac function-improving effect of ASV therapy.

**Discussion**

Along with increments in clinicopathological and biochemical knowledge about CHF, pharmacotherapeutic strategies for the disease have changed evolutionally: digitalis and diuretics to treat congestion and edema since the late 1950s; vasodilators to treat hemodynamic abnormalities since the 1970s; and ACE inhibitors, ARBs, and β-blockers to treat neurohumoral factor abnormalities since the late 1980s. In particular, ACE inhibitors, and β-blockers have the proven effect of improving prognosis, the true endpoint for patients with CHF. Despite these therapeutic efforts and advances in pharmacotherapy, HF severe enough to require hospitalization is more “malignant” with regard to 5-year survival than many of the common types of cancer, with the exception of lung cancer. This alarming fact clearly indicates the therapeutic limitations of the current GDMT and how critically important are the early diagnosis and treatment of CHF and the prevention of disease progression, which drove us to seek a novel, noninvasive, nonpharmacological modality that could be added to the current GDMT.

To examine whether ASV therapy could become such a modality, we established LVEF as the primary endpoint and a surrogate variable for the assessment of the true endpoint. Subsequently, we conducted the present study on the following assumption based on prior studies that had suggested increases in stroke volume and cardiac output due to NPPV and LV reverse remodeling due to ASV: the addition of ASV therapy to GDMT might additively improve the cardiac function of CHF patients in conjunction with LV reverse remodeling. In the present study, however, a statistically significant difference between the ASV group and the control group was not found with respect to LVEF and BNP, although these variables at completion improved significantly as compared with the baseline values in both groups. One conceivable reason for these findings for LVEF and BNP is that the stabilization of clinical status (GDMT and the absence of medication initiation/modification and medication dose increment within 3 months prior to study enrollment) was not established as an inclusion criterion in our consideration of the actual usage of the ventilator in the real-world clinical setting. Consequently, patients for whom medication with β-blockers was initiated or their dose was increased within 30 days and 90 days prior to the study onset accounted for 35% and 55% of the study population, respectively. Beta-blockers have an established suppressive effect on LV remodeling through their inhibitory effect on sympathetic nerve overactivity, which leads to reductions in LV oxygen consumption and LV filling pressure. On the other hand, ASV therapy was suggested to stabilize respiration, resulting in suppression of sympathetic nerve overactivity. Therefore, we speculate that ASV therapy and β-blockers probably exert their cardiac function-improving effect through these common pathways within the putative mechanisms of action to such an extent that no statistically significant difference could be detected between the ASV group and the control group in the present study.

Symptoms improved significantly after intervention as observed in SAVIOR-R; furthermore, symptoms and CCR (ie, clinical status), as well as ADL improved significantly in the ASV group compared with the control group. On the other hand, QOL improved after intervention but showed no intergroup difference; this result is probably related to the fact that the QOL of patients in the control group improved more than we expected, which resulted in no demonstration of superiority of ASV therapy in improving QOL over the control group. Nevertheless, the ASV group was superior to the control group in the symptom-improving effect. Furthermore, adherence is a consequence of subjective benefits that the patient experiences in therapeutic interventions. Therefore, the improved clinical status of the patient through awareness of alleviated symptoms will contribute to an improvement in QOL.

A prior single-center observational study described the significantly decreased incidence of event-free survival, which serves as the assessment of 1 of the objectives of CHF treatment: prevention of disease progression at 1 year of follow-up. Therefore, the tendency for dissociation observed with the Kaplan-Meier curves for event-free survival in the present study might generate a statistically significant difference if patients were followed up for 1 year.

In other countries, the AutoSet CS was originally developed for the treatment of SDB in patients with HF; therefore, ASV therapy using the device is conducted exclusively for patients who are complicated by SDB. In Japan, on the other hand, ASV therapy is used to treat patients with HF, regardless of SDB severity, because of its hemodynamic effects (eg, reduction in preload and an increase in intrathoracic pressure). In fact, the analysis of LVEF, cardiac events without HF deterioration, BNP, and CCR stratified by AHI in the present study revealed no enhancement of the effects of ASV therapy. Namely, the hemodynamic effects of ASV therapy were not influenced by SDB severity as previously suggested by SAVIOR-R.

**Study Limitations**

First, the effects of ASV therapy on the primary endpoint could not be duly assessed because the present study was conducted in real-world settings where the clinical status of the patient undergoing GDMT was not necessarily stable. Second, the present study could not be blinded because of allowing ASV therapy at home (ie, AutoSet CS). Therefore, the possibility of biases (eg, selection bias, evaluator bias, and participant expectation bias) cannot be ruled out. However, physicians, technicians, and statisticians were all blinded to treatment assignment. Third, the true endpoint of ASV therapy (patient prognosis) was assessed indirectly by surrogate markers (eg, LV remodeling and BNP). The endpoint needs to be categorized as a surrogate endpoint.
be assessed as the primary endpoint in a future clinical study.

Conclusions

Under the conditions of the present study, we could not demon-istrate the superiority of ASV therapy at home to GDMT in the cardiac function-improving effect on patients with CHF. Nevertheless, ASV therapy showed improving effects on symptoms, ADL, and CCR, thus providing a given level of clinical benefit for this outpatient population.

Acknowledgments

The authors are grateful to the members of the Central Adjudication Com-mittee for their great contribution to the present study and to Satoshi Hiroshi, M.D., for the linguistic review of the manuscript. The research fund for SAVIOR-C was provided to the Comprehensive Support Project for Clinical Research of Lifestyle-Related Disease of the Public Health Research Foundation by Teijin Pharma Limited.

Conflict of Interest

Shin-ichi Momomura, lecture fee from Teijin Pharma Limited; Yasuki Kihara, lecture fee from Teijin Pharma Limited.

References

21. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al; Chamber Quantification Writing Group; American Society of Echocardiography’s Guidelines and Standards Commit-tee; European Association of Echocardiography. Recommendations for chamber quantification: A report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18: 1440 – 1463.

Appendix 1

Lists of Steering Committee, Central Adjudication Committee, Study Promotion Committee, and Adviser

Steering Committee

Shin-ichi Momomura (Principal Investigator, Saitama Medical Center, Jichi Medical University), Yoshishiko Seino (Nippon Medical School Chiba Hokusoh Hospital), Yasuki Kihara (Hiroshima University Graduate School of Biomedical & Health Sciences), Yoshihiko Adachi (Gunma Prefectural Cardiovascular Center), Yoshio Yasumura (Osaka National

Appendix 2

List of Investigators at the Participating Medical Institutions of SAVIOR-C