Long-Term Adaptive Servo-Ventilator Treatment Prevents Cardiac Death and Improves Clinical Outcome

Teruhiko IMAMURA, MD, Koichiro KINUGAWA, MD, Daisuke NITTA, MD, and Issei KOMURO, MD

Summary

Adaptive servo-ventilation (ASV) is a recently developed, noninvasive therapeutic tool for the treatment of heart failure (HF). However, the efficacy of ASV therapy in patients with advanced HF remains uncertain, especially as regards its contribution to freedom from cardiac replacement therapy. A total of 85 patients with advanced HF (New York Heart Association [NYHA] class IV, 71%, inotropic infusion-dependent 34%) refractory to guideline-directed medical therapy, received ASV therapy, irrespective of sleep-disordered breathing, at our institute between 2008 and 2014. Among these 85 patients, 46 continued ASV therapy for > 1 month (continued group), whereas 39 discontinued the therapy after < 1 month because of intolerance (discontinued group). There were no significant differences in baseline variables between the two groups. Heart rate indicating sympathetic activity, left ventricular (LV) reverse remodeling assessed by LV diastolic diameter, LV ejection fraction, and the grades of mitral and tricuspid regurgitations, HF severity assessed by NYHA class and plasma level of B-type natriuretic peptide, and end-organ dysfunction, improved significantly at 6 months following the initiation of ASV therapy (P < 0.05 for all). All-cause mortality and cardiac death rate were significantly lower during 2-year follow up in the continued group (P < 0.05 for both). In conclusion, ASV is a novel therapeutic tool prior to cardiac replacement therapy in patients with advanced HF and may prolong the period until cardiac replacement therapy becomes necessary. (Int Heart J 2016; 57: 47-52)

Key words: Ventricular assist device, Prognosis, Heart failure

Recent developments in cardiac replacement therapy, ie, heart transplantation and ventricular assist device (VAD) therapy, have tremendously improved survival rates in patients with advanced heart failure (HF). However, most patients face a variety of obstacles, including a shortage of donor hearts, severely limited inclusion criteria, and high invasiveness. At the same time, current guideline-directed medical therapies (GDMT), including β-blockers, angiotensin-converting enzyme inhibitors, and aldosterone antagonists, are not sufficient to improve the prognosis in patients with advanced HF. Therefore, development of a next generation therapy, which could delay the timing of cardiac replacement therapy or possibly even become an alternative to it, is warranted.

Adaptive servo-ventilation (ASV), one of the forms of noninvasive positive pressure ventilation, offers superior tolerability and simple operability based on the provision of support pressure. The positive pressure is synchronized to the respiratory patterns of each patient through its unique algorithm. This treatment was originally developed to treat sleep-disordered breathing (SDB), but has been widely indicated for the treatment of HF patients even in the absence of SDB.

Recently, several authors reported the efficacy of ASV in improving clinical outcomes during a short (~days) or mid-term (~months) study period in patients with mild to moderate HF (New York Heart Association [NYHA] class II-III) complicated by SDB. However, the long-term efficacy of ASV therapy in patients with advanced HF is uncertain. Moreover, most of the previous studies demonstrated improvement only in surrogate markers but not hard endpoints. In this study, we investigated 2-year survival prior to cardiac replacement therapy in patients with advanced HF receiving ASV therapy who were refractory to GDMT.

Methods

Patient selection: A total of 85 patients received de novo ASV treatment between 2008 and 2014 and were followed at the University of Tokyo Hospital, one of the largest VAD institutes in Japan. Patients with advanced HF with NYHA class III or IV were eligible for inclusion, regardless of the existence or absence of SDB. All patients had been treated with GDMT, unless contraindicated. ASV treatment was indicated by the attending physicians in patients with worsening HF despite GDMT. No patient received aggressive cardiac rehabilitation during the study period. Written informed consent was obtained from all participants before enrollment. The study protocol was approved by the Ethics Committee of our institutes.
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**ASV Procedure**: An advanced bi-level positive airway pressure unit, ASV (AutoSet-CS; ResMed, Sydney, Australia), was used, together with a best-fitted full face mask (ResMed). The device detects the patient breathing patterns automatically, provides proper pressure support that is synchronized to them through its fuzzy logic algorithms, and generates smooth pressure waveforms that mimic the patient’s normal respiratory patterns. It was set to deliver 5-cmH2O expiratory positive airway pressure and suitable minimum-maximum inspiratory support, which was within the minimum manufacturer’s setting range of 3–10 cmH2O.

Effective ASV treatment was defined as device usage > 4 hours per night. Some patients refused ASV therapy or could not tolerate ASV therapy because of mask discomfort. Patients who discontinued ASV therapy after < 1 month were assigned to the “discontinued group”. Those who were able to continue ASV therapy for > 1 month were assigned to the “continued group”.

**Baseline variables**: Baseline data, including demographic, laboratory, and echocardiographic variables, were obtained within 24 hours before the initiation of ASV therapy. Echocardiographic data were obtained using 2-dimensional, M-mode, or Doppler echocardiography. Left ventricular (LV) ejection fraction (LVEF) was calculated from the apical 2- and 4-chamber views using the modified biplane Simpson’s method. All sonographers were blinded to the study protocol.

**Clinical outcomes**: The variables for the assessment of clinical outcomes were obtained at 6 months following the ASV initiation, or just before death or VAD implantation if such events occurred. Echocardiographic data were obtained in the same manner as described above. All-cause mortality and cardiac deaths during the 2-year follow-up were recorded. VAD implantation was counted as cardiac death. Clinical outcomes after transfer to another hospital were also obtained.

**Statistical analyses**: Data are expressed as the mean ± SD, unless otherwise indicated. Continuous variables were compared using the unpaired t-test or Mann–Whitney U test as appropriate, and categorical variables were compared using the chi-square test or Fisher’s exact test as appropriate. Clinical outcomes were compared with baseline variables using the paired t-test. Changes in the distribution of NYHA classes during ASV treatment were compared using Wilcoxon’s signed rank sum test. Kaplan–Meier analyses were performed to compare survival rate and VAD-free survival rate between the continued and discontinued groups. Cox regression analyses were performed to assess the prognostic impact of ASV treatment. All statistical analyses were performed using SPSS Statistics 22 (SPSS Inc, Chicago, IL, USA). Statistical tests were 2-tailed, and a P-value < 0.05 was considered significant.

**Results**

**Baseline characteristics**: Baseline characteristics are presented in the Table. Patients in the discontinued group underwent
ASV therapy for 18 ± 9 days (1–29 days), and those in the continued group for 272 ± 254 days (48–730 days). Among the discontinued group, the reasons for terminating ASV therapy were occurrence of critical HF so that patients could not continue ASV therapy (n = 6), transfer to another hospital (n = 3), or discomfort (n = 30). Among the continued group, 34 (74%) underwent ASV therapy until the endpoint. Other patients terminated ASV therapy because of critical HF (n = 8) or transfer to another hospital (n = 4). Participants were classified as NYHA III (29%) or IV (71%), and 34% were receiving infusion of inotropes at the time of ASV initiation. There were statistically no significant differences in the baseline background between the continued group and discontinued group (P > 0.05 for all). The numbers of patients who received cardiac rehabilitation were comparable between both groups.

**Clinical outcomes:** Differences in the clinical outcomes during the 6-month study period were compared between the continued group and the discontinued group (Figure 1). Heart rate, LV diastolic diameter, serum total bilirubin, estimated glomerular filtration rate, and plasma BNP were significantly lower in the continued group compared with the discontinued group (Figure 1A, B, D-F; *P* < 0.05 for all comparison). LVEF was significantly greater in the continued group compared with the discontinued group (Figure 1C; *P* < 0.05). Aortic regurgitation remained unchanged in both groups. Mitral regurgitation (from 2.0 ± 0.8 to 1.7 ± 0.9, *P* < 0.05) and tricuspid regurgitation (from 1.7 ± 0.8 to 1.5 ± 0.7, *P* < 0.05) improved significantly in the continued group, whereas both regurgitations remained unchanged in the discontinued group.

NYHA class improved in the continued group (Figure 2A; *P* < 0.05) but remained unchanged in the discontinued group (Figure 2B). Doses of carvedilol at 6 months were comparable between the continued group and the discontinued group (8.0 ± 6.9 versus 10.0 ± 9.1 mg/day, *P* = 0.267).

**Differences in prognosis between groups:** Overall, 24 patients died and 10 underwent VAD implantation during the study period. Comparisons of the 2-year prognosis between the continued group and the discontinued group are presented in Figure 3. Survival rate (Figure 3A) and cardiac death-free rate (Figure 3B) were significantly higher in the continued group compared with the discontinued group (*P* < 0.05 for both). Univariate Cox regression analyses demonstrated that continued ASV treatment was a significant predictor of a higher survival rate (*P* = 0.041, hazard ratio 2.424) and a higher cardiac death-free rate (*P* = 0.040, hazard ratio 2.067).

**Discussion**

This study showed that patients with advanced HF (NYHA class IV 74%, inotrope infusion-dependent 28%) experienced better 2-year survival and cardiac death-free rates, irrespective of the existence of SDB, when ASV therapy was continued for > 1 month. The patients receiving ASV therapy also showed suppression of sympathetic nerve activity, facilitation of left ventricular reverse remodeling, improvement of HF symptoms, and recovery of end-organ function during the 6-month ASV treatment.
Concomitance of SDB: ASV was originally developed to treat SDB, and most evidence was accumulated in patients with HF complicated by SDB. Recent studies demonstrated that ASV therapy improved the short-term prognosis (< 1 year) in patients with HF, irrespective of SDB. A Japanese multicenter observational study consistently reported that ASV therapy was indicated without prior screening for SDB in approximately 62% of all enrolled patients who received ASV therapy in real-world practice. We also performed ASV therapy without prior screening for SDB.

Mid-term clinical outcomes: Most previous studies demonstrated that short- or mid-term (~6 months) ASV therapy improved clinical outcomes in patients with mild to moderate HF together with SDB, ie, NYHA class II-III, inotrope-free, and receiving inadequate anti-HF medical therapy. We here demonstrated the efficacy of ASV therapy at 6 months in patients with advanced HF, mainly represented by NYHA class IV (74%), some of them dependent on inotrope infusion (34%), and all receiving GDMT as far as tolerated (β-blocker, 88%; angiotensin-converting enzyme, 75%; aldosterone antagonist, 62%).

At 6 months, the patients’ heart rate had decreased significantly, which indicated suppression of sympathetic nerve activity, owing to the relaxation of the respiratory muscles, and a decrease in pulmonary capillary wedge pressure through a reduction in venous return. Consistently with previous reports, facilitation of left ventricular reverse remodeling and an improvement in HF symptoms were also achieved in patients with advanced HF receiving GDMT. Mitral and tricuspid regurgitations improved after ASV treatment probably owing to the left ventricular reverse remodeling. ASV therapy improved these clinical outcomes irrespective of the dose of β-blocker during the study period. Cardiac unloading by ASV did not result in further hypotension, even in already hypotensive patients with advanced HF; and we believe that ASV therapy can be indicated in such an advanced HF population. A recently published muti-center, randomized, controlled study using ASV therapy did not observe a better clinical course compared with the control group receiving GDMT, because both groups achieved improvement of clinical courses during a 6-month study period. Patients with advanced HF refractory to GDMT may be better candidates for ASV therapy compared with less sick patients who have not yet received GDMT.

We also showed that ASV therapy improved end-organ dysfunction, which is often complicated in patients with advanced HF owing to congestion or hypoperfusion of the end-organ. Efficacy of ASV therapy in the recovery of end-organ dysfunction has rarely been reported, probably because ASV was used in patients who were less seriously ill than those we enrolled in this study. Amelioration of hemodynamics by ASV therapy may improve end-organ perfusion. Recovery of end-organ function is beneficial even in patients who undergo VAD implantation, because it improves the post-VAD prognosis.

Long-term prognosis relating to cardiac replacement therapy: Previous studies showed the prognosis of ASV therapy by assessing the surrogate markers during a short- or mid-term study period (< 1 year), whereas we showed the advantage of ASV therapy in terms of 2-year survival rate and VAD-free survival rate. Considering the hazard ratio of 2.067 for continuous ASV therapy in relation to the 2-year VAD-free survival rate, ASV therapy seems to be effective from the viewpoint of delaying the timing of VAD implantation.

Suppression of perioperative sympathetic nerve activity is associated with a better postoperative clinical outcome, owing to its anti-inflammatory and cardiac protective effects. The postoperative benefits of ASV therapy prior to VAD implantation should also be confirmed in a future trial.

Study limitations: 1) This study evaluated a small population from a single center. The findings need to be confirmed in a future multi-center large-scale population study. 2) Among the discontinued group, most patients terminated ASV therapy because of discomfort. Sufficient explanation of the efficacy of ASV therapy to the patients and optimal selection of a best-fitted facial mask might improve their compliance with the treatment. We could not find any significant differences in patient background data between the continued group and the discontinued group. Other baseline variables that were not included in this study, such as patient personality or mental conditions, may have affected their tolerance of ASV therapy. A further study to analyze the characteristics that disturb continuing ASV therapy may improve patient compliance with the therapy. 3) We assumed that ASV therapy for > 4 hours per night during > 1 month was sufficient, and defined such patients as the continued group, based on previous studies. Whether
more aggressive ASV therapy would improve the prognosis or not could be a future concern. 4) Among the continued group, LVEF was rather decreased in 8 patients (17%). Some patients did not respond to ASV therapy. Prediction of responsiveness to ASV therapy would be a future concern. 5) The indication of ASV treatment was worsening HF despite of GDMT, which was determined by the attending physicians. Therefore, inclusion bias may have existed in this study. 6) We did not perform Cox regression analyses for all baseline variables because we focused on the efficacy of continuous ASV treatment. 7) We demonstrated the improvement of clinical variables at 6 months after ASV initiation. Longer-term changes in the clinical data are a future concern.

Conclusion: ASV is a novel therapeutic tool prior to cardiac replacement therapy in patients with advanced HF and can improve long-term prognosis.

DISCLOSURES

None.

REFERENCES

novel predictor of left ventricular reverse remodeling during treatment with a left ventricular assist device. J Artif Organs 2015. (in press)