Shorter Heart Failure Duration Is a Predictor of Left Ventricular Reverse Remodeling During Adaptive Servo-Ventilator Treatment in Patients With Advanced Heart Failure

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Summary

Adaptive servo-ventilation (ASV) is a recently developed, noninvasive therapeutic tool for the treatment of heart failure (HF). However, prediction of responsiveness to continuous ASV therapy remains uncertain, especially in patients with advanced HF receiving guideline-directed medical therapy. A total of 47 patients with advanced HF (NYHA class IV 74%, inotrope infusion dependent 38%) received continuous ASV therapy at our institute between 2008 and 2014. Of these 47 patients, 12 (26%) were responders, whose left ventricular ejection fraction increased ≥ 5% during the 6-month study period. Shorter HF duration (< 17.2 × 10^2 days) was a significant predictor of responsiveness to ASV therapy by logistic regression analysis and receiver operating characteristics analysis. Patients with shorter HF duration achieved improved HF symptoms, recovery of renal function, and a lower readmission ratio compared with the longer HF duration group during ASV therapy. In conclusion, early ASV introduction may be beneficial to achieve left ventricular reverse remodeling during ASV therapy in patients with advanced HF. (Int Heart J 2016; 57: 198-203)

Key words: Ventricular assist device, Prognosis

A daptive 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.31 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 recently for the treatment of heart failure (HF) patients even in the absence of SDB.2-4

Several authors reported the efficacy of ASV in improving clinical outcomes in patients with mild to moderate HF (New York Heart Association [NYHA] class II-III).4-10 ASV is also adopted in patients with NYHA class IV or those dependent on inotrope infusion in current clinical practice. However, the prediction of responsiveness to ASV therapy remains uncertain. Non-responsiveness to ASV therapy may decrease patient quality of life or even be fatal, especially in patients with advanced HF. Consistently, Cowie, et al recently demonstrated increased mortality in patients with HF along with central sleep apnea receiving aggressive ASV therapy when compared with the control group.20 Therefore, optimal patient selection for ASV therapy in such a population is warranted. We here soak predictors of responsiveness to ASV therapy in patients with advanced HF.

Patient selection: A total of 47 patients received de novo ASV treatment for > 1 month between 2008 and 2014 and were followed at our institute. Patients with advanced HF with NYHA class III/IV were eligible, regardless of the existence or absence of SDB. ASV treatment was indicated by the attending physicians in patients with worsening HF despite guideline-directed medical treatment (GDMT).17 ASV therapy was discontinued ≤ 1 month in 39 patients because of the occurrence of critical HF (n = 6), transfer to another hospital (n = 3), or discomfort (n = 30), and these patients were excluded from the study. Written informed consent was obtained from all participants before their enrollment. The Ethics Committee of our institute approved the study protocol beforehand.

ASV procedure: An advanced bi-level positive airway pressure unit, ASV (AutoSet-CS; ResMed, Sydney, Australia), was adopted, together with a best-fitted full-face mask. The device learns the patient’s breathing patterns automatically, and provides appropriate pressure support that is synchronized to them through its fuzzy logic algorithms. 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.

Baseline variables: Baseline data, including demographic,
laboratory, and echocardiographic variables, were obtained within 24 hours beforehand. 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. Valvular regurgitation was graded as follows: none (0), trace (1), mild (2), moderate (3), and severe (4). HF duration was defined as the time between the diagnosis of HF and the ASV initiation. The dose of β-blocker was standardized as the equivalent dose of carvedilol as appropriate. The dose of angiotensin converting enzyme inhibitor (ACEI) was also integrated as the equivalent dose of enalapril as appropriate.

Clinical outcomes: The data of the clinical outcomes were obtained at 6 months following the ASV initiation, or just before death or ventricular assist device (VAD) implantation if such events occurred. Patients who achieved improvement of LVEF ≥ 5% were defined as “responders”. Data of the clinical outcomes after transfer to another hospital were also obtained. Re-admission due to a cardiovascular event during the 2-year study period was counted. Death or VAD implantation was counted as cardiac death.

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. Logistic regression analyses were performed to identify the predictors of responsiveness to ASV therapy among the baseline variables. Receiver operating characteristic (ROC) analyses were performed to assess the cutoff level of each predictor. Clinical outcomes were compared with baseline variables using the paired t-test. Changes in the distribution of NYHA classes were compared using Wilcoxon’s signed rank sum test. Kaplan–Meier analyses were performed to compare readmission-free survival and cardiac death-free survival between the short and long HF duration groups. All statistical analyses were performed using SPSS Statistics 22 (SPSS Inc, Chicago, IL, USA).

RESULTS

Baseline characteristics (Table I): All 47 patients (36 male, 56 ± 17 years old) received ASV therapy (275 ± 252 days, 54-730 days), which was performed > 4 hours/day during nighttime or daytime. All patients were assigned to NYHA class III (12 [26%]) or IV (35 [74%]), and 18 (38%) were dependent on inotrope infusion.

Predictor of responsiveness to ASV therapy: Twelve patients (26%) achieved the endpoint, ie, improvement of LVEF ≥ 5%. Logistic regression analyses demonstrated that shorter HF duration was the only significant predictor of responsiveness to ASV therapy among all baseline variables (Table II, P = 0.033, odds ratio 0.945). ROC analysis showed the cutoff value of HF duration was 17.2 × 10^2 days (area under curve, 0.714, sensitivity, 0.657, and specificity, 0.750). Differences in the baseline characteristics were comparable between the short HF group (< 17.2 × 10^2 days) and the long HF group (≥ 17.2 × 10^2 days) (Table III).

Clinical courses: Differences in the clinical outcomes during the 6-month study period were compared between the short HF group and the long HF group (Figure 1). Heart rate, LV diastolic diameter, serum creatinine, and plasma B-type natriuretic peptide (P-BNP) in the short HF group became significantly lower compared with the long HF group (Figure 1A, B, D, F; P < 0.05 for all comparisons). Serum total bilirubin levels were comparable between both groups (Figure 1E). LVEF became significantly greater in the short HF group compared with the long HF group (Figure 1C; P < 0.05). NYHA class improved in the short HF group (Figure 2A; P < 0.05) but remained unchanged in the long HF group (Figure 2B). Doses of β-blocker (8.4 ± 7.1 versus 7.6 ± 6.7 mg/day, P = 0.710) and ACEI (2.0 ± 1.5 versus 1.9 ± 1.4 mg/day, P = 0.639) at 6 months were comparable between the two groups. Among 40 patients (85%) who could be discharged,
those with short HF duration had higher readmission-free survival compared with the long HF duration group during the 2-year study period (Figure 3A, P < 0.05). Eight patients died and 5 patients received VAD implantation during the 2-year study period. Cardiac death-free survival rates were comparable between the two groups (Figure 3B). There were no significant differences in the 2-year cardiac death-free survival rate between the responders and non-responders (64% versus 71%, P = 0.748).

**DISCUSSION**

This study showed that a shorter HF duration (< 17.2 × 10^5 days) was a significant predictor of responsiveness to ASV therapy, ie, achievement of an increase in LVEF ≥ 5% during 6-month ASV therapy, among patients with advanced HF with NYHA class III/IV. Patients with a shorter HF duration enjoyed better clinical outcomes compared with the longer HF duration group during the 6-month study period, and higher readmission-free survival compared with the longer HF duration group during the 2-year study period.

**Definition of responsiveness to ASV therapy:** Previous studies demonstrated that short- or mid-term (~6 months) ASV therapy improved clinical outcomes in patients with mild to moderate HF, ie, NYHA class II-III.5-13 We recently reported that ASV therapy improved the clinical course compared with the discontinued group in patients with advanced HF. However, there are few reports discussing the responsiveness to ASV therapy. In this study, 26% were responders, whose LVEF improved > 5% at 6 months. This relatively lower rate of responders may be because the population in this study was too sick. The prevalence of responders may increase when ASV therapy is indicated in less sick patients, as discussed below.

The definition of responsiveness to ASV therapy varies, ie, clinical criteria including re-hospitalization for HF, NYHA class, 6-minute walk distance, quality of life assessed by questionnaires, and mortality; biological variables such as P-BNP; and imaging criteria including LVDd and LVEF. Here the improvement of LVEF as the endpoint, because these imaging criteria may directly represent ASV-induced reverse remodeling.30 As previously discussed, LV reverse remodeling results from various favorable effects induced by ASV: decreased preload due to reduced venous return and reduced afterload due to relaxation of respiratory muscle and repressed sympathetic nerve activity.21 We assessed the endpoint at 6 months according to the previous studies.5,9,12,15

**Shorter HF duration and responsiveness to ASV therapy:**
Among baseline variables, shorter HF duration was the only significant predictor of responsiveness to ASV therapy in patients with advanced HF. Patients with shorter HF duration enjoyed LV reverse remodeling due to amelioration of congestion and suppression of sympathetic nerve activity by ASV therapy. Improved cardiac function reduces HF symptoms and ameliorates end-organ function. These favorable effects remain and avoid the worsening of congestive HF as well as re-admission due to cardiovascular events.

However, we could not show here an improvement in cardiac death-free survival in the responders over the non-responders. We previously demonstrated higher cardiac death-free survival during ASV therapy compared with the control group. Continuous ASV therapy improves survival in patients with advanced HF irrespective of responsiveness to ASV therapy, and may ameliorate patient quality of life, especially in the responders to ASV therapy.

Although there were no significant differences in background variables irrespective of HF duration (Table III), patients with shorter HF duration may have more preserved “cardiac reserve”, and have a potential to respond to ASV therapy. We consistently showed in a previous study that a preoperative
shorter HF duration was associated with LV reverse remodeling during VAD treatment. Early initiation of ASV therapy (within several years considering our cutoff value) would be recommended to achieve LV reverse remodeling along with favorable clinical outcomes in patients with advanced HF.

A recently published multi-center randomized controlled study could not show a better clinical course in ASV therapy compared with the control group receiving conventional medical treatment among a mild-moderate HF population with NYHA class II/III. Clinical courses improved in both groups during the study period, most likely due to enhancement of GDMT. GDMT should be recommended prior to ASV therapy in patients with mild HF, and we do not at all recommend initiation of ASV therapy in less sick patients not receiving GDMT. In patients with advanced HF, early ASV therapy within several years is encouraged so as not to lose the optimal timing considering our results.

Although we could not demonstrate direct evidence of cardiac reserve in this study, several examinations have been proposed for the estimation of cardiac reserve before VAD therapy: fibrosis of myocardium, iodine-123 metaiodobenzylguanidine imaging, and cardiopulmonary exercise testing. Such modalities may improve the predictability of responsiveness to ASV therapy.

**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) Hemodynamic study was not performed routinely before ASV initiation. Yamada, et al showed higher pulmonary capillary wedge pressure was associated with better responsiveness to ASV therapy, probably due to effective reduction of preload. Such parameters may be useful to predict responsiveness to ASV therapy. However, patients who are too sick with elevated pulmonary capillary wedge pressure during long HF duration may not respond to ASV therapy because of irreversibly remodeled LV with a low cardiac reserve. 3) The indication of ASV treatment was worsening HF despite GDMT, which was decided by the attending physician. Therefore, inclusion bias may have existed in this study. Also, our results may not simply be extrapolated to a less sick population. 4) We demonstrated the improvement of clinical variables at 6 months after ASV initiation. Longer-term changes in the clinical data are a future concern. 5) We excluded patients intolerant to continuous ASV therapy in this study. Although the precise reason for such intolerance to ASV therapy remains uncertain, such a population would also be called “non-responders” in a broad sense of the meaning. 6) Overall, 5 patients received VAD implantation during the study period. The indication of VAD implantation was decided upon taking into consideration our institutional criteria, and there would be a selection bias. However, our institutional criteria were strict and established. Patients receiving VAD implantation would not be able to survive for several months without the devices. Therefore, the bias would not weaken our conclusion.

**Conclusion:** Among patients with advanced HF receiving GDMT, a short HF duration was associated with responsiveness to ASV therapy and better subsequent clinical courses.

**DISCLOSURES**

None.

**REFERENCES**


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