What is the Optimal Strategy for Adaptive Servo-Ventilation Therapy?

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Summary
Clinical advantages in the adaptive servo-ventilation (ASV) therapy have been reported in selected heart failure patients with/without sleep-disorder breathing, whereas multicenter randomized control trials could not demonstrate such advantages. Considering this discrepancy, optimal patient selection and device setting may be a key for the successful ASV therapy. Hemodynamic and echocardiographic parameters indicating pulmonary congestion such as elevated pulmonary capillary wedge pressure were reported as predictors of good response to ASV therapy. Recently, parameters indicating right ventricular dysfunction also have been reported as good predictors. Optimal device setting with appropriate pressure setting during appropriate time may also be a key. Large-scale prospective trial with optimal patient selection and optimal device setting is warranted.

Key words: PEEP, Heart failure, Ventilation, Congestion

Various pharmacological therapies have developed to treat patients with heart failure (HF), whereas many patients are still struggling with refractory HF. Mechanical circulatory supports such as ventricular assist device have also been developed to overcome advanced HF. However, these therapies are invasive, expensive, painful, and uncomfortable. Furthermore, many patients cannot satisfy the strict indication of mechanical circulatory support therapies.

Recently, noninvasive positive pressure ventilation therapies have been focused on. These therapies are less invasive, less expensive, and comfortable. Of them, adaptive servo-ventilation (ASV) therapy offers superior tolerability regarding the provision of support pressure. The positive pressure is synchronized with the respiratory pattern of each patient through its unique algorithm as if an ocean wave. This treatment was originally developed to treat sleep-disordered breathing (SDB) but is recently used for HF patients irrespective of the existence of SDB in many cases.

However, recent large-scale, multi-center, randomized control trials could not show obvious clinical advantages in the ASV therapy over the medical therapy. Considering this discrepancy in the results between single-center and multi-centers trials, optimal patient selection and/or optimal device setting may be a key for the successful ASV therapy. In this review article, we will overview the efficacy of ASV therapy following discussion about optimal patient selection and device setting.

Efficacy of ASV Therapy Shown in a Single-Center

ASV was originally used only to treat SDB, but it is currently used for the patients with acute decompensated HF or chronic HF at moderate-to-severe grade irrespective of the existence of SDB. In the retrospective multi-center observational study (SAVIOR-R), 60% of patients received ASV therapy not to treat SDB.Various clinical effects have been reported including a meta-analysis. ASV reduces both preload and afterload, which results in a decrease in systemic vascular resistance and increase in cardiac output (CO). These acute effects are observed during 10-30 minute ASV support.

Various clinical effects have been reported including a meta-analysis. ASV reduces both preload and afterload, which results in a decrease in systemic vascular resistance and increase in cardiac output (CO). These acute effects are observed during 10-30 minute ASV support. Such effect reduces volume and pressure loads in the left ventricular (LV) cavity, which facilitates LV reverse remodeling, accompanied by decrease in plasma level of B-type natriuretic peptide (BNP) and E/e', recovery of the degree of mitral regurgitation, improvement in LV ejection fraction (LVEF), and reduction in LV volume after several months of ASV support.

Not only the hemodynamic stabilization but also the stabilization of respiratory pattern results in the suppression of sympathetic nerve activity. Harada, et al. showed that ASV therapy reduced muscle sympathetic nerve activity by slowing respiratory rate and stabilizing respiratory pattern. Sympathetic nerve activity during ASV therapy is also assessed by urinary catecholamine, heart rate variability, plasma catecholamine, or meta-iodobenzylguanidine scintigraphy.

As a result, ASV therapy shortened the length of
hospitalization and reduced intubation rate in patients with acute decompensated HF. In patients with chronic HF, HF recurrence, cardiovascular events, or cardiac death were reduced, and patient quality of life was improved during long-term ASV therapy. Improvement of peripheral circulation normalizes end-organ function. Stabilization of sympathetic nerve dysfunction results in the reduction of ventricular arrhythmias or atrial fibrillation.

**Large-Scale Multi-Center Trial**

Clinical advantage in the ASV therapy has not been proven obviously in large-scale, multi-center trials. In the SERVE-HF trial, ASV therapy did not have an advantage in the primary composite endpoint (death from any cause, lifesaving cardiovascular intervention, and hospitalization due to worsening HF) and rather increased mortality compared with the medication group in HF patients with reduced LVEF and predominantly central sleep apnea.

In hospitalized patients with moderate-to-severe sleep apnea, ASV therapy did not improve 6-month cardiovascular outcomes compared with the medical therapy (CAT-HF trial). However, the Japanese multi-center, randomized control trial, included 60% of patients with NYHA II, and the HF duration was less than 1 year in 60% of patients.8 The central sleep apnea may not be good target for the ASV therapy, whereas the ongoing ADVENT-HF trial is investigating the efficacy of ASV therapy for patients with obstructive sleep apnea.

**Stage of HF:** The SAVIOR-R, the Japanese randomized control trial, included 60% of patients with NYHA II, and the HF duration was less than 1 year in 60% of patients.34) ASV therapy had no statistical advantage in the clinical outcome over the optimal medical therapy. The ASV therapy may not necessarily have a therapeutic priority over the optimal medical therapy, particularly in less sick HF patients.

In contrast, 6-month ASV therapy improved LV reverse remodeling in patients with relatively shorter HF duration (<5 years) compared with the longer HF duration group (>5 years).35) In chronic HF patients, ASV therapy may better be considered before the LV remodeling becomes completely irreversible.

**LV parameters:** Elevated pulmonary capillary wedge pressure (PCWP) and advanced degree of mitral regurgitation were associated with an increase in CO during ASV therapy.36) Similar result was originally reported by Bradley, et al., who showed improvement in CO during continuous positive airway pressure support in patients with PCWP > 12 mmHg at baseline. Another investigator showed that E/e’ was associated with an increase in CO during ASV support. Considering that these parameters indicate the existence of pulmonary congestion, we should realize again that the main target of ASV therapy is "pulmonary congestion," and we should certify the existence of pulmonary congestion, i.e., a therapeutic target, before ASV therapy (Figure 1).

Another important parameter is LVEF. Considering the adverse results of SERVE-HF trial, we should at least pay special attention to the ASV therapy in patients with LVEF < 45% (inclusion criteria of the trial). The ASV therapy improved cardiovascular outcomes only in HF patients with preserved LVEF in the CAT-HF trial. HF patients with preserved LVEF also achieved improvement of

**Optimal Patient Selection**

There are some predictive parameters that have a deep association with the efficacy of ASV therapy. We discuss each parameter as follows:

**Existence and treatment of SDB:** ASV therapy has originally been used to treat SDB, and many studies have been performed in patients with HF and SDB. However, ASV is recently used not necessarily to treat SDB but rather to ameliorate hemodynamics in many cases. Consistently, Koyama, et al. showed that the degree of SDB had no impact on the efficacy of ASV therapy.

In the SERVE-HF trial, relatively higher pressure was used to completely suppress central sleep apnea-dominated SDB. Central sleep apnea may have a compensatory role in patients with advanced HF. Central sleep apnea may improve oxygenation, activate parasympathetic nerve activity through the expansion of lung, let the respiratory muscle take a rest and recover, and increase CO via internal positive end-expiratory pressure. Therefore, it may be rather harmful to aggressively treat central sleep apnea as performed in the SERVE-HF trial. The central sleep apnea may not be good target for the ASV therapy, whereas the ongoing ADVENT-HF trial is investigating the efficacy of ASV therapy for patients with obstructive sleep apnea.

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symptoms, cardiac diastolic function, and arterial stiffness during ASV therapy compared with the medical group in the other study.

In contrast, Takama, et al. showed that the 6-month ASV therapy improved LVEF and BNP level in HF patients with LVEF < 30% as well as in those with LVEF 30%-50%. We reported higher cardiac death-free survival rate during 2-year ASV therapy over the medical therapy, although they had 33% of LVEF on average (Figure 2). Furthermore, the ASV therapy was administered more smoothly in patients with lower LVEF compared with those with higher LVEF among those with reduced LVEF population in another study. Considering these results, reduced LVEF may not simply be a contraindicator of ASV therapy.

When we consider the ASV therapy in patients with reduced LVEF, we should better confirm some clues indicating pulmonary congestion beforehand. In other words, it is not suggested to consider the ASV therapy in patients with reduced LVEF without pulmonary congestion. Among them, particularly those with SDB may experience worse clinical outcomes during ASV therapy, considering the results of SERVE-HF (see marked area in Figure 1).

**Right ventricular parameters:** Recently, not only LV but also right ventricular (RV) parameter has been focused on as predictors of the successful ASV therapy probably because of a deep association of both ventricles via interventricular septum. The lower tricuspid annular plane systolic excursion and enlarged RV cavity were reported as predictors of improvement in CO during ASV support. The authors speculated the mechanism as follows: the recovery of RV dysfunction during ASV support also improves LV diastolic dysfunction and increases CO via a geometric shift in the interventricular septum.

We recently reported that a significant reduction in RV end-diastolic pressure (RVEDP) from the elevated RVEDP level during the procedure was a key for the improvement of CO during the ASV support. Because the transmural LV end-diastolic pressure (LVEDP) is calculated by subtracting RVEDP from the intracavity LVEDP, we cannot ignore the impact of RVEDP when LVEDP is elevated (Figure 3A, B). Considering this formula, transmural LVEDP will increase when RVEDP decreases during ASV support as a reduction of preload. Increased transmural LVEDP will result in the improvement of CO (Figure 4A). In other words, we can discuss the efficacy of ASV simply on the ascending limb of Frank-Starling’s law, instead of the descending limb (Figure 4B).

In this paper, baseline high intracavity LVEDP was also a significant predictor of ASV response, although its impact was statistically lower than baseline RVEDP. In other words, the elevation of RVEDP secondary to the elevation of intracavity LVEDP is a good marker of the responder. Patients with pure RV dysfunction may not be good candidates for the ASV therapy.

These predictors eventually indicate the existence of pulmonary congestion, one of the main targets of ASV therapy. We should try to confirm the existence of pulmonary congestion beforehand. Otherwise, the ASV therapy would not be effective or rather be harmful. The prospective randomized control study is warranted only in the responders to ASV therapy who satisfy these predictors.

**Optimal Device Setting**

Optimal device setting would also be important for the successful ASV therapy. Currently, the device setting may vary widely among each institution. However, there is a scarcity of papers studying the relationship between the ASV procedure and clinical outcomes.

Koyama, et al. showed that LVEF, BNP level, and LV volume improved significantly in patients who had re-

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**Figure 2.** Comparison of survival (A) and cardiac death-free survival (B) between the ASV continued group and the ASV discontinued group during the 2-year study period.
received ASV therapy ≥ 1 hour compared with those with ASV therapy < 1 hour. The frequency of ASV use was a strong predictor for the improvement of LVEF during 6-month ASV therapy. The compliance for ASV therapy may be a key for the successful ASV therapy.

In the SERVE-HF trial, patients received ASV therapy at a relatively high-pressure setting to treat central sleep apnea. This may be one of the major reasons why the ASV group had higher mortality than the medical group. The pressure setting might have been inappropriately higher than the pressure sufficient to treat pulmonary congestion, and CO might have rather decreased during ASV therapy.

Each patient may have an optimal pressure setting that is suitable to treat his/her pulmonary congestion. We recently reported a case in which the optimal pressure setting was soaked considering hemodynamics and heart rate variability during a pressure ramp test (Figure 5). In this case, the patients with congestive HF received ASV support at each positive end-expiratory pressure (PEEP) setting (from 4 cmH2O to 8 cmH2O), during which hemodynamics, heart rate variability, and blood noradrenaline level were monitored. PCWP decreased at incremental PEEP, and CO was at the highest level at PEEP 5 cmH2O and decreased at over 5 cmH2O of PEEP. Sympathetic nerve activity, which was estimated by the low-frequency/high-frequency level of heart rate variability test and plasma noradrenaline level, was activated at incremental PEEP mainly because of a decrease in CO. Inappropriately high PEEP setting rather increases RVEDP particularly when baseline RVEDP is low, which leads to increase in transmural LVEDP and decrease in CO.

The optimal pressure setting with the highest CO, the lowest PCWP, and the most suppressed sympathetic nerve activity may result in better clinical outcomes, although it should be demonstrated by large-scale prospective trial.

Furthermore, such assessments may better be repeated during the ASV therapy. The degree of pulmonary congestion may change during long-term ASV therapy, and the device setting should also be adjusted. Recently, pulmonary artery sensors and transmitted daily pulmonary artery pressure readings from home (CardioMEMS, Inc., Atlanta, GA) have become widely used to adjust medical therapies in outpatients with HF. Noninvasive technologies such as remote dielectric sensing are also used recently to quantify lung fluid content including PCWP level. These devices may have an advantage to monitor patient pulmonary congestion status considering their non-
invasiveness. When the ASV support does not bring any favorable effect at any setting, ASV therapy should be terminated.

**Conclusion**

The optimal patient selection and optimal device setting are keys for the successful ASV therapy in HF patients with/without SDB. We should perform the ASV therapy only for the responders satisfying predictors of good response to ASV therapy at appropriate device setting. A large-scale, multi-center prospective study considering such strategy is warranted.

**Disclosures**

**Conflicts of interest:** T.I. has a potential conflict of interest with Teijin Pharma Co. including consulting fees.

**References**


