Association Between Adaptive Servo-Ventilation Therapy and Renal Function

Teruhiko Imamura, MD, Masakazu Hori, MD, Nikhil Narang, MD and Koichiro Kinugawa, MD

Summary
Cardio-renal syndrome is a challenging clinical entity to manage, and is often associated with increased morbidity and mortality. We hypothesized that adaptive servo-ventilation (ASV), non-invasive positive pressure ventilation that ameliorates systemic/pulmonary congestion, may improve renal function in patients with symptomatic heart failure complicated by the cardio-renal syndrome. Patients with symptomatic congestive heart failure who underwent ASV therapy for over 1 month were included in this retrospective study. The trajectory of the estimated glomerular filtration ratio (eGFR) between the pre-1 month period and the post-one-month period (on ASV) were compared. A total of 81 patients (median 65 years old, 65 men) were included. eGFR decreased during the pre-1 month period from 52.7 (41.7, 64.6) down to 49.9 (37.3, 63.5) mL/minute/1.73 m² ($P < 0.001$) whereas we observed an increase following one-month of ASV therapy up to 53.4 (38.6, 68.6) mL/minute/1.73 m² ($P = 0.022$). A reduction in furosemide equivalent dose following the initiation of ASV therapy was independently associated with increases in eGFR with an adjusted odds ratio of 13.72 (95% confidence interval 3.40-55.3, $P < 0.001$). In conclusion, short-term ASV therapy was associated with the preservation of renal function, particularly when the dose of loop diuretics was concomitantly reduced.

Key words: Non-invasive positive pressure support, Hemodynamics, Heart failure

Adaptive servo-ventilation (ASV; AutoSet-CS; ResMed, Sydney, Australia) is non-invasive positive pressure ventilation that can stabilize respiratory mechanics, downregulates detrimental sympathetic nervous system upregulation, and ameliorates pulmonary and systemic congestion via decreasing preload and afterload in selected patients with congestive heart failure, irrespective of the presence of sleep-disordered breathing.1)

The presence of chronic kidney disease (CKD) is an established independent risk factor of mortality in patients with heart failure.2) The existence of heart failure vice versa may lead to an additional long-term decrement in renal function, making it more difficult to introduce risk-modifying medical therapies. ASV might have renoprotective effects by increasing renal blood flow while reducing renal congestion, in addition to allowing for a reduction of loop diuretic dosing.3) In this study, we investigated the change in renal function before and after the initiation of ASV therapy in patients with congestive chronic heart failure.

Methods
Patient selection: Patients with congestive heart failure who continued ASV therapy for over one month at our institute between April 2008 and September 2020 were retrospectively included in this analysis. The indication of ASV therapy was at the discretion of the attending heart failure physicians. In brief, chronic heart failure patients with symptomatic systemic and/or pulmonary congestion, which was assessed by multimodities including physical examination, chest X-rays, and transthoracic echocardiography, refractory to guideline-directed medical therapy, were considered to receive ASV therapy.4) Patients who did not tolerate ASV therapy were excluded. Those dependent on hemodiafiltration for end-stage renal disease were excluded. Written informed consent was obtained from the participants. The Ethics Committee of our institute approved the study.

ASV therapy: We utilized an advanced bi-level positive airway pressure unit, ASV, together with a fitted full-face mask.5) The device analyzes the breathing pattern automatically and provides pressure support, which is synchronized with breathing via logic algorithms. It was set to deliver 5-cmH2O positive end-expiratory pressure and suitable minimum-maximum inspiratory support, which was within the manufacturer’s minimum setting range of 3-10 cmH2O. The expiratory positive airway pressure was adjusted between 1-5 cmH2O considering the patient’s comfortableness. ASV therapy was performed for over 4 hours per night. ASV therapy was terminated when the patient’s congestion was ameliorated.
Clinical data: Baseline data were retrieved from retrospective chart review. In the transthoracic echocardiography, left ventricular end-diastolic diameter was measured via the long-axis view; right ventricular end-diastolic diameter was measured via the right ventricle-focused 4-chamber view. Medications and estimated glomerular filtration ratio (eGFR) were obtained before the initiation of ASV therapy, at the time of ASV therapy initiation (baseline), and at one month following the initiation of ASV therapy (on ASV). The primary endpoint was a trajectory of the dose of loop diuretics (pre-1 month and post-1 month). The secondary endpoint was a trajectory of eGFR during the study period. A dose of loop diuretics was expressed as furosemide equivalent dose. Similarly, doses of angiotensin-converting enzyme II inhibitor and mineralocorticoid receptor antagonist were expressed as enalapril equivalent and spironolactone equivalent doses, respectively.

Statistical analyses: Continuous variables are expressed as the median and interquartile. Categorical variables are expressed as numbers and percentages. Trend analyses for continuous variables at multiple timings were performed using Friedman tests and ad-hoc Wilcoxon signed-rank test for two-group comparison. Logistic regression analyses were performed to investigate variables associating with any increases in eGFR following the initiation of ASV. Variables with \( P < 0.20 \) in the univariate analyses were included in the multivariate analyses. Correlation between changes in furosemide dose and eGFR following the initiation of ASV therapy was assessed by Pearson’s correlation coefficient. All statistical analyses were performed using the SPSS 22. All statistical outcomes with \( P < 0.05 \) were considered significant.

Results

Baseline characteristics: Among 105 patients who initiated ASV therapy, 20 patients did not continue ASV therapy due to the following reasons: 9 hospital transfers, 4 hospitalizations, 6 treatment completions, and 1 death. Four patients dependent on hemodialysis were excluded. The actual study cohort consisted of 81 patients. Median age was 65 (56, 76) years old and 80.2% (n = 65) were men. Median left ventricular end-diastolic diameter was 63 (55, 76) mm and left ventricular ejection fraction was 32% (22%, 45%). All patients had symptomatic systemic/pulmonary congestion refractory to guideline-directed medical therapy at baseline. All patients continued effective ASV therapy for over one month without any device-related complications (Table I).

Trajectory of clinical parameters: For the primary endpoint, eGFR decreased significantly from 52.7 (41.7, 64.6) mL/minute/1.73 m² down to 49.9 (37.3, 63.5) mL/minute/1.73 m² for the 1 month prior to ASV therapy (\( P < 0.001 \); Figure 1A). Following the initiation of ASV therapy, eGFR increased up to 53.4 (38.6, 68.6) mL/minute/1.73 m² one month later (\( P = 0.022 \)). A median change in eGFR during the pre-1 month was -3.6 (-8.6, 0.0) versus 2.5 (-0.8, 7.0) mL/minute/1.73 m² during the post-1 month on ASV (\( P < 0.001 \); Figure 1B). A similar trend was observed in a sub-group analysis with eGFR < 60 mL/minute/1.73 m² at 1 month prior to baseline (Supplemental Figure).

### Table I. Baseline Characteristics

| Variable                                      | Value                      |
|-----------------------------------------------|----------------------------|
| Demographics                                  |                            |
| Age, years                                    | 65 (56, 76)                |
| Men                                           | 65 (80%)                   |
| Body mass index                               | 22.9 (20.1, 27.1)          |
| Comorbidity                                   |                            |
| Atrial fibrillation                           | 37 (46%)                   |
| Diabetes mellitus                             | 29 (36%)                   |
| Ischemic heart disease                        | 27 (33%)                   |
| Chronic obstructive pulmonary disease         | 16 (20%)                   |
| Echocardiography                              |                            |
| Left ventricular end-diastolic diameter, mm   | 63 (55, 76)                |
| Left ventricular ejection fraction, %         | 32 (22, 45)                |
| Moderate or greater mitral regurgitation      | 27 (33%)                   |
| Moderate or greater tricuspid regurgitation   | 18 (22%)                   |
| Right ventricular end-diastolic diameter (basal), mm | 41 (36, 45)            |
| Right ventricular/left ventricular diameter ratio | 0.68 (0.54, 0.76)        |
| Maximum inferior vena cava diameter, mm       | 19 (14, 24)                |
| Medication                                    |                            |
| Furosemide, mg/day                            | 30 (20, 40)                |
| Enalapril, mg/day                             | 2.5 (1.25, 3.75)           |
| Spironolactone, mg/day                        | 25 (0, 25)                 |
| Tolvaptan, mg/DL                              | 0 (0, 0)                   |
| eGFR, mL/minute/1.73 m²                       | 49.9 (37.3, 63.5)          |

eGFR indicates estimated glomerular filtration ratio. Continuous variables are expressed as the median and interquartile and categorical variables as numbers and percentage.
Advance Publication 3

RENO-PROTECTIVE EFFECT OF ASV THERAPY

Figure 1. Trajectory of eGFR at pre-1 month, baseline, and post-1 month (on ASV) (A) and changes in eGFR during pre-1 month and post-1 month (on ASV) (B). *P < 0.05 by Wilcoxon signed-rank test.

Figure 2. Trajectory of equivalent doses of furosemide (A), enalapril (B), and spironolactone (C) at pre-1 month, baseline, and post-1 month (on ASV). *P < 0.05 by Wilcoxon signed-rank test.

For the secondary endpoint, the trajectory in diuretic dose is summarized in Figure 2. A furosemide equivalent dose remained unchanged during the pre-1 month (P = 0.070) and decreased following the initiation of ASV (P = 0.009; Figure 2A). Of note, the dose of furosemide decreased in 30 patients due to incremental urine output following the initiation of ASV therapy. Equivalent doses of enalapril and spironolactone remained unchanged during the observational period irrespective of the add-on ASV therapy (P = 0.45 and P = 0.54, respectively; Figure 2B, C). The dose of tolvaptan also remained unchanged (0 [0, 0] mg, 0 [0, 0] mg, and 0 [0, 3.75] mg; P = 0.22).

Factors associating with preservation of renal function during ASV therapy: In the univariate and multivariate analyses, a reduction in furosemide dose following the initiation of ASV therapy was independently associated with an increase in eGFR with an adjusted odds ratio of 13.43 (95% confidence interval 3.59-50.3, P < 0.001; Table II). Patients who achieved a more significant decrease in furosemide dose following the initiation of ASV therapy had a greater observed improvement in eGFR (r = -0.366, P = 0.001, Figure 3).

Discussion

In this study, we observed a reno-protective effect of ASV therapy compared with the pre-treatment period in patients with congestive heart failure, irrespective of the presence of sleep-disordered breathing. An improvement in renal function was specifically associated with concomitant dose reduction in loop diuretics.

Reno-protective effect of ASV: There is little published data on the effects of ASV therapy in renal function. In a previous study, eGFR improved following one-day ASV therapy in 50 patients with heart failure and sleep-disordered breathing.3) Another study observed an improvement in renal function following one-year ASV therapy in 43 patients with heart failure and sleep-disordered breathing.9) Given the recent results of the SERVE-HF trial that demonstrated a negative impact of ASV therapy when performed at higher pressure settings to treat a concomitant sleep disorder,6) recommendations have been made to adjust the device pressure as low as possible which may have less of a benefit in the sleep-disordered breather but a greater impact on congestion status.13)

Several mechanisms may explain the reno-protective effects of ASV therapy. Respiratory stabilization suppresses detrimental neurohormonal activation,7) reduces glomerular over-filtration,8) and ameliorates intermittent hypoxia,9) all of which are associated potential reno-protective effects of ASV.

ASV therapy may also impact intra-cardiac hemodynamics.10) ASV increases cardiac output via reduction in systemic vascular resistance, decrease in preload, and
Incremental greater improvement in renal function. Diuretics dose was associated with improvement in renal function. A greater dose reduction was associated with improvement in renal function. Further studies are warranted to validate the implications of ASV and concomitant diuretics dose reduction strategy on preserving renal function.

**Study limitations:** This is a single-center retrospective analysis of a moderate-sized cohort. Clinical management in routine patient care remained unchanged except for loop diuretics; uninvestigated factors which we could not account for may have affected clinical outcomes. Patients who did not complete one-month ASV therapy were excluded. The impact of changes in renal function on hard endpoints including mortality needs further assessment in larger-sized study cohorts. Not all patients experienced dose reduction in loop diuretics. Further studies are required to investigate who can achieve such an aggressive dose reduction in loop diuretics.

We cannot deny there is selection bias. Clinicians attempted their best to select appropriate patients for the ASV therapy. Consistently, many patients seem to have tolerated their best to select appropriate patients for the ASV therapy.
used conventional procedures including chest X-rays, echocardiography, and physical examination as well as patient symptomology to assess for evidence of systemic/pulmonary congestion. Alternative methods including a remote dielectric sensing system would be useful for optimal patient selection and device pressure adjustment to enjoy improvement in renal function.\textsuperscript{14}

### Conclusion

Short-term ASV therapy in patients with acute heart failure was associated with improvements in renal function, particularly when the dosage of the loop diuretics was decreased.

### Disclosure

**Conflicts of interest:** None.

### References

1. Momomura S, Seino Y, Kihara Y, \textit{et al.} Adaptive servo-ventilation therapy for patients with chronic heart failure in a confirmatory, multicenter, randomized, controlled study. Circ J 2015; 79: 981-90.
2. House AA, Wanner C, Sarnak MJ, \textit{et al.} Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2019; 95: 1304-17.
3. Yoshihisa A, Suzuki S, Owada T, \textit{et al.} Short-term use of adaptive servo ventilation improves renal function in heart failure patients with sleep-disordered breathing. Heart Vessels 2013; 28: 728-34.
4. Tsutsui H, Isobe M, Ito H, \textit{et al.} JCS 2017/JHFS 2017 Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure- Digest Version. Circ J 2019; 83: 2084-184.
5. Koyama T, Watanabe H, Terada S, \textit{et al.} Adaptive servo-ventilation improves renal function in patients with heart failure. Respir Med 2011; 105: 1946-53.
6. Cowie MR, Woehrle H, Wagscheider K, \textit{et al.} Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. N Engl J Med 2015; 373: 1095-105.
7. Amann K, Koch A, Hofstetter J, \textit{et al.} Glomerulosclerosis and progression: effect of subantihypertensive doses of alpha and beta blockers. Kidney Int 2001; 60: 1309-23.
8. Sklar AH, Chaudhary BA, Harp R. Nocturnal urinary protein excretion rates in patients with sleep apnea. Nephron 1989; 51: 35-8.
9. Zoccali C, Mallamaci F, Tripepi G. Nocturnal hypoxemia predicts incident cardiovascular complications in dialysis patients. J Am Soc Nephrol 2002; 13: 729-33.
10. Imamura T, Kinugawa K. Right Ventricular End-Diastolic Pressure Is a Key to the Changes in Cardiac Output During Adaptive Servo-Ventilation Support in Patients With Heart Failure. Int Heart J 2017; 58: 536-43.
11. Felker GM, O’Connor CM, Braunwald E; Heart Failure Clinical Research Network Investigators. Loop diuretics in acute decompensated heart failure: necessary? Evil? A necessary evil? Circ Heart Fail 2009; 2: 56-62.
12. Imamura T, Kinugawa K. Update of acute and long-term tolvaptan therapy. J Cardiol 2019; 73: 102-7.
13. Vardeny O, Claggett B, Kachadorian J, \textit{et al.} Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARADIGM-HF trial. Eur J Heart Fail 2019; 21: 337-41.
14. Imamura T. How to predict response to adaptive servo-ventilation therapy? Heart Vessels 2019; 34: 1895-6.

### Supplemental Files

Supplemental Figure

Please see supplemental files: https://doi.org/10.1536/ihj.21-202