Respiratory Resynchronization
– A Novel Therapeutic Strategy –
Shin-ichi Ando, MD, PhD

Noninvasive positive pressure ventilation (NPPV) has been successfully used for the emergency treatment of acute cardiogenic pulmonary edema,¹,² but it also has been widely applied for the treatment of patients with severe chronic heart failure (HF) with obstructive sleep apnea (OSA) and/or central sleep apnea with Cheyne-Stokes respiration (CSA-CSR) especially these past 20 years.³,⁴ The rationale for using NPPV in the treatment of HF patients with OSA is easily understood when we consider that both the moderate pressurization of congested lungs and opening of occluded airways by NPPV should be beneficial by ameliorating the symptoms of the patients and improving their prognosis. The mechanism of generating and maintaining CSA-CSR is more complex than OSA and the existence of CSA-CSR has been principally interpreted as a result of depressed cardiac function (Figure).⁵,⁶ If CSA-CSR is merely the result of congestion or low cardiac output, therapy targeting the removal of CSA-CSR itself has no meaning. However, as some researchers have pointed out, CSA-CSR further activates sympathetic nervous activity (SNA), even in the patients with HF in whom SNA is already highly stimulated, implying that CSA-CSR is a therapeutic target.⁷ Thus, whether to remove CSA-CSR itself is beneficial or not has been a matter of debate.

Figure. Pathophysiology of central sleep apnea in heart failure. HF leads to increased left ventricular (LV) filling pressure that activates lung vagal irritant receptors and results in hyperventilation and hypocapnia. Arousals cause further abrupt increases in ventilation and drive PaCO₂ below the threshold for ventilation, triggering a central apnea. Central sleep apneas are sustained by recurrent arousals resulting from apnea-induced hypoxia and the increased effort to breathe during the ventilatory phase. BP, blood pressure; HR, heart rate; SNA, sympathetic nervous activity. (Reproduced with permission from Mann DL.⁸)
Adaptive servonventilation (ASV) is a novel NPPV that has quickly spread as a powerful tool to treat HF patient. The resultant regular breathing is generally taken as a favorable sign and of effective suppression of the enhanced SNA. The difficulty, however, in giving a clear answer to whether suppressing CSA-CSR by ASV really has a therapeutic effect arises from the fact that ASV works to synchronize irregular respiration with inevitably some degree of end-expiratory pressure (EEP). To separate the effect of resynchronization and pressurization has been difficult in the clinical setting. Yoshida et al previously tried to clarify the effect of pressure support that NPPV, including ASV, delivers to synchronize respiration over EEP and found that PS increased cardiac output in most of the patients, though the averaged pressure was higher with NPPV treatment. This implies that respiratory assistance with pressure support may mechanically increase cardiac output or decrease peripheral arterial tonus through reduction of the SNA.

In this issue of the Journal, Ushijima et al try to unravel this problem by applying the same average pressure by continuous positive airway pressure (CPAP) and ASV while recording muscle SNA in 57 patients with HF with or without periodic breathing. They found that only ASV improved respiratory abnormality and decreased muscle SNA. Most importantly, only ASV exerted sympathoinhibitory effects only in the patients with periodic breathing. Whether CSA-CSR affects HF patients positively or negatively has not been determined yet. In the short term, CSA-CSR enhances cardiac output and this may result in better peripheral perfusion. Naughton insisted that although CSA-CSR can be detrimental in terms of intermittent hypoxemia, arousals and autonomic dysregulation, it is also associated with the beneficial effects of hyperventilation-related increases in end-expiratory lung volume, intrinsic positive airway pressure, assistance to stroke volume, avoidance of hypercapnic acidosis and finally the provision of periodic rest to fatigue-prone respiratory pump muscles. Ushijima et al clearly answer the question of which type of NPPV is more effective and which type of respiration of HF patients will be benefitted, resulting in attenuation of SNA. They showed that only patients with CSA-CSR would benefit from ASV, which resynchronizes desegreted respiration, and only ASV not CPAP was effective, though at the moment this new finding may be applicable only to awake patients. Because the pressure levels of the devices were almost identical in the experiment, the beneficial effects of ASV for pulmonary congestion must have almost been the same. Therefore, the fact that muscle SNA decreased in HF patients with periodic breathing after respiratory resynchronization suggests the sympatho-excitative effect of CSA-CSR. When we take all this new information together, CSA-CSR can be defined as a short-term compensatory mechanism against HF conditions to improve peripheral perfusion and pulmonary congestion at the expense of a negative effect of sympathetic excitation in the long run. ASV treatment, therefore, may be an analog of β-blocker therapy for severe HF patients with CSA-CSR.

At the moment, however, several issues are waiting for answers. First, will the difference in the sympatho-inhibitory effect of ASV and CPAP continue during 1 night’s sleep or more long term such as 1 year? If this beneficial effect accumulates during 1 night or over the long term, this therapy would definitely improve the prognosis of such HF patients. The result of Yoshihisa et al that 1 night of ASV suppressed sympathetic activity more may give a clue to the answer to this question. Second, how can the result of the CANPAP study in which half of the HF patients with CSA-CSR showed improvement of their respiration be explained in the light of this new finding by Ushijima et al? Again, there might be different sympatho-inhibitory effects between short- and long-term use of NPPV. Finally, does the existence of CSA-CSR mean increased severity of HF, even though none of the markers of HF severity showed correlation with the sympatho-inhibitory effect in Ushijima’s study? As the existence but not the severity of CSA-CSR is reportedly more related to prognosis, CSA-CSR may be a warning of a critical situation even without an increase in known markers. We have to pay more attention to the close mutual relation and interdependence between the heart and lungs and sincerely listen to the “Breath” and select the best therapeutic approach as shown in figure 3 of Ushijima’s study.

References
1. Momii H, Tashima Y, Kadokami T, Narita S, Yoshihisa M, Ando S. Experience of step-wise protocol using non-invasive positive pressure ventilation for treating cardiogenic pulmonary edema. *Eur J Emerg Med* 2012; 19: 267 – 270.
2. Vital FM, Saconato H, Ladeira MT, Sen A, Hawkes CA, Soares B, et al. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary edema. *Cochrane Database System Rev* 2008; 3: CD005351.
3. Kaneko Y, Floras JS, Usui K, Plante J, Tkacova R, Kubo T, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *N Engl J Med* 2003; 348: 1233 – 1241.
4. Yoshihisa A, Suzuki S, Miyata M, Yamaki T, Sugimoto K, Kunii H, et al. ‘A single night’ beneficial effects of adaptive servo-ventilation on cardiac overload, sympathetic nervous activity, and myocardial damage in patients with chronic heart failure and sleep-disordered breathing. *Circ J* 2012; 76: 2153 – 2158.
5. Mann DL. Management of heart failure patients with reduced ejection fraction. *In: Bonow RO, editor. Braunwald’s heart disease. 9th edn. Philadelphia: Elsevier Saunders;* 2012: 567.
6. Monomura S. Treatment of Cheyne-Stokes respiration-central sleep apnea in patients with heart failure. *J Cardiol* 2012; 59: 110 – 116.
7. Bradley TD, Floras JS. Sleep apnea and heart failure. Part II: Central sleep apnea. *Circulation* 2003; 107: 1822 – 1826.
8. Yoshihisa A, Suzuki S, Yamaki T, Sugimoto K, Kunii H, Nakazato K, et al. Impact of adaptive servo-ventilation on cardiovascular function and prognosis in heart failure patients with preserved left ventricular ejection fraction and sleep-disordered breathing. *Eur J Heart Fail* 2012; 15: 543 – 550.
9. Haruki N, Takeuchi M, Kaku K, Yoshitani H, Kuwaki H, Tamura M, et al. Comparison of acute and chronic impact of adaptive servo-ventilation on left chamber geometry and function in patients with chronic heart failure. *Eur J Heart Fail* 2011; 13: 1140 – 1146.
10. Yoshihisa M, Kadokami T, Momii H, Hayashi A, Ursashi T, Narita S, et al. Enhancement of cardiac performance by bilevel positive airway pressure ventilation in heart failure. *J Cardiol* 2012; 59: 912 – 918.
11. Ushijima R, Joho S, Akahane T, Oda Y, Inoue H. Differing effects of adaptive servonventilation and continuous positive airway pressure on muscle sympathetic nerve activity in patients with heart failure. *Circ J* 2014; 78: 1387 – 1395.
12. Yumino D, Kasai T, Kimmerly D, Amirthalingam V, Floras JS, Bradley TD. Differing effects of obstructive and central sleep apneas on stroke volume in patients with heart failure. *Am J Resp Crit Care Med* 2013; 187: 433 – 438.
13. Naughton MT. Cheyne-Stokes respiration: Friend or foe? *Thorax* 2012; 67: 357 – 360.
14. Bradley TD, Logan AG, Kimoff RJ, Series F, Morrison D, Ferguson K, et al. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med* 2005; 353: 2025 – 2033.
15. Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. *J Am Coll Cardiol* 2007; 49: 2028 – 2034.