Sympathetic nervous system, systolic heart failure, and central sleep apnea: Are we about to find the missing link?

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Sympathetic nervous system (SNS) activation has long been known to be a cardinal feature in the pathophysiology of cardiac remodeling and systolic heart failure (SHF). It was reported to have implications for both disease progression and survival. SNS activation is assumed to be secondary to the decrease of sympatho-inhibitory reflexes usually driven by the stimulation of afferent mechanoreceptors and by the increase of efferent sympatho-excitatory mechanisms associated with alteration in autonomic regulation.¹ Activation of cardiac and peripheral sympathetic nervous systems has been linked to the rate of disease progression and sudden death.² The main retrospective and prospective studies have shown that cardiac neuronal uptake based on Heart-Mediastinum Ratio (HMR) by ¹²³I-Metaiodobenzylguanidine (MIBG) imaging was a prognostic indicator of severe heart failure and/or ventricular arrhythmia if HMR was less than 1.6 in patients with a left ventricular ejection fraction less than 35%.^{3–5} These findings have been the rationale for the use of beta-adrenergic blocking agents in the management of patients with SHF.

Several observations have suggested that ventricular systolic dysfunction *per se* was not the principal

stimulus to sympathetic activation. If the decrease of sympatho-inhibitory reflexes is directly linked to the ventricular systolic dysfunction though the decrease of the cardiac output, mechanisms underlying the autonomic dysregulation seem more generalized. Among the parameters acting on nonbaroreflex-mediated sympatho-excitation, sleep-disordered breathing is one of the main actors.

SYSTOLIC HEART FAILURE AND CENTRAL SLEEP APNOEA

Sleep-disordered breathing is highly prevalent in patients with SHF: central sleep apnoea with Cheyne Stokes respiration (CSA-CSR) occurs in about a third of patients with SHF.⁶ CSA is characterized by repetitive suspension (apnea) or reduction (hypopnea) of breathing, causing intermittent oxygen desaturation. Interestingly, improving cardiac function through medications, devices or surgery relieves CSA-CSR.⁶ It is considered that CSA-CSR is a marker of greater heart failure severity and probably an independent risk factor for mortality.⁶ SNS activation likely contributes to this increased risk of adverse cardiovascular events.

CENTRAL SLEEP APNOEA AND SYMPATHETIC NERVOUS SYSTEM ACTIVATION

Central sleep apnea has deleterious effects including activation of different set of stimuli to the SNS.⁷ Hypoxia and hypercapnia induced by repetitive apnea and hypopnea interrupt the normal tonic inhibition of efferent sympathetic activity from pulmonary receptors, leading to an increase in sympathetic discharge.⁸ Higher rates of cardiac and total body norepinephrine spillover were reported in subjects with CSA than in heart failure

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patients without CSA.⁹ Ventricular remodeling, heart failure progression, and consequently sudden death are long-term consequences of sustained adrenergic activation.^{9,10}

DOES ADAPTIVE SERVO-VENTILATION AND SUBSEQUENT ELIMINATION OF CENTRAL SLEEP APNEA CAN BE BENEFICIAL IN PATIENTS WITH SYSTOLIC HEART FAILURE?

CSA have adverse cardiovascular effects that are reversed with adaptive servo-ventilation (ASV). ASV has been shown to improve cardiovascular function in CSA patients in small randomized clinical trials.⁶ But the benefit of ASV for the purpose of extending life is still controversial.¹¹ Recent multinational randomized, controlled trial has suggested that ASV increases all-cause and cardiovascular mortality in patients who had SHF.¹² This result opened an interesting discussion of whether CSA-CSR reflects worsening heart failure or it is an adverse risk factor for death in its own right.^{13,14}

DOES ELIMINATION OF CENTRAL SLEEP APNEA FORESTALL OR REVERSE SYMPATHETIC DISCHARGE?

Treatment of patients with heart failure and CSA with ASV attenuates the magnitude of SNS activation.¹⁵ However, it is important to consider that the alteration in autonomic regulation, which occurs early during the course of heart failure, is selective, rather than generalized.¹⁶ This complex pathophysiology, linking SNS activation, CSA, and SHF, leads to temporal, regional, and inter-individual heterogeneity of SNS activation.¹ Consequently, exploration of local cardiac sympathetic nerve activity is determinant point in the understanding of the effects of ASV on CSA and SHF.

In the current issue of the *Journal*, Toyama *et al.* evaluated the impact of ASV on cardiac sympathetic nerve activity assessed by ¹²³I-MIBG imaging and functional capacity in patients with SHF. They prospectively randomized 31 consecutive patients with both SHF and CSR-CSA between groups with or without ASV for 6 months in addition to guideline-based medical management for heart failure. The authors show that ASV decreases apnea-hypopnea index, which is accompanied by a decrease of the total defect score and the washout rate, and an increase in the heart-to-mediastinum activity ratio of the ¹²³I-MIBG images. Furthermore, the patients with ASV show a decrease of the total mismatch score between the ¹²³I-MIBG images and the ^{99m}Tc-MIBI images. These effects on cardiac sympathetic activity were accompanied by an improvement in functional parameters as showed by the increase in left ventricular

ejection fraction, and the decrease in NHYA functional class and the specific activity scale. In contrast, the patients without ASV showed no change in any of these parameters. This study demonstrates the beneficial effects of ASV therapy on cardiac sympathetic nerve activity, cardiac function, and functional capacity, as well as apnea-hypopnea index, over a period of 6 months. These results highlight the link between CSA reduction and reversion of cardiac sympathetic discharge. Only one study had previously assessed the impact of ASV on cardiac sympathetic activity by exploring the effects of ASV on cardiac norepinephrine spillover.¹⁷ The gain of ¹²³I-MIBG over circulating catecholamine dosage is to explore the mean effect of ASV on cardiac sympathetic activity and not only the acute effect, which is reflected by the half-life of the catecholamine. As mentioned previously, the autonomic dysregulation that accompanying SHF has temporal, regional, and inter-individual heterogeneity and requires long term rather than acute evaluation. With their study, Toyama *et al.* show that the benefit of ASV on cardiac sympathetic activity is sustained over the time. Finally, these results are going versus the compensatory theory, which suggest that CSA is a compensatory mechanism of SHF rather than comorbidity.

FUTURE DIRECTIONS

This evidence of the beneficial effects of ASV on cardiac sympathetic nerve activity and functional capacity in patients with both SHF and CSA, questions about the contradictory results of the SERVE-HF trial.¹² The benefit of ASV depends probably on the basal level of cardiac sympathetic activity. Univariate subgroup analyses from the SERVE-HF trial provide some points to consider: when baseline left ventricular ejection fraction was >30%, the data suggested that the cardiovascular safety signal for ASV might disappear.¹⁸ This analysis suggests that ASV therapy benefits only for the more severe patients. As ¹²³I-MIBG images are well correlated with left ventricular ejection fraction, we can suppose that, in the future, ¹²³I-MIBG could be use as a tool for the selection of patients with SHF who will benefit from ASV therapy. Further work investigating the place of ¹²³I-MIBG images for the selection and the monitoring of patients with SHF who will benefit from ASV therapy is needed.

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