What Determines the Hemodynamic Benefit of Positive Airway Pressure Therapy in Patients With Chronic Heart Failure?  
– A Revision of Unloading Therapy –  

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It has been more than 10 years since much of the medical community began to consider sleep-disordered breathing (SDB) as a target for the treatment of patients with chronic heart failure (CHF). However, the prognostic role of sleep support therapy has remained uncertain. Recently, Koyama et al reported that adaptive servo-ventilation (ASV) may improve the prognosis of patients with CHF, regardless of SDB severity, suggesting that the effectiveness of positive airway pressure (PAP) therapy is independent of the apnea-hypopnea index. Clinicians may be trapped by the frequently encountered dogma that abnormality must be normalized.

The unloading effect of PAP therapy decreases both preload and stroke volumes (SV) in patients with low pulmonary capillary wedge pressure (PCWP), based on the Frank-Starling law. In contrast, PAP therapy increases SV in a state of high PCWP in patients with either exacerbated or stable CHF. This intriguing phenomenon can be explained by diastolic ventricular interaction.

The compliance of one ventricle influences that of the other under conditions of high pericardial pressure. Lower body negative pressure decreases both right ventricular (RV) and left ventricular (LV) end-diastolic volumes, thereby decreasing SV in patients without CHF. In contrast, unloading the RV by lower body negative pressure in patients with severe CHF reduces the external constraint on LV filling, resulting in the paradoxical dilation of the LV with a rightward shift of the interventricular septum. Under these circumstances, the Frank-Starling law predicts an increase in SV or stroke work (SW).

An abrupt occlusion of the inferior vena cava immediately reduces the RV volume, coincident with an initial increase in the LV end-diastolic volume, despite a fall in LV end-diastolic pressure, in patients with severe CHF (Figure). This phenomenon, termed diastolic ventricular interaction, has been observed in approximately half of the patients with CHF and is related to the clinical observation that the descending limb of the Frank-Starling curve (SW-PCWP relationship) indeed exists in patients with severe CHF. PAP therapy decreases both RV and LV volumes in healthy volunteers. In contrast, bilevel PAP therapy increases LV end-diastolic volume and SV in patients with CHF. If PAP therapy relieves, even partially, the external constraint of LV filling, the LV filling pressure would decrease with the increase in LV end-diastolic volume, thereby effectively generating force. Thus, the notion that the positive inotropic effect of PAP therapy is dependent on LV filling pressure is reasonable.

Another target of PAP therapy is functional mitral regurgitation (MR). In this issue of the Journal, Yamada et al demonstrated that the severity of MR faithfully predicted responders to ASV therapy. However, their study did not show whether or not ASV reduced MR. Haruki et al reported that ASV treatment for 30 min increased cardiac output and decreased systemic vascular resistance, but did not change LV end-diastolic volume, left atrial volume, or the vena contracta of the MR jet. These observations suggest that a reduction in MR may not have contributed to the beneficial effect of ASV. However, Haruki et al did not quantitatively evaluate the regurgitant volume in MR. In contrast, Bellone et al demonstrated that both continuous PAP and bilevel PAP significantly decreased the area of functional MR in patients with exacerbated CHF. Functional MR depends not only on afterload, but also on the LV shape, as determined by LV compliance and LV loading. Thus, many factors appear to affect the relationship between PAP therapy and functional MR.

The third theory assumes that the hemodynamic benefit of PAP therapy is exerted by attenuation of sympathetic nerve activity. ASV, continuous PAP, and bilevel PAP increase cardiac output and decrease both systemic vascular resistance and heart rate, which can be explained by the sympathoinhibitory effect exerted through the baroreflex. If a diastolic ventricular interaction occurs, the paradoxical LV dilatation may activate the LV mechanoreceptor and reduce sympathetic outflow, leading to attenuation of vasoconstriction, or vasodilatation. In addition, the stabilized respiration resulting from PAP therapy would decrease sympathetic nerve activity. Furthermore, PAP therapy will reduce SDB-induced overactivity of the sympathetic nervous system. Thus, the neural modulation resulting from PAP therapy is an important pathway for the treatment of CHF.

So far, there has been little evidence of unloading therapy...

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using diuretics for treatment of CHF, but the facts do not mean the ineffectiveness of diuretics. Every clinician knows that diuretic can effectively unload the LV and is essential in the management of CHF. Compared with conventional drug-based unloading therapy, PAP therapy can unload the LV directly and quantitatively, but its indications and long-term effects remain unclear. The research into PAP therapy in patients without SDB has just started.

**References.**

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**Figure.** Example of the end-diastolic pressure-volume relationship during inferior vena cava occlusion in a patient with severe heart failure and significant external constraint. Numbered markers represent successive beats after inferior vena cava occlusion. Left ventricular end-diastolic volume (LVEDV) initially increases for several beats, despite a fall in LV end-diastolic pressure (LVEDP). After the external constraint has been removed, both LVEDV and LVEDP decrease along the end-diastolic pressure-volume relationship. (Reproduced from Bleasdale et al with permission.© (2004) Walters Kluwer Health.)