Continuous Positive Airway Pressure and Increased Ejection Fraction in Heart Failure and Obstructive Sleep Apnea

Is There a Metabolic Cost or Benefit?*

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Despite many advances in the treatment of heart failure (HF) over the past several decades, mortality remains high (1). Recent clinical trials of newer pharmacologic agents have reported only limited impact on the high residual mortality of optimally treated HF patients and underscore the need for additional novel treatment strategies (2). The coexistence of obstructive sleep apnea (OSA) and its adverse implications in HF patients are increasingly recognized and highlight an important therapeutic consideration (2). Treatment of OSA by continuous positive airway pressure (CPAP) has many salutary effects that may benefit cardiac function, including a reduction in nocturnal and daytime sympathetic nervous system activation and attenuation of hypoxic episodes (2). The prevalence of OSA and HF and their comorbidity are expected to increase with the progressive aging of the population and the obesity epidemic (3). It is therefore important to define whether and how treatment of OSA affects cardiac function in HF patients.

Recent data suggest that OSA is associated with left ventricular (LV) systolic dysfunction and may lead to progression of HF or refractoriness to therapy via several mechanisms, including: 1) extremes of negative intrathoracic pressure, leading to an increase in LV afterload and a decrease in LV preload; 2) hypoxia, which is cardiotoxic and may impair cardiac contractility; and 3) sympathetic activation producing intermittent surges in blood pressure (4), further increasing afterload and wall stress. Several small studies have demonstrated an improvement in LV ejection fraction with the use of CPAP in patients with OSA and LV systolic HF (5–7). Although the benefits of CPAP therapy are becoming apparent in HF patients, the precise mechanisms underlying this improvement in cardiac function are not well understood. Given the key role of mechano-energetic uncoupling in HF (8), a clinically relevant question is whether a metabolic cost is incurred for this improvement. This is especially important because there are no data addressing whether CPAP therapy of OSA in HF has any effect on mortality. Heart failure therapies that improve cardiac function at the expense of cardiac efficiency, such as inotropic agents, are associated with poorer outcomes (9). In contrast, HF therapies that improve cardiac function while preserving myocardial efficiency, such as beta-blockers and angiotensin-converting enzyme inhibitors, are associated with improved outcomes (10,11).

In this issue of the Journal, Yoshinaga et al. (12) examine the effects of short- and long-term (6-week) nocturnal CPAP therapy on myocardial energy expenditure assessed by C-11 acetate positron emission tomography (PET) and echocardiography in 7 patients with symptomatic moderate LV systolic dysfunction and concomitant OSA. The PET tracer C-11 acetate, a simple 2-carbon carboxylic acid, is taken up by the myocardium and rapidly converted to acetyl coenzyme A (13). Because of tight coupling of the tricarboxylic acid cycle and oxidative metabolism, myocardial turnover of C-11 acetate reflects overall flux in the tricarboxylic acid cycle and provides an estimate of myocardial oxidative metabolism. In this study, longer-term CPAP significantly increased LVEF and tended to decrease LV oxidative metabolism while maintaining stroke volume index (SVI), thereby significantly improving myocardial efficiency. These changes were evident even though blood pressure and heart rate were not reduced by CPAP. In the five HF patients without OSA and without CPAP therapy who served as controls, there were no significant changes in any of the measurements between baseline and follow-up.

Because LVEF is a predictor of survival (14), these data suggest the potential for improved outcome with this therapy in patients with concomitant HF and OSA. The additional longer-term energy-sparing effects of CPAP may also be favorable. In some aspects, the effects of CPAP may be analogous to the chronic effects of beta blockade in HF, which also improves cardiac function while maintaining favorable myocardial energetics (10,15). However, the effects of CPAP are achieved non-pharmacologically by reducing afterload and increasing preload, thereby lowering oxygen demand and increasing oxygen supply, and by attenuating sympathetic activation (2).

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Although CPAP therapy is a promising strategy for improving LV function, and perhaps even survival, in patients with co-existent HF and OSA, several limitations lessen our enthusiasm until more data are available. First, Yoshinaga et al. (12) noted only very modest changes with CPAP in a small group of 7 patients, all male, with coexistent HF and OSA. Second, the control population was a group of patients with HF but without OSA who were mostly not obese, had predominantly ischemic HF, and did not receive CPAP. In the CPAP-treated patients with co-existent HF and OSA, most patients were morbidly obese, and both ischemic and nonischemic HF etiologies were present. As the authors point out, the response of myocardial energetics to CPAP may differ depending on HF etiology. These factors underscore the need for larger randomized trials of patients with HF and OSA. Third, given the central role of PET C-11 acetate measurements in this study, factors that might affect the measurement of myocardial oxidative metabolism should be considered. The accuracy of exponential fitting of myocardial C-11 acetate may be affected by the rate of delivery of tracer to the heart during image acquisition (16). Slower initial tracer delivery to the mycardium and more tracer recirculation may result in slower clearance rates and lower estimates of myocardial oxidative metabolism. This effect is expected to be more pronounced with mono-exponential fitting, which was used in this study, as opposed to bi-exponential fitting (17). Nevertheless, the impact of this approach was likely small, given the moderate severity of the LV systolic dysfunction. Exponential fitting may also be affected by spillover from the blood or lungs (18). The latter may be significant owing to increased lung tracer activity in patients with symptomatic HF and may also lead to underestimation of myocardial oxidative metabolism. Changes in fluid status and pleural effusion between the baseline and follow-up PET scans would be associated with altered lung tracer activity, which could influence the results. Last, myocardial efficiency is derived from a combination of SVI, systolic blood pressure, heart rate, and myocardial oxidative metabolism. In this study, measurement of SVI was obtained by echocardiography, which may have limited acoustic windows in the treatment group, where body mass index averaged 36.5 kg/m², but less so in the control group, where body mass index averaged 30.3 kg/m². Another disadvantage of this dual-imaging approach is that differences in hemodynamic conditions between the 2 imaging sessions may affect the calculation of myocardial efficiency.

In any event, it is still unknown whether these improvements in cardiac function and efficiency will translate into improvements in cardiovascular outcomes. Functional benefits of CPAP, and improvements in surrogates of survival, such as ejection fraction, have been documented in several small series. Although the interesting observations reported by Yoshinaga et al. (12) provide further basis for expecting improved outcomes with CPAP therapy in HF patients with OSA, carefully designed large randomized trials are needed to clarify the true effects of CPAP therapy on survival in patients with HF and OSA.

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