A recent enhanced appreciation of sleep–cardiovascular interactions, particularly in patients with congestive heart failure (CHF), has prompted careful consideration of the relevance of sleep-disordered breathing to CHF pathophysiology, progression, and treatment. Sleep-disordered breathing may be broadly classified as either obstructive sleep apnea (OSA) or central sleep apnea (CSA). The former is characterized by repetitive collapse of the upper airway, whereas in patients with CHF, the latter is most often due to periodic alternation of diminished ventilatory drive and compensatory hyperventilation typical of Cheyne-Stokes respiration (Figure 1). CSA is likely a consequence rather than a cause of CHF. Although the mechanisms that underlie CSA/Cheyne-Stokes respiration in patients with CHF are not well understood, pulmonary congestion with increased lung J-receptor stimulation and greater chemosensitivity may play a role in the genesis of the periodic breathing that characterizes this disorder. 

Because OSA and CSA have different primary causes, optimal therapy may differ for these 2 distinct disorders. However, for patients with CHF, a paucity of data exists from prospective, randomized, controlled trials addressing the potential benefits of treatment for either OSA or CSA. Such studies have generally been limited to evaluation of the short-term effects of continuous positive airway pressure (CPAP) on left ventricular ejection fraction in patients with OSA. An exception is the Canadian Continuous Positive Airway Pressure for Patients With Central Sleep Apnea and Heart Failure (CNPAP), described later.

As yet, no consensus exists on management strategies for the treatment of sleep apnea associated with CHF that have been endorsed by either sleep medicine or CHF specialists. Because CSA is likely secondary to CHF, it follows that optimization of heart failure therapy may resolve CSA. In observational studies, therapies that appear to attenuate or eliminate CSA include diuretics, 6–8 β-blockers, 6 biventricular pacing, 6 and cardiac surgery. 6 For those patients with persistent CSA, potential adjunctive treatment includes nocturnal oxygen, 6 adaptive servoventilation, and CPAP, 6 each of which may reduce the frequency of central apneas in selected patients. Originally devised for the treatment of OSA, CPAP acts as a pneumatic stent to promote upper airway patency. The benefit to cardiac function in patients with OSA may be mediated by improved nocturnal oxygen saturation, reduced sympathetic neural activation, and increased intrathoracic pressure. However, in contrast to OSA, the mechanisms by which CPAP may yield benefit for CSA are not intuitive; by definition, no upper airway obstruction is present in this disorder. One proposed mechanism of benefit has been that CPAP may favorably modulate left ventricular function by promoting an increase in intrathoracic pressure, which in turn decreases transmural left ventricular pressure. Hence, CPAP may in theory act as both a short-term and a long-term hemodynamic intervention for CHF by functioning as an external, noninvasive appliance that reduces left ventricular afterload and thereby lowers cardiac filling pressures with resolution of CSA.

The CANPAP trial was a prospective, randomized, controlled study that attempted to establish the efficacy of CPAP for the treatment of CSA/Cheyne-Stokes respiration associated with CHF by evaluation of the primary end point of transplant-free survival. Subjects with optimally managed CHF with left ventricular ejection fraction <40% and CSA with an apnea-hypopnea index (AHI) >15 were randomized to receive either CPAP or continued conventional therapy. On average, the AHI was reduced from 40 to 19 after 3 months of CPAP, and this reduction was associated with improved left ventricular ejection fraction, decreased norepinephrine concentration, increased nocturnal oxygen saturation, and increased 6-minute walk time.
However, CPAP had no effect on the primary end point of transplant-free survival compared with conventional therapy alone. In fact, there was a suggestion of early poorer outcomes in the CPAP-treated group. The study was terminated because of lower-than-expected subject recruitment and better-than-anticipated survival regardless of randomization. Although lack of benefit from CPAP in the main analysis of CANPAP was unequivocal, in this issue of Circulation, Arzt and colleagues present data from this same trial describing the apparent benefits of suppression of CSA by CPAP in a subset of subjects from the original study cohort. In this post hoc analysis, subjects were stratified into 3 subgroups: control subjects, those treated with CPAP with suppression of CSA (defined as AHI <15), and those treated by CPAP in whom CSA was not suppressed (defined as AHI >15). The investigators hypothesized that suppression of the AHI to <15 after 3 months of treatment by CPAP improves left ventricular ejection fraction and heart transplant–free survival. They observed that for subjects in whom CSA was suppressed by CPAP, left ventricular ejection fraction and survival were significantly improved compared with both the untreated controls and the subjects in whom CSA was not suppressed.

Concerns that limit confidence in this most recent interpretation of the outcomes of the CANPAP study include the inherent shortcomings of post hoc analysis and differences in baseline characteristics between the control subjects and the 2 CPAP-treated groups. The investigators addressed the latter concern by an adjusted analysis in which they evaluated for potential confounding factors, including age, AHI, and the proportion of central apnea or hypopnea; no confounding factors were identified. However, it is noteworthy than on average the “CSA-suppressed” group (with better outcomes) was 5 years younger than the “CSA-not-suppressed” group. In the context of a high-mortality condition such as heart failure, older patients may simply be more likely to die sooner. Perhaps most important, the CSA-suppressed group had a pre-CPAP baseline AHI of 34, substantially less than that of the CSA-not-suppressed group, which had a mean AHI of 47. Furthermore, because the CSA-not-suppressed group had both a higher AHI and a higher proportion of central events, the difference between the total number of disordered breathing events of central origin was considerable. If one accepts the premise that more severe cardiac dysfunction with higher filling pressures may produce a higher central AHI, these data suggest that the CSA-not-suppressed group had more severe underlying cardiac dysfunction at baseline, not evident by measurement of left ventricular ejection fraction alone. Moreover, there appears to be a strong and independent relationship between the severity of CSA as assessed by the AHI and prognosis (Figure 2). Another concern is whether differences in β-blocker treatment and dose may have contributed to the different outcomes for the study subgroups treated by CPAP. This is potentially important because the main analysis of CANPAP suggested a strong interaction between β-blocker therapy and survival. A related issue is that the CANPAP trial also bridged the era during which β-blocker therapy became standard of care, raising concern as to whether CHF patients on maximum tolerated β-blocker obtain any incremental and measurable survival benefit from CPAP because sympatholytic effects may theoretically contribute to the benefit of each of these therapies.

The above-stated concerns notwithstanding, the study by Arzt and colleagues is a valuable contribution to the discussion of
whether CSA may be an important therapeutic target for selected patients with CHF. The challenges going forward will include identifying patients who may respond to therapy (and understanding why some do not respond) and developing therapeutic strategies that more reliably suppress CSA. It needs be emphasized that in the CANPAP trial, after 3 months of treatment, the residual mean AHI still exceeded the threshold for enrollment (>15). In addition, the mean duration of CPAP therapy per night was ≈ 4 hours over 3 months of follow-up and < 4 hours at the 12-month follow-up. These observations indicate that, in the CANPAP trial, on average only a fraction of the burden of CSA was suppressed by CPAP. Hence, CPAP is less than ideal for reducing the AHI with obvious potential for suboptimal therapeutic outcomes. In contrast, the present study by Arzt and colleagues in the present study by Arzt and colleagues does not seem prudent to recommend that treatment effectively suppresses the AHI, whether by standard pharmacotherapy, various modalities of positive airway pressure, or other emerging devices.

Better clarification of optimal management strategies for CHF patients with CSA will require prospective, suitably controlled and adequately powered studies evaluating cardiovascular endpoints in well-characterized subjects to identify which patients to target for specific interventions and what the intermediate and long-term benefits of such treatment may be. We agree with Arzt and colleagues that in the interim, given the possibility of early adverse outcomes associated with CPAP as reported in the primary results of the CANPAP trial, it does not seem prudent to recommend that clinicians routinely implement CPAP as a standard of care for patients with CHF and CSA.

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References

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