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HIGHLIGHTED TOPIC | *Physiology and Pathophysiology of Sleep Apnea*

Influence of cardiac function and failure on sleep-disordered breathing: evidence for a causative role

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Caples, Sean M., Robert Wolk, and Virend K. Somers. Influence of cardiac function and failure on sleep-disordered breathing: evidence for a causative role. *J Appl Physiol* 99: 2433–2439, 2005; doi:10.1152/jappphysiol.00676.2005.—Heart failure is an increasingly common public health problem that is strongly linked to both central and obstructive sleep apnea, collectively referred to as sleep-disordered breathing. Much attention has been given to the deleterious effects of sleep-disordered breathing on the failing heart and potential mechanisms by which treatment of sleep-disordered breathing may result in improved cardiac performance and long-term outcomes. However, there is compelling evidence that cardiac dysfunction may contribute to sleep-disordered breathing. Although there is recognized overlap between pathophysiological mechanisms in central sleep apnea and obstructive sleep apnea, data supporting the role of cardiac function are certain forms of central sleep apnea are well established, whereas investigation into the relationship with obstructive sleep apnea is less mature but continues to evolve. This review will examine experimental and observational data that explore possible pathophysiological mechanisms and potential targets for therapy in heart failure and sleep-disordered breathing.

obstructive sleep apnea; central sleep apnea

SLEEP-DISORDERED BREATHING, encompassing obstructive sleep apnea (OSA) and central sleep apnea (CSA), is a common clinical entity associated with sleep fragmentation and daytime symptoms such as sleepiness and impaired executive function. There is evidence that consequences of sleep-disordered breathing, such as repetitive hypoxemia and arousals from sleep, may be causative in the pathophysiology of cardiovascular disease. Conversely, accumulating data suggest that heart function may play a role in the genesis of sleep-disordered breathing. In fact, heart failure (HF) is widely believed to be a cause of Cheyne-Stokes respiration (CSA-CSR), a form of CSA exhibiting oscillation of central nervous system respiratory output. More common is OSA, associated with upper airway collapse classically thought to result from anatomical influences. However, emerging data suggest that cardiac function influences upper airway patency in OSA through such intermediary mechanisms as ventilatory drive changes, alterations in circulation time, edema accumulation, and neurohumoral control. Given the prevalence and public health burden of both sleep-disordered breathing and HF, the implications for effective treatment of these often comorbid conditions are enormous.

SLEEP-DISORDERED BREATHING AND HF: THE SCOPE OF THE PROBLEM

HF is considered to be an epidemic, affecting more than 5 million Americans, with increasing prevalence due in large

part to an aging population (19). Care for HF comprises the single largest Medicare expense. The burden of HF may be underestimated, since population-based studies suggest that a substantial portion of those with systolic dysfunction are asymptomatic. However, even in the absence of symptoms, impaired ventricular function is associated with an increased mortality risk (50).

The prevalences of OSA and CSA in HF are not well delineated because of a lack of epidemiological studies specifically addressing this relationship. The best available data suggest a prevalence of OSA ranging from 11% in consecutive HF patients undergoing polysomnography to 37% in a referral population (25, 58). The prevalence is slightly higher in men than in women. Given the increasing obesity levels in the general population (27), as well as in HF patients, it is likely that the prevalence of OSA in CHF is increasing accordingly. Some data suggest that those with OSA and HF tend to report less symptoms of daytime sleepiness than those without HF (26, 58), the reasons for which remain to be defined.

Generally, CSA is more frequently encountered in those with HF than in those without, with estimates of 33–40% of HF patients exhibiting CSA on polysomnography (25, 58). CSA has also been described in patients with asymptomatic left ventricular (LV) dysfunction (33). As in OSA, women appear to be at lower risk of CSA in HF than men, with pooled estimates showing a prevalence in women of 18% (21). The onset of menopause, however, is associated with a marked increase in prevalence (58), which suggests a protective role of female sex hormones, even though one report found no asso-

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ciation between menstrual cycle phase and ventilatory instability (81).

VENTILATORY CONTROL DURING NORMAL SLEEP

Respiratory stimuli from higher cortical centers related to daily living behaviors, such as visual and auditory cues, phonation, and deglutition, are lost with the onset of sleep. Ventilation during sleep, therefore, is driven by so-called automatic stimuli that include chemical (arterial P_{O_2} and P_{CO_2}) as well as vagally mediated mechanical (lung and chest wall receptors) input (66).

Non-rapid eye movement (REM) sleep is associated with a twofold increase in upper airway resistance (35), which appears to be related in part to reduced electromyographic activity in upper airway muscles. This reduction in upper airway neuromuscular control originates primarily from the tonic background, although effects may be seen on phasic stimulation during inspiration (39). These regional effects, coupled with reductions in both the hypoxic and hypercapnic ventilatory response, result in modest hypoventilation associated with 2–4% reductions in oxyhemoglobin saturation and a 3- to 6-Torr increase in P_{CO_2} . Further decrements in the ventilatory response occur during REM sleep, despite the return of behavioral cortical activity, which is characterized by an irregular breathing pattern thought to be associated with dreaming (11). There is some evidence to suggest that premenopausal women maintain ventilatory responsiveness during the state change from wakefulness to non-REM sleep (74), a finding that may be important in explaining the reduced risk of OSA noted in the same population (80).

During both wakefulness and sleep, the most sensitive determinant of ventilation is arterial P_{CO_2} , the blood tension of which is linearly related to minute ventilation (\dot{V}_E). Oxygen (O_2) tension also plays a role, but relatively large decrements (arterial $P_{O_2} < 60$ Torr) are required before an appreciable increase in \dot{V}_E is encountered (a hyperbolic response) (10).

The goal of the ventilatory control system is to maintain homeostasis of blood gas tensions within a tightly controlled range. The determinants of this system have been modeled after an engineering concept known as loop gain (29, 30), which considers the overall gain of a system based on feedback from multiple inputs. In its most simplistic terms, as outlined by Khoo et al. (29), the ventilatory system is under the influence of 1) respiratory pump and gas exchange capabilities of the lungs and body tissues (“plant gain”), 2) central and peripheral chemoreflexes (“controller gain”), and 3) circulatory time (as determined by fluctuations in cardiac output and cerebral blood flow).

As will be discussed, this homeostatic model forms the basis for some of the fundamental pathophysiological mechanisms related to cardiac function and both CSA and OSA.

OSA

OSA is characterized by upper airway narrowing or collapse resulting in repetitive episodes of hypoxemia, swings in intrathoracic pressure, and sleep fragmentation from arousals. It is thought that anatomical influences in OSA predominate as a cause of upper airway collapse, and this is probably most applicable to those with marked truncal and cervical obesity or oropharyngeal mass lesions such as tonsillar hypertrophy.

However, a considerable proportion of those with OSA do not have such obvious anatomical abnormalities, suggesting other potential mechanisms for obstructive upper airway events.

There is accumulating evidence that failure of neuromuscular mechanisms related to ventilatory drive play some role in OSA, including those related to loop gain (78, 79). The evidence to support a role for the peripheral chemoreceptors in the pathogenesis of OSA, however, has been conflicting. Narkiewicz and colleagues (41) found potentiation of the peripheral O_2 chemoreceptors in otherwise healthy OSA patients compared with control subjects matched for body mass index and gender and proven free of OSA. However, Redline et al. (51) found decrements in O_2 responsiveness in studies of familial OSA. Considerable differences in age (and, by inference, duration of OSA) and body weight may partially explain the disparity in findings. As will be discussed later, there is also a potential role of cardiac function in ventilatory control mechanisms in OSA.

CSA AND CSA-CSR

By definition, CSA is characterized by episodes of apnea related to loss of ventilatory output from the central respiratory generator in the brain stem to the respiratory pump. Although it is classically and ideally measured in the sleep laboratory with the use of an esophageal pressure catheter, central apnea is increasingly characterized by plethysmographic measurement of chest wall and abdominal motion, a technique with reasonable reliability (65). Although the vernacular is not universally agreed on, a form of CSA commonly encountered in the setting of HF is CSA-CSR, a breathing pattern characterized by crescendo-decrescendo tidal volumes with intervening central apneas. This waxing and waning pattern has been also referred to as periodic breathing. Idiopathic CSA, characterized by abrupt increases in ventilation following breathing pauses distinct from CSA-CSR, is a well-recognized but rarer form of central apnea that needs mentioning but will not be discussed further given the scope of this review. In contrast to OSA, where arousals typically occur with apnea termination, arousals from sleep in CSA-CSR tend to occur at the height of the hyperpneic phase following apnea. Considering this propensity for sleep disruption, it is not clear why daytime symptoms in CSA-CSR are not as prominent as in OSA.

The main clinical importance of CSA in HF may rest with its association with increased mortality. The severity of CSA is thought to be, to some extent, a reflection of underlying cardiac dysfunction, which could partially explain the mortality association. However, multivariate analyses suggest that CSA may be an independent risk factor for mortality (31). Potential mechanisms may relate to cardiac decompensation associated with apnea-induced hypoxemia, sympathetic activation, or repetitive arousals and sleep fragmentation (32). Perhaps as a consequence, CSA in HF has been associated with cardiac pathologies that could further worsen prognosis, such as atrial fibrillation (58).

ASSOCIATION BETWEEN CENTRAL AND OBSTRUCTIVE SLEEP-DISORDERED BREATHING

There are features of OSA and CSA that are physiologically distinctive. For example, obstructive apneas are most profound and frequent during REM sleep, as a result of muscle atonia

during this stage. Conversely, central events, especially CSA-CSR, are rare during REM sleep, which probably relates to the relatively minor role of P_{CO_2} in driving ventilation during this stage (9) where behavioral influences become more prominent. Still, there appears to be considerable overlap between pathophysiological mechanisms in OSA and CSA.

It is unusual to encounter pure CSA without discernible superimposed obstructive events either within an apnea (so-called "mixed apnea") or coexisting during a single night. This coupling likely represents overlap of the pathophysiological and neuromuscular mechanisms that govern aspects of both ventilatory control and upper airway patency. There are several lines of evidence to suggest that OSA and CSA may share common pathophysiological mechanisms. Central apneas in CSA-CSR have been found to be frequently accompanied by upper airway occlusion (1). Induction of periodic breathing with hypoxic gas mixtures results in upper airway narrowing in both snorers (71) and normal volunteers (46), an effect confirmed by electromyographic recordings of upper airway muscles (17). In HF, there is evidence for an overnight shift in predominance of obstructive apneas to central apneas, an effect that may be mediated by deteriorating cardiac function (70). Further evidence of the association between upper airway narrowing and central events is derived from an observed increase in central apneas in the supine position (55) and a reduction in central events with the use of continuous positive airway pressure (CPAP) treatment (16, 20). It is worth noting that, although reductions in central apneas in response to CPAP are frequently reproducible in the sleep laboratory, this does not appear to translate into improved clinical outcomes (3).

MECHANISMS OF CSA IN HF: IMPLICATIONS FOR THERAPY

Although the integrated reflexes and pathways are certainly complex and multifactorial, current evidence suggests that many of the pathophysiological mechanisms in HF and central apnea relate to abnormalities in ventilatory control as outlined in the model above. Circulatory delay in association with reduced cardiac output in systolic HF is reproducible in models of CSA in animals (8) and usually is present in human patients with HF and CSA-CSR (5, 28). Naughton and colleagues (42) showed that circulatory delay appears to play an important role in determining CSA-CSR cycle length.

On the other hand, interindividual variation in central and peripheral chemoreflex sensitivity (controller gain) may explain why some patients with HF do not develop central apnea. HF patients with CSA-CSR have consistently been found to have heightened ventilatory responses to blood CO_2 tensions, often resulting in hypocapnia (22, 62, 76). Javaheri and Corbett (24) reported that hypocapnia is often modest (P_{CO_2} range of 32–34 Torr) and is not invariably present during wakefulness. However, since a stable ventilatory rhythm is normally maintained by a 3- to 6-Torr rise in P_{CO_2} associated with non-REM sleep, small decrements in P_{CO_2} below the apneic threshold are often sufficient to destabilize the system, resulting in ventilatory oscillations manifesting as CSA-CSR (22, 24). The intervening apneas perpetuate the vicious cycle as resulting hypercapnia elicits an exaggerated ventilatory response on subsequent cycles.

Sensitivity to CO_2 positively correlates with the severity of the CSA as determined by the number of apneas and hypo-

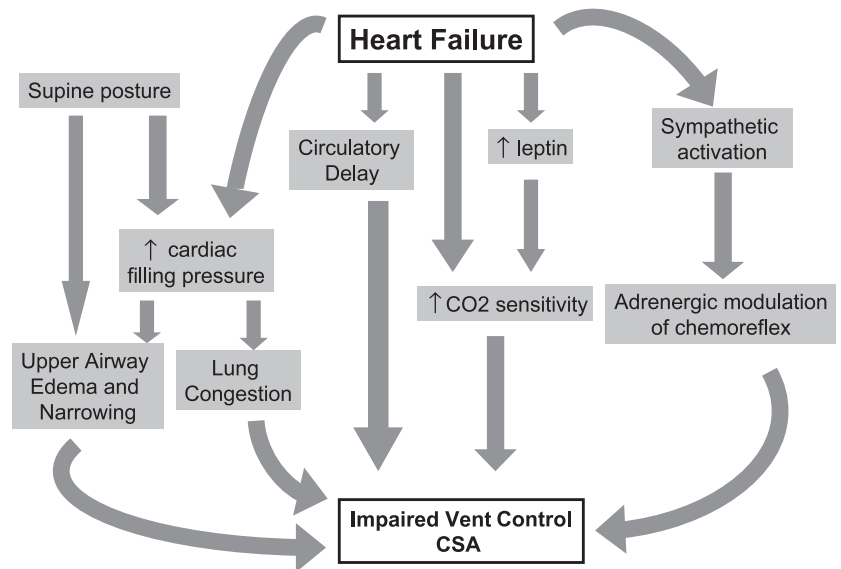
pneas per hour [apnea-hypopnea index (AHI)] of sleep (22). It is interesting to note, and possibly representative of global derangements in CO_2 metabolism, that patients with HF also have enhanced CO_2 sensitivity and relative hyperventilation during exercise (represented by the \dot{V}_E/\dot{V}_{CO_2} slope), a finding that has been shown to be of prognostic importance (6, 75). A nonrandomized observation of CPAP compared with O_2 therapy in HF with CSA showed improvement of the \dot{V}_E/\dot{V}_{CO_2} slope in the CPAP group but not in those treated with O_2 (2). Finally, very recent data suggest that hypocapnia-induced destabilization of ventilatory control appears to be specific to systolic dysfunction and circulatory delay in HF. A prospective evaluation of stroke patients showed that those with systolic dysfunction and hypocapnia had a higher prevalence of CSA independent of stroke type or brain location (44). Hepatic cirrhotics, in response to metabolic derangements and alterations in pulmonary hemodynamics, frequently present with hypocapnia (40, 53). Nevertheless, cirrhotics with normal LV function (ejection fraction of 60%) matched with HF patients (ejection fraction of 23%) for P_{CO_2} levels showed little to no CSA compared with the high rate in the HF group (23).

Research into leptin, the protein product of the adipocyte *ob/ob* gene, has provided a novel and exciting potential mechanism for understanding interactions between cardiac dysfunction and ventilatory control. Although leptin is predominantly implicated in appetite, weight, and metabolism regulation, it has also been linked to CO_2 sensitivity (69). In a knockout model of obese mice, leptin infusions appeared to prevent respiratory depression, particularly during REM sleep (45). Disturbed leptin metabolism in HF (75) may conceivably contribute to the heightened CO_2 sensitivity (controller gain) and predisposition to CSA in HF.

Heightened peripheral chemoreflex sensitivity has also been identified in animal models of HF. Pacing-induced cardiomyopathy in rabbits is associated with enhanced peripheral chemoreflex activity along with increased sympathetic nerve activity (68). A follow-up study suggested that carotid body input was responsible for enhanced ventilatory sensitivity, modulated perhaps by impaired nitric oxide production (67). The contribution from the carotid bodies was maintained even with an *ex vivo* vascularly isolated preparation, suggesting that changes were independent of acute cardiovascular alterations but rather irreversibly diseased by HF. Similar mechanisms could be at work in humans based on an analysis of CSA patients who underwent cardiac transplantation. At 6 mo post-transplant, despite normalization of cardiac systolic function and reductions in sympathetic nerve activity, some patients demonstrated persistent CSA, albeit of lesser severity based on the AHI (37). How impaired baroreflex gain in HF may relate to altered chemoreflex sensitivity (63) remains to be determined, as does any role for HF-induced sympathetic activation with consequent adrenergic modulation of the chemoreflex.

Increased cardiac filling pressures (pulmonary capillary wedge pressures) have been associated with worsening of CSA (61). This may explain the increase in CSA severity as HF worsens, as well as when HF patients change from the upright to the supine posture (55). Although overt alveolar flooding is probably needed to stimulate ventilation on the basis of hypoxemia, subtle pulmonary interstitial edema commonly resulting from increases in cardiac filling pressures in HF can increase ventilation by stimulation of vagally mediated lung

Fig. 1. Potential pathways linking heart failure (HF) to central sleep apnea (CSA). Instability of ventilatory control, a primary intermediary mechanism, may be induced by a number of tertiary pathways. Direct mechanical effects due to elevated venous pressures and tissue edema in addition to loss of neuromuscular control mechanisms may also contribute to the pathophysiology of CSA.



irritant receptors (36, 79), thereby leading to mild chronic hypoxemia. There may also be interactions between the respiratory control center and cardiac mechanoreceptors or other pressure-sensitive cardiac receptors that elicit reflex changes in ventilatory control. Figure 1 summarizes possible pathophysiological mechanisms in HF and CSA.

Further evidence from a recent interventional trial also implicates increased cardiac filling pressures and resultant instability of ventilatory control in the pathogenesis of CSA-CSR. Sinha and colleagues (60) found that, in 14 patients with HF (LV ejection fraction of $25 \pm 5\%$), intraventricular conduction delays, and CSA, cardiac resynchronization therapy (CRT) markedly reduced CSA at 17 wk of follow-up (mean AHI 19 ± 10 to 4.6 ± 4.4 ; Fig. 2). LV ejection fraction increased to a mean of 35%, and significant improvements were noted in quality of life. At baseline, CSA-CSR patients demonstrated increased ventilatory responses to exercise (\dot{V}_E/\dot{V}_{CO_2} slope) in keeping with other studies showing abnormalities in CO_2 metabolism in these patients (6, 75). However, CRT resulted in a reduction in this measure that was comparable to that of 10 other subjects without CSA-CSR who underwent CRT. Although long-term outcome data are not yet available, it is possible that some of the survival benefit attributed to CRT in HF patients in very recently published large-scale studies may be related to amelioration of central

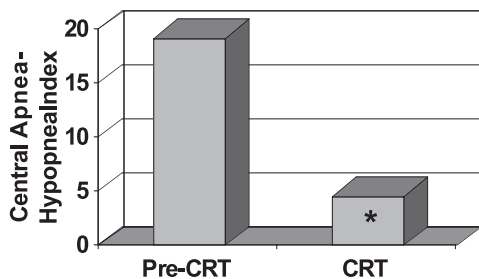


Fig. 2. Reduction in central apnea-hypopnea index (AHI) in 14 patients with HF (left ventricular ejection fraction of $25 \pm 5\%$), cardiac conduction abnormalities, and CSA following cardiac resynchronization therapy (CRT). * $P < 0.001$. Figure is modified from Ref. 60.

apnea in this patient population (4, 7). It is likely that CRT-related stabilization of loop gain is at least partly responsible for the improvement in CSA, although further study will be needed to clarify other mechanisms and whether any further benefit is afforded to those HF patients with coexisting OSA and CSA.

There are currently no defined criteria for treatment of CSA. CPAP is known to acutely reverse episodes of central apnea in the laboratory. In addition, aside from its reversal of apnea, CPAP has salutary effects on cardiac function on account of inspiratory muscle unloading and reduction of cardiac afterload related to increasing intrathoracic pressure (43). A controlled trial of CPAP or usual care followed those with HF with and without CSA. CPAP was associated with an increase in ejection fraction and reduced risk of heart transplant only in those with CSA (59). However, these findings have not been borne out in a larger multicenter study of outcomes (3).

Supplemental O_2 has also been a popular treatment choice for CSA. Its mechanism of action is not completely clear, but it probably acts to suppress ventilatory drive and hyperventilation, thus moving the arterial P_{CO_2} away from the apneic threshold. It is also conceivable that O_2 improves cardiac function, thereby indirectly reducing periodic breathing. A randomized controlled trial yielded a greatly reduced AHI in men with severe HF and nocturnal hypoxemia (15).

Further research will be needed to explore whether directed treatment of CSA with the above methods affords any further benefit over and above aggressively treating underlying HF.

HEART FUNCTION AND FAILURE AND OSA

There is increasing evidence that OSA exerts deleterious effects on cardiac function, particularly in the compromised heart. The potential mechanisms are numerous and include effects of hypoxemia (47), enhanced sympathetic drive (64), oxidative stress (12), and inflammation (56). Given the high rate of coexistence of OSA and HF, one cannot exclude the possibility that cardiac function may modulate upper airway function, hence predisposing to sleep-disordered breathing.

Cardinal features of HF include circulatory overload and dependent edema resulting from organ hypoperfusion and associated neurohormonal imbalances. There is evidence to suggest that tissue edema, especially position-dependent redistribution, may influence upper airway dimensions and mechanics. Utilizing computed tomography images, Shepard and colleagues (57) found that, in men with known OSA, experimental changes in central venous pressure were associated with alterations in upper airway cross-sectional area. The most significant changes were observed with reductions in central venous pressure (by blood pressure cuff inflation of the legs), where increases in airway cross-sectional area were seen at end-inspiratory tidal volume, suggesting that increases in venous return to the chest associated with negative intrathoracic pressure reduces venous blood volume in the neck and pharynx. In chronic HF patients recovering from acute LV dysfunction, assumption of the supine position results in rapid dyspnea (orthopnea) and marked increases in measured airway resistance (77). Resolution of symptoms and normalization of airway resistance ensued with return to the seated position. Although these acute effects could have been related to increased peripheral airway resistance associated with pulmonary interstitial edema, the evidence is compelling for position-dependent modulation of upper airway caliber and mechanics in HF.

In a provocative study, Garrigue and colleagues (13) reported a >50% improvement in the overall (central and obstructive) AHI after atrial overdrive pacing in a small group of patients with an implanted pacemaker. Mean heart rate was increased from 57 to 72 beats/min in this group, comprised primarily of men with a mean age just under 70 yr and relatively preserved LV function (mean ejection fraction of 54%). Polysomnographic data showed that, although more than one-half of the AHI reduction was related to central events, there were also clear reductions in obstructive apneas and hypopneas. The authors hypothesized a vagally mediated effect on the upper airway musculature resulting from the increase in heart rate. Another possible mechanism, as proposed by others (73), is that the pacing-induced increase in cardiac output stabilized the respiratory pattern by reducing loop gain.

Although these data support the biological plausibility of ventilatory control mechanisms being susceptible to modulation by atrial overdrive pacing, two randomized trials subsequent to the Garrigue paper failed to show similar benefit in OSA (36, 48). However, it is worth mentioning that, although one study showed no change in those with mostly severe OSA (mean AHI of 46) (48), the study of those with OSA of moderate severity (mean AHI of 21) demonstrated statistically significant reductions in obstructive hypopneas (13.4–10.9). (36) This subtle contrast to the original paper may leave the door open to future directed research in those with less-than-severe OSA.

Indeed, there is evidence for instability of ventilatory control in OSA, which, in accordance with the loop gain model, appears to be modulated at least in part by cardiac function. As early as 1978, Remmers and colleagues (52) noted periodicity in genioglossal electromyographic activity in 10 obese subjects now recognized to have OSA. More recent experiments suggest a role for ventilatory instability in OSA (18, 72), particularly in those with more severe disease based on AHI (79), although these studies did not directly measure cardiac func-

tion. How the high leptin levels noted in both OSA (49) and HF (34) relate to ventilatory control in HF patients with OSA remains to be defined.

Bradley and colleagues have published a series of articles exploring the impact of ventilatory control on sleep-disordered breathing as it relates to underlying cardiac function. They first demonstrated that circulatory delay, as measured by the lung-to-ear circulation time, was more prominent in those with CSA-CSR and HF compared with idiopathic CSA and normal cardiac function (14) and was found to correlate with hyperpnea cycle length rather than apnea duration. These findings were recently extended to the setting of OSA, where patients with HF demonstrated periodic breathing that appeared to relate to a prolonged lung-to-ear circulation time, in contrast to the absence of periodic breathing and shorter lung-to-ear circulation time seen in those with normal cardiac function (Fig. 3) (54).

FUTURE DIRECTIONS FOR RESEARCH

Mechanistic studies outlined above suggest an important role for cardiac function in the causation of sleep-disordered breathing, particularly CSA. However, the effects of various

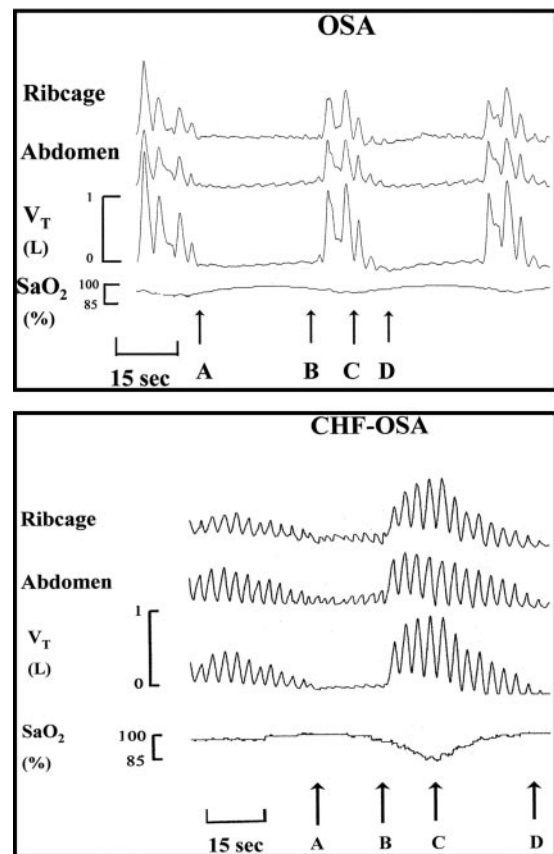


Fig. 3. Typical polysomnographic recordings from a patient with obstructive sleep apnea (OSA) and normal cardiac systolic function (*top*) and from a patient with OSA and HF (*bottom*). Obstruction is indicated by out-of-phase ribcage and abdominal movements. In the HF patient, the duration of cycle (A to D), hyperpnea (B to D), and lung-to-ear circulation time (B to C) are substantially longer than in the patient without HF. Note the architectural differences between the hyperpneic waveforms, with longer transitions in the HF patients. Figure is reproduced from Ref. 54, with permission from the publisher.

treatments in CSA [O₂, CPAP, ventilatory support (bilevel)] and their impact on heart function, sleep parameters, and mortality are not well known. Furthermore, will specific treatment of CSA have any additive or synergistic effects when combined with aggressive medical or mechanical (CRT) treatment of HF? Interventional trials assessing long-term outcomes are needed to answer these questions.

HF, largely through effects on airway characteristics, but also through ventilatory control mechanisms, also may contribute to OSA. The public health burden related to the high prevalences of both OSA and HF will dictate further research into shared pathophysiological mechanisms. Further elucidation of potential targets of therapy will be important given the problems with patient adherence to CPAP therapy as well as the reported ceiling effect of pharmacological treatment of HF (38).

What is clear is that the prevalences of HF, OSA, and CSA are high and rising and that treatment options for these individual disorders remain inadequate. Recognition of the frequent coexistence of these conditions, as well as their pathophysiological interactions, which serve to perpetuate and worsen each other, is crucial to more rational, comprehensive, and effective therapeutic strategies.

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