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/japplphysiol.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-
ciation between menstrual cycle phase and ventilatory insta-
ibility (81).

VENTILATORY CONTROL DURING NORMAL SLEEP

Respiratory stimuli from higher cortical centers related to
daily living behaviors, such as visual and auditory cues, pho-
nation, and deglutition, are lost with the onset of sleep. Ven-
tilation during sleep, therefore, is driven by so-called automatic
stimuli that include chemical (arterial $PO_2$ and $PCO_2$) 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 ap-
pears to be related in part to reduced electromyographic activ-
ity in upper airway muscles. This reduction in upper airway
neuromuscular control originates primarily from the tonic
background, although effects may be seen on phasic stimula-
tion during inspiration (39). These regional effects, coupled
with reductions in both the hypoxic and hypercapnic ventila-
tory response, result in modest hypoventilation associated with
2–4% reductions in oxyhemoglobin saturation and a 3- to
6-Torr increase in $PCO_2$. Further decrements in the ventilatory
response occur during REM sleep, despite the return of behav-
ioral 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 de-
terminant of ventilation is arterial $PCO_2$, the blood tension
of which is linearly related to minute ventilation ($VE$). Oxygen
($O_2$) tension also plays a role, but relatively large decrements
(arterial $PO_2 < 60$ Torr) are required before an appreciable
increase in $VE$ 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 in-
trathoracic 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 neuromuscu-
lar 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. Nar-
kiewicz and colleagues (41) found potentiation of the periphe-
ral $O_2$ 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 infer-
ence, 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 measure-
ment 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 charac-
terized by crescendo-decrescendo tidal volumes with interven-
ing central apneas. This waxing and waning pattern has been
also referred to as periodic breathing. Idiopathic CSA, charac-
terized 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 pro-
pensity for sleep disruption, it is not clear why daytime symp-
toms 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 asso-
ciation. 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 re-
petitive 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

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during this stage. Conversely, central events, especially CSA-
CSR, are rare during REM sleep, which probably relates to the
relatively minor role of PCO2 in driving ventilation during this
stage (9) where behavioral influences become more prominent.
Still, there appears to be considerable overlap between patho-
physiological 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 con-
firmed by electromyographic recordings of upper airway mus-
cles (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 ex-
plain 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 CO2 tensions,
often resulting in hypcapnia (22, 62, 76). Javaheri and Corbett
(24) reported that hypcapnia is often modest (PCO2 range of
32–34 Torr) and is not invariably present during wakefulness.
However, since a stable ventilatory rhythm is normally main-
tained by a 3- to 6-Torr rise in PCO2 associated with non-REM
sleep, small decrements in PCO2 below the apneic threshold are
often sufficient to destabilize the system, resulting in ventila-
tory oscillations manifesting as CSA-CSR (22, 24). The inter-
vening apneas perpetuate the vicious cycle as resulting hyper-
capnia elicits an exaggerated ventilatory response on subse-
cquent cycles.

Sensitivity to CO2 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 CO2 metabolism, that patients with HF also
have enhanced CO2 sensitivity and relative hyperventilation
during exercise (represented by the VE/VCO2 slope), a finding
that has been shown to be of prognostic importance (6, 75). A
nonrandomized observation of CPAP compared with O2 ther-
apy in HF with CSA showed improvement of the VE/VCO2
slope in the CPAP group but not in those treated with O2 (2).
Finally, very recent data suggest that hypopacnia-induced de-
stabilization 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 hypopacnia had a higher prevalence of CSA
independent of stroke type or brain location (44). Hepatic
cirrhosis, in response to metabolic derangements and alter-
atations in pulmonary hemodynamics, frequently present with
hypopacnia (40, 53). Nevertheless, cirrhotics with normal LV
function (ejection fraction of 60%) matched with HF patients
(ejection fraction of 23%) for PCO2 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 mech-
anism for understanding interactions between cardiac dysfunc-
tion and ventilatory control. Although leptin is predominantly
implicated in appetite, weight, and metabolism regulation, it
has also been linked to CO2 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 CO2 sensitivity (controller gain)
and predisposition to CSA in HF.

Heightened peripheral chemoreflex sensitivity has also been
identified in animal models of HF. Pacing-induced cardiomy-
opathy in rabbits is associated with enhanced peripheral che-
moreflex activity along with increased sympathetic nerve ac-
tivity (68). A follow-up study suggested that carotid body input
was responsible for enhanced ventilatory sensitivity, modu-
lated perhaps by impaired nitric oxide production (67). The
contribution from the carotid bodies was maintained even with
an ex vivo vascularity 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 deter-
mained, 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
irritant receptors (36, 79), thereby leading to mild chronic hypocapnia. 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 ± 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 (V˙E/V˙CO₂ slope) in keeping with other studies showing abnormalities in CO₂ 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 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 O₂ 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 PCO₂ away from the apneic threshold. It is also conceivable that O₂ 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 function. 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 hypopnea 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

![Image](http://jap.physiology.org/)

**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), hypopnea (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 hypopneic 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.

REFERENCES

Influence of Cardiac Function on Sleep-Disordered Breathing


