AMERICAN THORACIC SOCIETY DOCUMENTS

Research Priorities for Patients with Heart Failure and Central Sleep Apnea

An Official American Thoracic Society Research Statement: Executive Summary

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Background: Central sleep apnea (CSA) is common among patients with heart failure and has been strongly linked to adverse outcomes. However, progress toward improving outcomes for such patients has been limited. The purpose of this official statement from the American Thoracic Society is to identify key areas to prioritize for future research regarding CSA in heart failure.

Methods: An international multidisciplinary group with expertise in sleep medicine, pulmonary medicine, heart failure, clinical research, and health outcomes was convened. The group met at the American Thoracic Society 2019 International Conference to determine research priority areas. A statement summarizing the findings of the group was subsequently authored using input from all members.

Results: The workgroup identified 11 specific research priorities in several key areas: *1*) control of breathing and pathophysiology leading to CSA, *2*) variability across individuals and over time, *3*) techniques to examine CSA pathogenesis and outcomes, *4*) impact of device and pharmacological treatment, and *5*) implementing CSA treatment for all individuals

Conclusions: Advancing care for patients with CSA in the context of heart failure will require progress in the arenas of translational (basic through clinical), epidemiological, and patient-centered outcome research. Given the increasing prevalence of heart failure and its associated substantial burden to individuals, society, and the healthcare system, targeted research to improve knowledge of CSA pathogenesis and treatment is a priority.

Keywords: sleep apnea; heart failure; respiration

Contents

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Overview

Central sleep apnea (CSA) is common among patients with heart failure and is strongly and independently associated with poor health and well-being outcomes. This American Thoracic Society (ATS) statement summarizes current literature, identifies gaps in knowledge, and outlines a path forward for research with specific recommendations.

Research Priorities

1. Advance basic and translational research regarding control of breathing.
2. Determine mechanisms that mediate breathing instability in CSA.
3. Examine CSA in diverse groups and across the adult life span.
4. Evaluate changes in CSA over time and the relationship with heart failure status.
5. Develop and validate tools to better characterize CSA (i.e., beyond the apnea–hypopnea index [AHI]).
6. Determine how sleep apnea physiology might contribute to—or protect against—heart failure progression.
7. Determine the impact of established and emerging heart failure therapies on CSA.
8. Clarify the role of positive airway pressure (PAP) therapy for CSA in those with heart failure.
9. Establish the utility of supplemental oxygen, inspired CO_2, and pharmacotherapy for treatment for CSA.
10. Determine factors influencing adherence to CSA treatments.
11. Characterize health disparities related to CSA across populations.

Introduction

CSA is common among patients with heart failure (1–3). The presence of CSA is associated with important prognostic implications as a marker of heart failure severity (4, 5). Furthermore, CSA is associated with sleep disruption, oxygen desaturation, and increases in sympathetic activity and thus may itself directly adversely impact patient outcomes. Despite sharing these manifestations with obstructive sleep apnea (OSA), CSA has been the focus of comparatively little research.

The aim of this statement is to outline a path forward for research regarding CSA as it pertains to those with heart failure, with the ultimate goal of improving outcomes for these individuals. Although the focus of this research priority statement is CSA in those with heart failure, we expect that progress will be broadly relevant to other forms of CSA, including idiopathic CSA and opioid-related CSA, among others.

Methods

This research statement was developed according to the guidelines specified by the ATS. Potential conflicts of interest were disclosed and managed in accordance with the policies and procedures of the ATS. Workgroup participants were selected on the basis of recognized expertise in the areas of control of breathing, sleep-disordered breathing, sleep, heart failure, PAP, treatment adherence, and population health. Candidate research topics were identified and prioritized on the basis of an iterative process, beginning with a face-to-face meeting of the workgroup in May of 2019, during which currently available evidence for each of the key areas outlined below was reviewed.

Findings

Key Area: Control of Breathing and Pathophysiology Leading to CSA

In contrast to fluctuations in OSA, fluctuations in breathing in CSA are primarily the result of transient changes in central respiratory output, rather than being driven by upper airway obstruction. Research over the past several decades has provided important insights into the neurobiological and physiological mechanisms underlying respiratory control that are relevant to CSA. However, many unresolved questions remain. Research priorities identified by the workgroup to address gaps in our understanding are provided below, with specific example areas in Table 1.

Research priority 1: advance basic and translational research regarding control of breathing. Control of breathing is complex, involving many sensory and high-order inputs, central processing areas, and key outputs; readers are referred to contemporary reviews (6, 7). The most widely recognized sensory inputs include the carotid and brain-stem chemoreflex sensors, which detect fluctuations in Pa_{CO_2}, pH, and Pa_{O_2}, with varying time scales for responsiveness (Figure 1). Importantly, this system exhibits remarkable and substantial plasticity in sensory components,

Table 1. Control of Breathing in CSA: Pathogenesis and Potential Therapeutic Targets

Carotid body	• Chemoreflex role in overall sympathetic activation in heart failure: common pathways • Purinergic signaling • Gasotransmitters
Brain stem	• Understanding complex integrative responses: RTN, pre-Bötzinger complex, etc. • Mechanisms underlying neuroplasticity: long-term facilitation and potentiation • Cerebral vasoreactivity: mechanisms and role of impairment
Sleep state and arousals	• Mechanisms of stability in REM • Arousal contribution to instability in CSA
Low cardiac output	• Shear-stress sensing in the carotid body • Interactions between circulatory delay and loop gain; heart–lung interactions • Fluid shifts in supine position • Mechanisms sensing pulmonary congestion
System-integrative	• Refined *in silico* models • CSA model organisms • Effects of aging, sex, and other systemic influences (e.g., metabolic dysregulation)

Definition of abbreviations: CSA = central sleep apnea; RTN = retrotrapezoid nucleus.

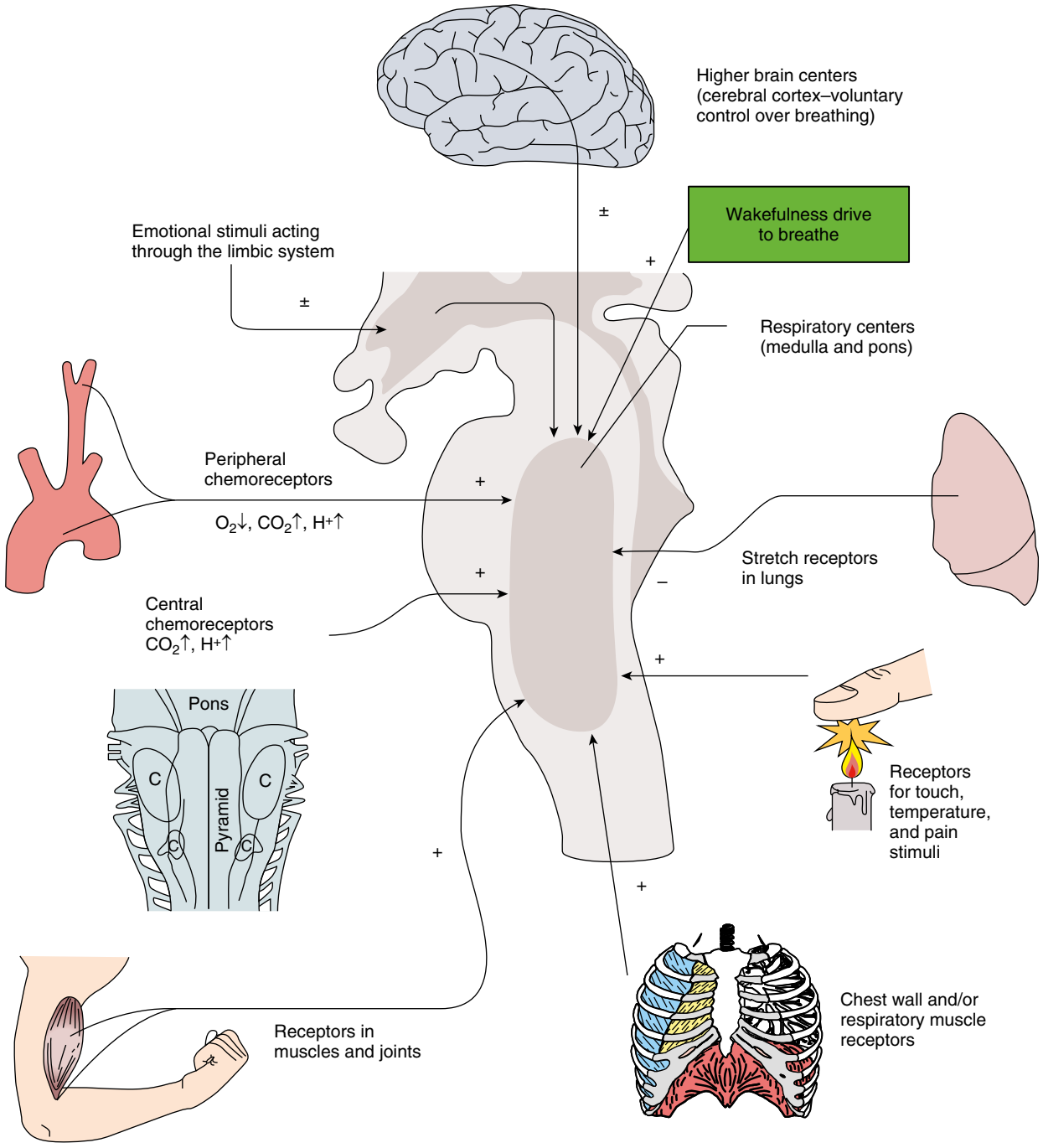

Figure 1. Schematic of ventilatory-control-system inputs/afferents that converge on integrating respiratory centers in the pons and medulla. Chemoreceptors include both peripheral and central centers. Other physical inputs to breathing include lung stretch and irritant receptors; movement/stretch receptors in muscles and joints, including receptors within the chest wall, larynx, and respiratory muscles (including in the upper airway); and peripheral pain receptors. Higher brain centers impact breathing via volitional drive, emotion, and sleep-versus-wake state (wakefulness drive to breathe). + = stimulate; − = inhibit; ± = stimulate or inhibit; C = location of respiratory groups in the medulla. Adapted by permission from Reference 142.

integrating centers, and output nuclei. Established factors stimulating plasticity include intermittent hypoxemia, inflammation, and aging (8, 9).

The overall responses of these respiratory-control components determine the persistence of rhythmic breathing or the development of breathing instability. Broadly, CSA may be a consequence of low-ventilatory-drive states (often associated with concurrent hypercapnia) or may be a consequence of a *hyperresponsive* system leading to instability (often associated with concurrent hypocapnia) (10–16). The latter appears to be generally more common and accounts for CSA in the settings of heart failure, high altitude, periodic breathing in infancy, and idiopathic CSA and in some

patients with OSA treated with continuous PAP (CPAP).

A concept borrowed from engineering describes the ability of the ventilatory system to maintain stability. A value of gain (also called "loop gain") is defined by the increase in drive following a decrease in ventilation. A threshold value of above 1.0 can produce periodic central apnea in response to a transient disturbance, whereas lower values may lead to unstable breathing with ongoing disturbances (17). Loop gain can become elevated by increased chemoreflex responses to blood gas changes (P_{O_2} and/or P_{CO_2}) (18), increased plant gain (e.g., low lung volume or high P_{CO_2}), and/or greater circulatory delay. Although the precise mechanisms contributing to instability may vary by specific etiology, most conditions involve augmented chemosensitivity. The propensity to develop central apnea varies across physiological and pathological conditions (19–26). A disconnect remains between these physiological studies and an understanding of the associated neurobiological pathways.

The importance of wake-versus-sleep state in control of breathing is also established. Specifically, non-REM sleep removes the wakefulness "drive to breathe" and renders respiration critically dependent on chemical influences, especially Pa_{CO_2}. In addition, there is unmasking of a threshold P_{CO_2} below which ventilation ceases. Thus, a small drop in prevailing P_{CO_2} causes central apnea during sleep. Clinical observations include the destabilizing effect of wake–sleep transitions and dramatic changes in respiratory-event frequencies in non-REM versus REM sleep. Again, little is known regarding the pathways that connect these observations to underlying mechanisms.

Research priority 2: determine mechanisms that mediate breathing instability in CSA. The most consistent pathophysiological determinant of CSA in heart failure is increased chemosensitivity to CO_2 and hypoxia (10–16). CSA severity is more strongly associated with peripheral CO_2 than with central CO_2 (11). Interestingly, CSA in patients with heart failure is equally well correlated with ventilatory responses to CO_2 and hypoxia; when both responses are augmented, CSA becomes particularly severe (16).

The precise pathway between heart failure and augmented chemosensitivity in CSA remains unclear. Chemoreflex sensitivity has been related to increased left heart filling pressures and pulmonary congestion in humans (27–29). In addition, changes in pulmonary blood volume from wakefulness/upright positioning to sleep/supine positioning ("rostral fluid shift") may be relevant (30). Alternatively, in a rabbit model, low carotid blood flow leads to diminished shear stress in the carotid body, augmented chemosensitivity, and emergent CSA (31).

Other factors beyond blood gas chemoreflex sensitivity *per se* can raise the functional ventilatory responsiveness to blood gases (and thus loop gain) and promote CSA, but the relative importance remains unclear in CSA in those with heart failure (10).

1. Low cardiac output contributes to a substantial delay between changes in Pa_{CO_2} (and also Pa_{O_2}) in the pulmonary capillaries and respiratory centers, which provides the background preconditions for CSA (32–35). Reducing circulatory delay with heart failure therapies can also improve or ameliorate ventilatory oscillations (36–38), yet it is unclear the extent to which circulatory delay itself contributes to CSA.
2. Impaired cerebral vasoreactivity to CO_2 can (in principle) hinder the damping of CO_2 swings in the brain stem, yielding augmented responses to swings in arterial P_{CO_2}.
3. Reaching the threshold to arousal from sleep acts to raise the functional responsiveness and loop gain (19, 39–43). Of note, CSA is most common in stage 1 non-REM sleep, in which sleep is fragile and arousals are frequent.
4. A propensity for upper airway collapse may also destabilize breathing, even in the absence of obstructive events (44–51). Upper airway collapsibility is prevalent in the general population and may be more common in patients with heart failure as a result of pharyngeal fluid accumulation (52). Moreover, there is substantial overlap between CSA and OSA in heart failure, including the presence of both obstructive and central events within many individuals (53).

Key Area: Variability in CSA across Individuals and over Time

Research priority 3: examine CSA in diverse groups and across the adult life span. Increasing age is a well-recognized risk factor for sleep-disordered breathing, in both OSA and CSA (54, 55). The most well-established effect of age relates to upper airway collapsibility (56). However, within those with heart failure, CSA increases with age, suggesting other effects of aging (3). Potential mechanisms require further study, but effects on control of breathing, lung function, and respiratory muscle activity are all potential contributors (57). In terms of sex, epidemiological studies have demonstrated a significantly higher prevalence of CSA in men compared with premenopausal women, with evidence implicating testosterone (21–23, 58). Accordingly, the role of menopause and aging in women requires specific investigation (59).

Established CSA risk factors include male sex, increasing age, lower left ventricular ejection fraction (LVEF), and comorbid atrial fibrillation (3). Key questions remain regarding potential risk factors such as race and ethnicity, medications (not only heart failure drug classes but also concurrent opioids, sedatives, etc.), heart failure etiology, etc.

From the standpoint of associated symptoms and clinical presentation, patients with heart failure and CSA (or OSA) may not report symptoms such as sleepiness or sleep disruption (60–62). Bed partners may note apneas or hyperpneas, and patients may report fatigue, insomnia, paroxysmal nocturnal dyspnea, and/or nocturnal angina, although the specificity regarding CSA is unknown. A priority is establishing the spectrum of symptoms, associated sleep comorbidities, and quality of life using validated questionnaires.

Research priority 4: evaluate changes in CSA over time and the relationship with heart failure status. CSA appears to be more common in decompensated heart failure (31, 63, 64). However, treatment of decompensated heart failure does not reliably resolve CSA (65). Identifying individuals with persistent CSA may help to define a group that needs sustained CSA therapy, versus supportive care or time-limited CSA treatment.

Conversely, variability in heart failure over time may be impacted by changes in CSA. Thus, there is clear potential for interactions between these two conditions

over time. For example, some have hypothesized that subclinical changes in cardiac function may trigger or worsen CSA, which may lead to further heart failure decompensation. Recognition of and intervention for CSA might present an opportunity to break a downward spiral. Further research will require technologies capable of monitoring changes in sleep apnea over time, such as "wearables."

Key Area: Techniques to Examine CSA Pathogenesis and Outcomes

Research priority 5: develop and validate tools to better characterize CSA (i.e., beyond the AHI). CSA is defined as at least 5 central events/h that comprise at least 50% of the total AHI (66). For CSA with Cheyne-Stokes respiration, there must be at least three consecutive central events in a crescendo–decrescendo pattern and a cycle length of at least 40 seconds. Nonetheless, there may be considerable variability between individuals in features of breathing, which may have important implications (53, 67–69).

There are two major reasons to identify and quantify aspects of CSA pathophysiology beyond a count of the frequency: *1*) to characterize the pathogenesis for the purposes of understanding how to treat the disorder and *2*) to determine better the risks associated with the untreated disorder.

Cycle duration. In heart failure, cycle durations are typically 40–90 seconds, with longer cycle lengths seen in patients with lower LVEF, lower cardiac output, and greater circulatory delays (70). Treatments may be dependent on cycle duration; for example, central events with longer cycle lengths have slower fluctuations in blood gases and thus may garner more input from central chemoreflexes such that supplemental oxygen could be less effective. Conversely, the cycle duration may provide important information about heart function (27).

Central versus obstructive contributions. The extent to which sleep apnea is driven by central versus obstructive components is challenging to ascertain and has therapeutic implications (71). Therapies for the central contribution, such as oxygen, are likely to fail in those with a substantial obstructive component. Although some events are clearly obstructive and others are clearly central, many events have a combined etiology. New methods aim to estimate the central versus obstructive nature of events using sleep studies (72).

Loop gain and ventilatory pattern. Loop gain can be readily quantified and can distinguish individuals nonresponsive to CPAP and respiratory stimulation (71). Alternative methods for predicting high loop gain have been proposed, including examining awake breathing, examining sighs, and quantifying the presence or absence of stable breathing (73, 74). Tailoring the magnitude of an intervention to the severity of the underlying magnitude of control instability thus has promise. Finally, changes in end-expiratory lung volumes (EELVs) during the hyperpnea phase of CSA may also be relevant.

Sleep state instability dependence. Some patients exhibit CSA that appears to be driven by the sleep–wake transition, and such patients might benefit from interventions that promote sleep (hypnotics). However, the potential for adverse effect of hypnotics must be carefully examined.

Oxygenation and arousal impacts. Central apnea results in cycles of hypoxia and reoxygenation and transient arousals from sleep. Several potentially relevant parameters can be extracted from the oximetry signal, including the number of oxygenation dips, the mean and nadir saturation, and the percentage of total sleep time with a saturation $< 90\%$. Other innovative metrics include the sleep apnea–specific hypoxia burden (75). Sleep state disturbance, as measured by the frequency of EEG arousals, has been associated with apnea-related sympathoexcitation. Prolonged circulation time may also have important prognostic implications (70).

Research priority 6: determine how sleep apnea might contribute to, or protect against, heart failure progression. CSA is independently associated with poor outcomes in patients with heart failure (76). Although the possibility exists that CSA is merely a marker of heart failure severity, several lines of evidence suggest that CSA *per se* contributes to adverse outcomes (77, 78). Briefly, autonomic activation is a key feature of heart failure as well as sleep-disordered breathing (in both CSA and OSA), and CSA treatment improves catecholamine concentrations and ventricular arrhythmias (79, 80). Intermittent hypoxemia has established adverse effects via autonomic and other pathways (such as those promoting hypertension). Intrathoracic pressure swings may lead to arousal but also increase transmural cardiac stress.

Another hypothesis that has been put forth is that CSA might be an adaptive response in heart failure, at least in some individuals (81). Although evidence remains sparse, Perger and colleagues recently examined EELV in patients with heart failure and CSA and found two patterns during hyperpnea—a positive pattern (i.e., preserved or increased EELV) and a negative pattern (i.e., reduced EELV) (82). This group found that stroke volume falls less in patients with the negative pattern than in patients with the positive pattern (83). Although these data are preliminary, the findings support the concept that there may be subgroups of patients with heart failure in whom CSA has adaptive benefit.

The potential "downstream" mechanistic cardiac consequences of CSA physiology/pathophysiology require exploration, including via imaging studies, novel heart failure biomarkers, and multiomics approaches. The extent to which negative or positive cardiovascular changes are driven by intermittent hypoxemia, arousal, lung volumes, respiratory muscle patterns, or intrathoracic pressure changes can be examined more precisely using endophenotyping techniques noted above or using model organisms to isolate these factors.

Key Area: Impact of Device and Pharmacological Treatment

A summary of therapeutic options and relevant clinical questions is provided in Table 2.

Research priority 7: determine the impact of established and emerging heart failure therapies on CSA. Effective heart failure treatment can clearly improve and even resolve CSA (36, 84, 85). Novel therapeutic strategies that may impact CSA should be considered for rigorous investigation:

1. Carotid body denervation has recently gained renewed interest as a potential therapy for heart failure (86). The importance of carotid bodies in breathing clearly mandates evaluation of respiratory effects.
2. Cardiac rehabilitation is another intervention that might impact sleep apnea via several pathways, and improvements in CSA thus might account for at least some of the benefits of rehabilitation (87).

Table 2. Current Questions about Potential Treatments for CSA

Potential Treatments for CSA	Current Question(s)
Heart failure therapies	• Is CSA a mediator or modulator of benefit?
CPAP	• Is CPAP effective in predicted responders, and who responds? • Should CPAP be used as a standard comparator?
Adaptive servoventilation	• Are there identifiable device and/or patient-level factors predicting harm or benefit? • Does better efficacy improve adherence?
Inspired CO_2	• What is the clinical feasibility? • Are there adverse effects related to hypercapnia or increased ventilation?
Supplemental oxygen	• Who will respond (AHI, symptoms, end-organ, etc.) to supplemental O_2? • Are there issues with adherence, and what strategies improve adherence?
Phrenic pacing	• What are the long-term outcomes and comparative effectiveness (including the "effective AHI")?
Pharmacotherapy	• What are the most promising targets? • Is there a role for combination or "rescue" therapy?

Definition of abbreviations: AHI = apnea–hypopnea index; CPAP = continuous positive airway pressure; CSA = central sleep apnea.

It remains unclear whether CSA represents an *independent* outcome of heart failure and, if so, whether titrating heart failure therapy to achieve resolution of CSA may be a goal. Nonetheless, the group felt strongly that inclusion of CSA as a key outcome in heart failure therapy studies is strongly warranted.

Research priority 8: clarify the role of PAP therapy for CSA in those with heart failure. CPAP may improve CSA by increasing lung volumes, decreasing preload and afterload, and stabilizing the upper airway. Nonetheless, the CANPAP (Canadian CPAP for Patients with CSA and Heart Failure) study found no overall improvement in survival with the use of CPAP (88). In *post hoc* analysis, those with an AHI $<$ 15 events/h on treatment had improved survival (78). A prospective study of CPAP in heart failure enrolling probable CPAP responders (using aforementioned predictors) is needed for definitive conclusions.

Adaptive servoventilation (ASV) is a modality specifically designed to control CSA by augmenting ventilation during hypopnea or apnea, stabilizing breathing and reducing the AHI. The SERVE-HF (ASV for CSA in Systolic Heart Failure) study found that among patients with reduced LVEF (LVEF $<$ 45%; heart failure with reduced ejection fraction [HFrEF]), ASV led to increased mortality (89). A contemporaneous study examining ASV in decompensated heart failure (CAT-HF [Cardiovascular Outcomes with $\dot{V}_E$-targeted ASV Therapy in Heart Failure]) was stopped early, noting that patients with preserved LVEF (heart failure with preserve ejection fraction) appeared to benefit (90). The ongoing ADVENT-HF (Effects of ASV on Survival and Frequency of Hospital Admissions in Patients with Heart Failure and Sleep Apnea) trial will further examine the use of ASV in HFrEF (91, 92). Risk factors and associated mechanisms by which ASV might lead to benefit versus harm remain unclear and should be examined (93–96).

Unilateral phrenic-nerve stimulation is Food and Drug Administration approved for treatment of CSA on the basis of improvement in AHI by approximately 50% and some subjective improvements in symptoms (97, 98). Nonetheless, long-term outcomes including the effect on heart failure and mortality have not been examined. In addition, not all individuals resolve CSA, suggesting a need for improved predictors of response.

Research priority 9: establish the utility of supplemental oxygen, inspired CO_2, and pharmacotherapy for treatment for CSA. Supplemental oxygen is often considered for CSA in patients with heart failure on the basis of American Academy of Sleep Medicine guidelines, although long-term data are lacking. The LOFT-HF (Impact of Low-Flow Nocturnal Oxygen Therapy on Hospital Admissions and Mortality in Patients with Heart Failure and CSA) trial is enrolling patients with HFrEF with predominant CSA and randomizing patients to oxygen or a sham. Endpoints include hospitalization due to heart failure and mortality. Prior physiological data suggest that supplemental oxygen will not suppress CSA in all individuals, and therapy thus may need to be individualized.

Delivery of CO_2 was proposed several decades ago as a strategy to stabilize breathing in CSA (99, 100). An increase in inspired CO_2 can be achieved either with exogenous CO_2 (i.e., from a tank) or via rebreathing of exhaled CO_2. Development of hypercapnia may be mitigated by isolating CO_2 delivery to hyperpneas (101). Similarly, applied dead space requires careful adjustment, which is facilitated by titratable devices (102, 103). Endotyping techniques have been shown to predict the response to inhaled CO_2 (104). Further advances are needed in patient selection, technologies, and examination of patient-oriented outcomes.

Pharmacotherapies that impact control of breathing have long been sought for CSA (105). Acetazolamide has been used in CSA at altitude (106, 107) and in heart failure (108–111). Physiologically, acetazolamide results in decreased plant gain (112, 113). Zolpidem has been used clinically for the treatment of idiopathic CSA (114). Buspirone has been examined in models (115, 116) and a few clinical reports (117–119). Although these agents show promise for CSA in general, their safety and efficacy in heart failure are unknown. Furthermore, effects from using these agents as monotherapies have been modest, suggesting a need for new drugs or combination strategies.

Studies are also needed to explore other novel candidate pharmacological targets: *1*) KLF2, signaling shear stress in the carotid (120); *2*) inflammation-related signaling (e.g., via TNFα and IL-6) in both the carotid body and central nervous system (8, 121, 122); *3*) carotid gasotransmitters CO and H_2S (123); and *4*) P2X3 receptors,

modulating autonomic receptor sensitivity (124). Notably, given that that carotid chemoreflex also protects against hypoxia, the ideal intervention reduces carotid body hyperreflexia but preserves physiological function (125).

Key Area: Implementing CSA Treatments for All Individuals

Research priority 10: determine factors influencing adherence to CSA treatments. Adherence to long-term therapy, including adherence to medications for chronic diseases such as hypertension, is suboptimal (126, 127). Evidence on CPAP adherence in patients with CSA is limited, in contrast to evidence in patients with OSA (128). Importantly, CSA is not fully controlled with CPAP in many individuals, and treatment efficacy may impact adherence (129).

With regard to ASV, in SERVE-HF, mean nightly use was 3.7 hours, and 27% of patients did not use treatment at all. This rate of adherence is similar to that of trials in OSA (130), although ASV usage may be better in interim analysis of ADVENT-HF (131). Adherence might be impacted by differences intrinsic to ASV versus CPAP (e.g., more complex therapy), across ASV devices/algorithms, or based on treatment efficacy.

Regarding oxygen, a systematic review found acceptable adherence (132). In a large trial among patients with OSA, there was a higher mean duration of use of supplemental oxygen than of CPAP (133); however, it is not clear whether objective data were available for oxygen.

Studies are needed to translate to CSA known effective strategies for increasing adherence, such as educational, supportive, and behavioral interventions (134). Identifying CSA-specific challenges to adherence will clearly be needed. Lastly, not all treatments are equally dependent on the patient actively engaging with the device; for example, phrenic-nerve stimulation is relatively "automatic" in that once turned on for the night, no further engagement is needed. Accordingly, research should make clear distinctions between the efficacy (i.e., control of the AHI during use) and effectiveness (i.e., considering the use pattern or the "effective AHI").

Research priority 11: characterize health disparities related to CSA across populations. A health disparity is defined as "a health difference that adversely affects defined disadvantaged populations, based on one or more health outcomes" (135). The NIH has designated U.S. health-disparity populations on the basis of the degree of social disadvantage due to historical and contemporary discriminatory policies and practices. Of note, minority health is defined as "health characteristics and attributes of racial and/or ethnic groups who are socially disadvantaged due in part to being subject to potential discriminatory acts" (136).

A recent workshop report highlighted research gaps, challenges, and opportunities in sleep and health-disparity research (137). Future research should focus on health-disparity causal pathways, together with sleep and circadian rhythm–related mechanisms, to better understand disparities. Strategies identified included *1*) focusing on sociocultural and environmental determinants, *2*) better integration of disparity-research field theories and methodologies, and *3*) designing multilevel interventions through transdisciplinary teams.

Data related to CSA are sparse. As an illustrative example, racial and ethnic minorities (especially Black individuals/African Americans) disproportionately experience sleep-disordered breathing, heart failure, and comorbidities (e.g., hypertension) that could impact CSA (138–141). Reasons for differences in underlying mechanisms should be identified, as determinants may differ and differences in treatment may be necessary. Other aspects deserving consideration for treatment of sleep apnea are the cost of therapy and health-literacy requirements. Disparities in CSA specifically are likely to exist, but more research is needed.

The following are *recommendations for future research* to be conducted to answer the aforementioned questions:

- Include sufficient sample sizes of populations impacted by health disparities and conduct race-specific investigations.
- Collect data on "upstream" (close to the root cause) factors like social and environmental determinants of health and health disparities to investigate their impact on CSA.

Regardless of findings, it will remain important to explicitly investigate and intervene in health-disparity populations, as their general health tends to be worse. The ultimate goal is achieving sleep-health equity, defined as "equal opportunities that are given to each individual and/or communities based on their need, no matter their age, sex, race/ethnicity, geographic location, and socioeconomic status, to obtain recommended, satisfactory, efficient amount of sleep with appropriate timing that promotes physical and mental well-being" (136).

Conclusions

Advancing care for patients with CSA in the setting of heart failure will require progress in the arenas of translational (basic through clinical), epidemiological, and implementation research. Given the increasing prevalence of heart failure and its associated substantial burden to individuals and society as well as the healthcare system, targeted research strategies to improve knowledge of CSA pathogenesis and treatment are a priority. ■

This research statement was prepared by an *ad hoc* subcommittee of the ATS Assembly on Sleep and Respiratory Neurobiology.

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