Research Priorities for Patients with Heart Failure and Central Sleep Apnea
An Official American Thoracic Society Research Statement: Executive Summary

Jeremy E. Orr, Indu Ayappa, Danny J. Eckert, Jack L. Feldman, Chandra L. Jackson, Shahrokh Javaheri, Rami N. Khayat, Jennifer L. Martin, Reena Mehra, Matthew T. Naughton, Winfried J. Randerath, Scott A. Sands, Virend K. Somers, and M. Safwan Badr; on behalf of the American Thoracic Society Assembly on Sleep and Respiratory Neurobiology

THIS OFFICIAL RESEARCH STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED DECEMBER 2020

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
Overview
Research Priorities
Introduction
Methods
Findings

Key Area: Control of Breathing and Pathophysiology Leading to CSA
Key Area: Variability in CSA across Individuals and over Time
Key Area: Techniques to Examine CSA Pathogenesis and Outcomes
Key Area: Impact of Device and Pharmacological Treatment
Key Area: Implementing CSA Treatments for All Individuals

Conclusions

ORCID IDs: 0000-0002-4498-5337 (J.E.O.); 0000-0003-3692-9412 (J.L.F.); 0000-0002-6222-2675 (R.M.); 0000-0003-2734-0841 (M.T.N.); 0000-0002-5010-8461 (W.J.R.).

Supported by the American Thoracic Society; the Intramural Program at the NIH, National Institute of Environmental Health Sciences (Z1A ES103325-01); NIH grant R01HL130552; and Veterans Health Administration Office of Research and Development grant I01CX001040.

This Executive Summary is part of the full official ATS research statement, which readers may access online at http://www.atsjournals.org/doi/abs/10.1164/rccm.202101-0190ST. Only the Executive Summary is appearing in the print edition of the Journal. The article of record, and the one that should be cited, is: Research Priorities for Patients with Heart Failure and Central Sleep Apnea: An Official American Thoracic Society Research Statement. Am J Respir Crit Care Med 2021;203:e11–e24.

Correspondence and requests for reprints should be addressed to Jeremy E. Orr, M.D., Division of Pulmonary, Critical Care, and Sleep Medicine, University of California, San Diego, 9300 Campus Point Drive, MC 7381, La Jolla, CA 92121. E-mail: j1orr@health.ucsd.edu.

Am J Respir Crit Care Med Vol 203, Iss 6, pp 678–688, Mar 15, 2021
Copyright © 2021 by the American Thoracic Society
DOI: 10.1164/rccm.202101-0190ST
Internet address: www.atsjournals.org
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 CO₂, 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 PaCO₂, pH, and PaO₂, 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 |
| Brain stem | Understanding complex integrative responses: RTN, pre-Bötzinger complex, etc. |
| Sleep state and arousals | Mechanisms of stability in REM |
| Low cardiac output | Shear-stress sensing in the carotid body |
| System-integrative | Refined in silico models |

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

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.
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 \(P_C_O_2\)) (18), increased plant gain (e.g., low lung volume or high \(P_C_O_2\)), 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 \(P_A_C_O_2\). In addition, there is unmasking of a threshold \(P_C_O_2\) below which ventilation ceases. Thus, a small drop in prevailing \(P_C_O_2\) causes central apnea during sleep. Clinical observations include the destabilizing effect of wake- versus 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 \(C_O_2\) and hypoxia (10–16). CSA severity is more strongly associated with peripheral \(C_O_2\) than with central \(C_O_2\) (11). Interestingly, CSA in patients with heart failure is equally well correlated with ventilatory responses to \(C_O_2\) 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 \(P_A_C_O_2\) (and also \(P_A_O_2\)) 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 \(C_O_2\) can (in principle) hinder the damping of \(C_O_2\) swings in the brain stem, yielding augmented responses to swings in arterial \(P_C_O_2\).

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 hypopneas, 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 arousals. 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).
Heart failure therapies

- Is CSA a mediator or modulator of benefit?
- Is CPAP effective in predicted responders, and who responds?
- Should CPAP be used as a standard comparator?

CPAP

- Are there identifiable device and/or patient-level factors predicting harm or benefit?
- Does better efficacy improve adherence?

Adaptive servoventilation

- What is the clinical feasibility?
- Are there adverse effects related to hypercapnia or increased ventilation?

Inspired CO₂

- Who will respond (AHI, symptoms, end-organ, etc.) to supplemental O₂?
- Are there issues with adherence, and what strategies improve adherence?

Supplemental oxygen

- What are the long-term outcomes and comparative effectiveness (including the “effective AHI”)?

Phrenic pacing

- What are the most promising targets?
- Is there a role for combination or “rescue” therapy?

Pharmacotherapy

- Is there a role for combination or 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 CO₂ was proposed several decades ago as a strategy to stabilize breathing in CSA (99, 100). An increase in inspired CO₂ can be achieved either with exogenous CO₂ (i.e., from a tank) or via rebreathing of exhaled CO₂. Development of hypercapnia may be mitigated by isolating CO₂ 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 CO₂ (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 gastransmitters CO and H₂S (123); and 4) P2X3 receptors,

---

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? |
| Adaptive servoventilation   | Are there identifiable device and/or patient-level factors predicting harm or benefit? |
| Inspired CO₂                | Does better efficacy improve adherence? |
| Supplemental oxygen         | Who will respond (AHI, symptoms, end-organ, etc.) to supplemental O₂? |
| Phrenic pacing              | Are there issues with adherence, and what strategies improve adherence? |
| Pharmacotherapy             | What are the most promising targets? |

Definition of abbreviations: AHI = apnea–hypopnea index; CPAP = continuous positive airway pressure; CSA = central sleep apnea.
modulating autonomic receptor sensitivity (124). Notably, given that that carotid chemoreflex also protects against hypoxia, the ideal intervention reduces carotid body hyperre 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.

Members of the subcommittee are as follows: Jeremy E. Orr, M.D. (Co-Chair)¹ M. Safwan Badr, M.D. (Co-Chair)²,³ Indu Ayappa, Ph.D.⁴ Danny J. Eckert, Ph.D.⁵ Jack L. Feldman, Ph.D.⁶ Chandra L. Jackson, Ph.D., M.S.⁷,⁸ Shahrokh Javaheri, M.D.⁹,¹⁰ Rami N. Khayat, M.D.¹¹,¹²,¹³ Jennifer L. Martin, Ph.D.¹⁴,¹⁵ Reena Mehra, M.D.¹⁶,¹⁷,¹⁸,¹⁹ Matthew T. Naughton, M.D.²⁰ Winfried J. Randerath, M.D.²¹ Scott A. Sands, Ph.D.²² Virend K. Somers, M.D., Ph.D.²³
Author Disclosures: J.E.O. received a partnered grant from the ATS Foundation/ResMed, I.A. received research support and royalties on continuous positive airway pressure titration patents from Fisher & Paykel. D.J.E. served as a consultant and on an advisory committee for Aпервmed; received research support from Bayer and Oventus Medical; and received a senior research fellowship from the National Health and Medical Research Council of Australia. S.J. served as a consultant for Respicardia; and received research support from the NIH for a trial on LOFT-HF. R.N.K. served as a consultant for Respicardia; and served as a speaker for Philips Respironics. R.M. served on an advisory committee for the American Board of Internal Medicine, Merck, and R.Token; served as a consultant for Respicardia; received research support from the American Heart Association, the NIH, Natus, Philips Respironics, and ResMed; and received royalties from UpToDate. W.J.R. served as a speaker for Bayer Vital, Berlin-Chemie, Bioprojet, Boehringer Ingelheim, Heinen & Löwenstein, Inspire, Novartis, Night Balance, Philips Respironics, ResMed, Vanda Pharma, and Weinman; and received research support from Heinen & Löwenstein and Philips Respironics. V.K.S. served as a consultant for Baker Tilly, Bayer, Jazz Pharmaceutical, GlaxoSmithKline, ResMed, Respipedia, and Roche; and received research support from the NIH, Philips Foundation, and Sleep Number. M.S.B., J.L.F., C.L.J., J.L.M., M.T.N., and S.A.S. reported no commercial or relevant noncommercial interests.

References

1. Javaheri S, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure: types and their prevalences, consequences, and presentations. Circulation 1998;97:2154–2159.

2. MacDonald M, Fang J, Pittman SD, White DP, Malhotra A. The current prevalence of sleep disordered breathing in congestive heart failure patients treated with beta-blockers. J Clin Sleep 2008;4:38–42.

3. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med 1999;160:1101–1106.

4. Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. Am J Cardiol 2007;99:2028–2034.

5. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence and in characteristics of 700 patients. Eur J Heart Fail 2007;9:251–257.

6. Dempsey JA, Smith CA. Pathophysiology of human ventilatory control. Eur Respir J 2014;44:495–512.

7. Del Negro CA, Feldman JL. Breathing matters. Nat Rev Neurol 2018;19:351–367.

8. Hooker AD, Stokes JA, Powell FL, Huxtable AG. The impact of inflammation on respiratory plasticity. Exp Neurol 2017;287:243–253.

9. Behan M, Zabka AG, Mitchell GS. Age and gender effects on serotonin-dependent plasticity in respiratory motor control. Respir Physiol Neurobiol 2002;131:65–77.

10. Javaheri S. A mechanism of central sleep apnea in patients with heart failure. N Engl J Med 1999;341:949–954.

11. Solin P, Roebuck R, Johns BP, Walters EH, Naughton MT, Peripheral and central ventilatory responses in central sleep apnea with and without congestive heart failure. Am J Respir Crit Care Med 2000;162:2194–2200.

12. Topor ZL, Johannson L, Kasprzyk J, Remmers JE. Dynamic ventilatory response to CO2 in congestive heart failure patients with and without central sleep apnea. J Appl Physiol 1985;1991:408–416.

13. Xie A, Skatrud JB, Pulso DS, Rahko PS, Dempsey JA. Apnea-hypopnea threshold for CO2 in patients with congestive heart failure. Am J Respir Crit Care Med 2002;165:1245–1250.

14. Francis DP, Willson K, Davies LC, Coats AJ, Piepoli M. Quantitative general theory for periodic breathing in chronic heart failure and its clinical implications. Circulation 2000;102:2214–2221.

15. Frasokowski P, Anker SD, Chua TP, Francis D, Banasiak W, Poole-Wilson PA, et al. Oscillatory breathing patterns during wakefulness in patients with chronic heart failure: clinical implications and role of augmented peripheral chemosensitivity. Circulation 1999;100:2418–2424.

16. Giannini A, Emdin M, Poletti BR, Brahant F, Prontera C, Piepoli M, et al. Clinical significance of chemosensitivity in chronic heart failure: influence on neurohumoral derangement, Cheyne-Stokes respiration and arrhythmias. Clin Sci (Lond) 2008;114:489–497.

17. Sands SA, Mebrate Y, Edwards BA, Nemati S, Manisty CH, Desai AS, et al. Resonance as the mechanism of daytime periodic breathing in patients with heart failure. Am J Respir Crit Care Med 2017;195:237–246.

18. Dempsey JA. Crossing the apnoeic threshold: causes and consequences. Exp Physiol 2005;90:13–24.

19. Chowdhuri S, Pranathiageswaran S, Loomis-King H, Salloum A, Badr MR. Aging is associated with increased propensity for central apnea during NREM sleep. J Appl Physiol (2015) 2018;124:83–90.

20. Salloum A, Rowley JA, Mateika JH, Chowdhuri S, Omran Q, Badr MS. Increased propensity for central apnea in patients with obstructive sleep apnea: effect of nasal continuous positive airway pressure. Am J Respir Crit Care Med 2010;181:189–193.

21. Zhou XS, Shahabuddin S, Zahn BR, Babcock MA, Badr MS. Effect of gender on the development of hypocapnic apnea/hypopnea during NREM sleep. J Appl Physiol (1985) 2000:89:192–199.

22. Zhou XS, Rowley JA, Demirovic F, Diamond MP, Badr MS. Effect of testosterone on the apneic threshold in women during NREM sleep. J Appl Physiol (1985) 2003;94:101–107.

23. Mateika JH, Omran Q, Rowley JA, Zhou XS, Diamond MP, Badr MS. Testosterone conversion blockade increases breathing stability in healthy men during NREM sleep. J Clin Endocrinol & Metabolism 2013;98:369–377.

24. Chowdhuri S, Bascom A, Mohan D, Diamond MP, Badr MS. Testosterone conversion blockade increases breathing stability in healthy men during NREM sleep, Sleep (Basel) 2013;36:1793–1798.

25. Chowdhuri S, Shanidze I, Pierchala L, Belen D, Mateika JH, Badr MS. Effect of episodic hypoxia on the susceptibility to hypocapnic central apnea during NREM sleep. J Appl Physiol (1985) 2010;108:369–377.

26. Chowdhuri S, Sinha P, Pranathiageswaran S, Badr MS. Sustained hypocapnia stabilizes breathing in healthy individuals during NREM sleep. J Appl Physiol (1985) 2010;109:1378–1383.
27. Lloyd TC Jr. Effect of increased left atrial pressure on breathing frequency in anesthetized dog. J Appl Physiol (1985) 1990;69: 1973–1980.

28. Lloyd TC Jr. Breathing response to lung congestion with and without left atrial distension. J Appl Physiol (1985) 1988;55:131–136.

29. Szollosi I, Thompson BR, Krum H, Kaye DM, Naughton MT. Impaired pulmonary diffusing capacity and hypoxia in heart failure correlates with central sleep apnea severity. Chest 2008;134:67–72.

30. White LH, Bradley TD. Role of nocturnal rostral fluid shift in the pathogenesis of obstructive and central sleep apnea. J Physiol 2019;199:1179–1188.

31. Mortara A, Sleigh P, Pinna GD, Maestri R, Capomolla S, Febo O, et al. Association between hemodynamic impairment and Cheyne-Stokes respiration and periodic breathing in chronic stable congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1999;84:900–904.

32. Hall MJ, Xie A, Rutherford R, Ando S, Flores JS, Bradley TD. Cycle length of periodic breathing in patients with and without heart failure. Am J Respir Crit Care Med 1998;164:376–381.

33. Solin P, Roebeck T, Swieca J, Walters EH, Naughton MT. Effects of cardiac dysfunction on non–hypercapnic central sleep apnea. Chest 1998;113:104–110.

34. Stanchina ML, Ellis K, Malhotra A, Anderson M, Kirk M, Benser ME, et al. The impact of cardiac resynchronization therapy on obstructive sleep apnea in heart failure patients: a pilot study. Chest 2007;132:433–439.

35. Orr JE, Auger WR, De Heyning PN, Kim NH, Malhotra A, Owens RL. Usefulness of low cardiac index to predict sleep-disordered breathing in chronic thromboembolic pulmonary hypertension. Am J Cardiol 2016;117:1001–1005.

36. Sinha AM, Skobel EC, Breithardt OA, Norra C, Markus KU, Breuer C, et al. Contribution of male sex, age, and obesity to mechanical instability of the upper airway during sleep. J Appl Physiol (1985) 2008;104:1618–1624.

37. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. Clin Interv Aging 2006;1:253–260.

38. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Reijn J, Vela-Bueno A, et al. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med 2001;163:608–613.

39. Rowley JA, Zhou XS, Diamond MP, Badr MS. The determinants of the apnea threshold during NREM sleep in normal subjects. Sleep 2006;29:95–103.

40. Arzt M, Young T, Finn L, Skatrud JB, Ryan CM, Newton GE, et al. Sleepiness and sleep in patients with both systolic heart failure and obstructive sleep apnea. Arch Intern Med 2006;166:1716–1722.

41. Soriano F, Campbell A, Yee B, Richards M, O’Meeghan T, Weatherall M, et al. Sleep-disordered breathing occurs frequently in stable outpatients with congestive heart failure. Chest 2005;128: 2116–2122.

42. Tarantino Montemurro, Floras JS, Millar PJ, Kasai T, Gabriel JM, Spaan J, et al. Inverse relationship of subjective daytime sleepiness to sympathetic activity in patients with heart failure and obstructive sleep apnea. Chest 2012;142:1222–1228.

43. Sharma S, Mather P, Efrid JT, Kahn D, Cheema M, Rubin S, et al. Photopletysmographic signal to screen sleep-disordered breathing in hospitalized heart failure patients: feasibility of a prospective clinical pathway. JACC Heart Fail 2015;3:725–731.

44. Solin P, Bergin P, Richardson M, Kaye DM, Walters EH, Naughton MT. Influence of pulmonary capillary wedge pressure on central apnea in heart failure. Circulation 1999;99:1574–1579.

45. Padeletti M, Green P, Mooney AM, Basner RC, Mancini DM. Sleep apnea: current perspectives. AMERICAN THORACIC SOCIETY DOCUMENTS 668 American Journal of Respiratory and Critical Care Medicine Volume 203 Number 6 | March 15 2021
