Sleep-Disordered Breathing in Heart Failure
— A Therapeutic Dilemma —

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Sleep-disordered breathing (SDB) occurs in approximately 50% of patients with reduced left ventricular ejection fraction receiving contemporary heart failure (HF) therapies. Obstructive (OSA) and central sleep apneas (CSA) interrupt breathing by different mechanisms but impose qualitatively similar autonomic, chemical, mechanical, and inflammatory burdens on the heart and circulation. Because contemporary evidence-based drug and device HF therapies have little or no mitigating effect on the acute or long-term consequences of such stimuli, there is a sound mechanistic rationale for targeting SDB to reduce cardiovascular event rates and prolong life. However, the promise of observational studies and randomized trials of small size and duration describing a beneficial effect of treating SDB in HF via positive airflow pressure was not realized in 2 recent randomized outcome-driven trials: SAVE, which evaluated the cardiovascular effect of treating OSA in a cohort without HF, and SERVE-HF, which reported the results of a strategy of random allocation of minute-ventilation-triggered adaptive servo-ventilation (ASV) for HF patients with CSA. Whether effective treatment of either OSA or CSA improves the HF trajectory by reducing cardiovascular morbidity or mortality has yet to be definitively established. ADVENT-HF, designed to determine the effect of treating both CSA and non-sleepy OSA HF patients with a peak-airflow triggered ASV algorithm, could resolve this present clinical equipoise concerning the treatment of SDB.

Key Words: Adaptive servo-ventilation; Central sleep apnea; Heart failure; Obstructive sleep apnea; Positive airflow pressure

A fundamental and as yet unresolved question for the heart failure (HF) community is whether coexisting obstructive (OSA) or central sleep apnea (CSA) should be specific targets of therapy. For individuals without HF, the principal clinical indication to treat sleep apnea is to improve quality of life (QOL) and alleviate daytime hypersomnolence. However, this indication does not pertain to the majority of patients with reduced left ventricular systolic function and sleep-disordered breathing (SDB) as they are not burdened by excess daytime sleepiness. In such individuals, the impetus to diagnosis and treatment is the hypothesis that attenuation or abolition of SDB will modify beneficially the natural history of HF. OSA and CSA interrupt breathing by different mechanisms but impose qualitatively similar autonomic, chemical, mechanical, and inflammatory burdens on the heart and circulation. Because contemporary evidence-based drug and device HF therapies have little or no mitigating effect on the acute consequences of such stimuli or on the long-term structural and functional adaptations they induce within the atria and ventricles, the brain and the peripheral vasculature, there is a sound mechanistic rationale for targeting SDB to reduce cardiovascular event rates and prolong life. Importantly, effective treatment is presently available for both OSA and CSA and cogent reasons for their deployment can be advocated (Table). However, the promise of observational studies and randomized trials of small size and duration describing a beneficial effect of treating SDB in HF via positive airflow pressure (PAP) was not realized in 2 recent randomized outcome-driven trials: SAVE, which evaluated the cardiovascular effect of treating OSA in a cohort without HF, and SERVE-HF, which reported the results of a strategy of random allocation of minute-ventilation-triggered adaptive servo-ventilation (ASV) for HF patients with CSA. Consequently, equipoise remains as to whether either OSA or CSA, once detected in a HF patient with reduced left ventricular ejection fraction (LVEF), should be therapeutically suppressed. The threefold purpose of this review was to: (1) summarize current knowledge concerning the prevalence, pathophysiology, and prognostic implications of SDB in HF in support of treatment; (2) examine and reflect upon the results of randomized controlled trials evaluating the effect of treating OSA or CSA on cardiovascular endpoints and mortality; and (3) illustrate how ADVENT-HF, a randomized controlled trial designed to determine the effect of treating HF patients with either CSA or non-sleepy OSA using a peak-airflow triggered ASV algorithm, could resolve the present clinical equipoise concerning the treatment of one or both forms of SDB.

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**Table. Sleep-Disordered Breathing in Non-Sleepy Patients With Heart Failure and Reduced Ejection Fraction: To Treat or Not to Treat?**

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**Prevalence**

Because sleep apnea in HF is more often than not unaccompanied by daytime sleepiness, clinicians and patients in general are unaware of its presence. Thus, data concerning its prevalence have been derived from epidemiological surveys or observational studies.

Moderate-to-severe SDB, presently quantified as the apnea-hypopnea index (AHI) and considered, by consensus, as ≥15 episodes per hour of sleep of either complete session (apnea) or a reduction in airflow >50% for >10 s accompanied by oxygen desaturation >3–4% (hypopnea), is evident in approximately 50% of chronic HF patients with reduced LVEF (HFrEF) receiving contemporary drug and device therapies8–10 (Figure 1). By contrast, in epidemiological surveys of the North American, European and Asian non-HF adult population of similar age, the prevalence of OSA (complete or partial pharyngeal collapse during sleep) with an AHI ≥15 was approximately 10% in men and 7% in women.11 CSA (complete or partial withdrawal of central respiratory drive to the muscles of respiration during sleep without upper airway obstruction) rarely affects the non-HF population12 and is distinctly uncommon in women with HF and reduced LVEF.3,11,14

Approximately 80% of HF patients with either reduced or preserved LVEF will be exposed to at least 5 apneas or hypopneas per hour; a greater proportion of the latter exhibit OSA.15 Of 784 patients with reduced LVEF requiring hospitalization for HF, enrolled in a prospective observational cohort study, involving sleep studies performed during admission, OSA was detected in 61% and CSA in 21%.16 Thus, SDB in some form and to some degree affects the majority of patients with either acute or chronic HF. This finding, in turn, raises 2 fundamental questions: does SDB exert independent malign effects on the pathophysiology and clinical course of HF, and if so, can these be mitigated if normal breathing patterns are restored?

**Pathophysiology**

**Acute Events**

Normal sleep, with normal breathing, is characterized falls in blood pressure (BP), heart rate (HR), and central sympathetic outflow.17,18 Cardiac metabolic gene expression anticipates and aligns with this circadian variation in myocardial workload.19 Synchrony of these metabolic, temporal and autonomic rhythms, fundamental to normal cardiovascular homeostasis,20 is disrupted profoundly by SDB.

The acute effects and long-term consequences of both OSA and CSA are described in detail in several recent reviews.4,6,21,22 In brief, with apnea, the pulmonary stretch receptor-reflex restraint of central sympathetic outflow ceases. Each inspiratory effort in the face of an occluded upper airway elicits an immediate and profound reduction in intrathoracic pressure, which acutely raises atrial, ventricular, and aortic wall tension and draws venous blood into the right heart. This abrupt generation of negative intrathoracic pressure is a cardiac afterload and remodeling force that is unique to OSA. It is not detected by peripheral BP measurement and not prevented by any conventional HF therapy. The consequent septal shift can compromise stroke volume by reducing LV diastolic filling. When ventricular systolic function is impaired, and hence afterload sensitive, stroke volume and arterial pressure falls,24 eliciting a further, arterial baroreceptor-reflex-mediated, increase in sympathetic vasoconstrictor nerve discharge.25 Progressive reduction, during apnea, in the partial pressure of oxygen and parallel increases in carbon dioxide tension will stimulate peripheral and central chemoreceptor-mediated reflex sympathetic excitation,26 itself augmented in HF.27 Any induction, by hypoxia, of pul-
monary vasoconstriction will increase right ventricular afterload and further reduce LV end-diastolic volume and stroke volume. Simultaneous chamber stretch and hypoxia-induced sympathetic and concurrent vagal firing could trigger atrial arrhythmias. Arousal from sleep defends against asphyxia but elicits a further, centrally-initiated increase in sympathetic nerve firing and withdrawal of vagal tone.

The oscillations in ventilation characteristic of CSA are accompanied by similar autonomic and chemical disturbances but by less variation in intrathoracic pressure. Hence stroke volume tends to rise subtly rather than fall with each central apnea or hypopnea.

OSA and CSA thus differ with respect to etiology but share a common nocturnal autonomic phenotype in which recurring cycles of apnea, hypoxia, hypercapnia and arousal from sleep trigger clusters of intense efferent sympathetic nerve firing, inducing marked surges in BP. These occur temporally when myocardial oxygen supply is diminished and the ventricle is ill-prepared metabolically for any increase in workload. Thus, in susceptible individuals such disturbances could acutely trigger ischemia or arrhythmias and the oxidative stress imposed by recurring cycles of hypoxia and re-oxygenation could induce inflammation and endothelial dysfunction. Importantly, aside from a modest effect of diuretics, likely caused in part by a reduction in peri-pharyngeal edema or pulmonary congestion or of biventricular pacing on the latter stimulus to CSA, contemporary evidence-based drug or device therapies have little or no effect on the obstructive or central events that initiate such pathology.

Long-Term Adaptations

With time, the intermittent transmural wall stress imposed by the combination of these recurring negative intrathoracic pressure loads plus surges in arterial pressure could promote LV hypertrophy. Similarly, chronic vascular exposure to inflammation could accelerate the development of carotid and coronary atherosclerosis. The autonomic disturbances accompanying SDB do not dissipate on awakening: muscle sympathetic burst incidence during wakefulness is increased significantly in patients with OSA or CSA relative to matched controls without SDB, regardless of whether HF is present or absent. These observations suggest the development of “autonomic neuroplasticity”, whereby recurrent hypoxia, peripheral chemoreceptor reflex sensitization or recurrent cortical or brainstem arousal from sleep induce structural or functional changes in peripheral and central networks involved in autonomic cardiovascular regulation.

Prognostic Implications

In individuals with preexisting vulnerability, or associated comorbidities such as hypertension, long-term exposure of the normal ventricle to the intrathoracic and autonomic loads imposed by OSA could promote ventricular remodeling, dilated cardiomyopathy, or premature death. Community-based prospective cohort studies reveal an inverse relationship between the AHI and 10–15-year survival. The Sleep Heart Health Study found men with an AHI ≥30/h were 58% more likely to develop HF than men with an AHI <5/h. Once systolic dysfunction develops, a chronic increase in sympathetic discharge directed at the kidney will stimulate renal sodium retention and systemic congestion.

Before the widespread prescription of β-adrenoceptor blockers to HFrEF patients, in small cohorts moderate-to-severe coexisting CSA was found to independently predict reduced survival. Recent observational studies involving patients receiving optimal contemporary HF therapy have identified a doubling of mortality risk, adjusted for confounding factors, if CSA or OSA are present but untreated, and significantly reduced survival over a mean of 47 months if moderate or severe OSA or CSA is diagnosed. If the etiology of chronic HF is ischemic cardiomyopathy, the presence of untreated CSA or OSA identifies individuals at threefold risk of death over the subsequent 32 months (Figure 2). If HFrEF patients required hospitalization for acute decompensation, post-discharge mortality increased significantly in those with either OSA or CSA.

A potential cause of the premature mortality associated with the presence of SDB in HFrEF may be a greater propensity to malignant ventricular arrhythmias. In a recent meta-analysis, the risk of appropriate implantable-defibrillator therapy was estimated to be 55% greater in patients with SDB than in those without SDB, with similar augmentation in those with OSA or CSA.

Treatment

Observational Studies

Continuous PAP (CPAP), which splints open the upper airway, effectively abolishes OSA in most patients, thus eliminating immediately its adverse mechanical, chemical and autonomic consequences. In a 1-month observational trial, CPAP treatment was accompanied by a significant increase in LVEF that regressed once CPAP was withdrawn. Subsequently, we found shortened survival in HFrEF patients among our ambulatory patients with OSA who declined treatment, as compared with those with only mild or no OSA (P=0.029), but no deaths in those who...
accepted CPAP treatment (P=0.07 vs. untreated OSA). Kasai et al documented a similar benefit but noted that a reduction in risk of death or hospitalization required good adherence to CPAP therapy. Damy et al also reported improved prognosis if SDB was treated rather than left untreated. In HFrEF patients with implanted defibrillators, those treated for CSA plus Cheyne-Stokes respiration (CSR) experienced significantly fewer arrhythmic events than those not treated for CSA or individuals without sleep apnea. Thus, one mechanism for improved survival with treatment may be fewer malign arrhythmias.

Randomized Trials With Surrogate Endpoints

When initially proposed, the concept of a large randomized trial of treating OSA in HFrEF with death or hard cardiovascular endpoints attracted little enthusiasm. The conviction within the sleep medicine community was that individuals with OSA should not be denied, through random assignment, the symptomatic benefit of treatment. Thus, initial clinical trials were small or modest in size and of short duration and evaluated surrogate endpoints only. Our group was the first of several to conduct a randomized clinical trial to evaluate the effects of CPAP in patients with HFrEF and OSA on ventricular systolic function. After 1 month, there was no change in AHI, LVEF, systolic BP or HR in the control group (n=12), whereas in the CPAP-treated group (n=12) the frequency of obstructive apneas fell from 30 to 4 events/h, systolic BP and HR after awakening also were reduced significantly and monotonically increased cardiac efficiency.

Subsequent trials, differing in entry criteria and treatment duration, reported a qualitatively similar effect of CPAP on LVEF. In a more recent trial evaluating myocardial sympathetic nerve function and cardiac energetics, 6–8 weeks of CPAP treatment increased cardiac retention of 11C-hydroxyephedrine, a norepinephrine (NE) analog and marker of myocardial sympathetic nerve function; in those with the most severe OSA, CPAP also improved cardiac efficiency.

Concurrently, investigations and trials involving non-sleepy subjects with OSA (and in one trial with coexisting coronary artery disease) but without HF detected no overall treatment effect on daytime alertness, QOL, neurocognitive function, BP, cardiovascular morbidity, or life expectancy. These observations, plus the demonstration that HFrEF patients with SDB are for the most part not hyper-somnolent, alleviated the sleep medicine community’s concerns and enabled large randomized trials evaluating the effect of treating OSA on mortality and cardiovascular events. Also discovered was that the magnitude of the daytime sleepiness in individuals with HFrEF and OSA correlates inversely to efferent sympathetic nerve firing, a marker of greater HF symptoms and worse prognosis.

Randomized trials of CPAP for HFrEF patients with CSA, generally of 3 months’ duration, conducted by the Bradley group documented in treated patients a 30% relative increase in LVEF, a reduction in mitral regurgitation, a decrease in nighttime urinary NE excretion and daytime plasma NE concentration, and improved QOL. In a randomized trial involving 66 patients with chronic HF (29 with CSA) for a median of 2.2 years, there was a significant relative risk reduction of 81% in the composite endpoint of death and transplantation in those CSA participants who adhered to their CPAP prescription. These investigations led to the Canadian Continuous Positive Airway Pressure of Central Sleep Apnea and Heart Failure trial (CANPAP). Randomized Trials With Mortality and Morbidity Endpoints

CANPAP The CANPAP trial investigators undertook to test the hypothesis that CPAP treatment would lengthen transplant-free survival of HFrEF patients with CSA. A total of 258 participants (mean LVEF 24.5%; AHI 40) with established optimal contemporary medical HF therapy were randomly provided CPAP then followed for a mean of 2 years. In the treated group, relative to control subjects, there were greater reductions in AHI (−1 vs. −2 events/h; P=0.001) and daytime plasma NE concentrations (−1 vs. 0 nmol/L; P=0.009) and greater increases in nocturnal oxygen saturation (1.6% vs. 0.4%; P<0.001), 1-min walk distance (20 vs. 1 m; P=0.016) and LVEF (2.2% vs. 0.4%; P=0.016) but at the trial’s conclusion transplant-free-survival was identical. Though, as a test of the hypothesis that applying conventional CPAP would improve transplant-free survival, the CANPAP trial was neutral and did not support the use of CPAP to extend survival in patients with CSA and HFrEF.

It was noted, however, that 3 months after initiating treatment, the AHI of 43% of subjects assigned CPAP remained above the trial’s entry criterion of 15 events/h. When considering the results of the Coronary Drug Project, Feinstein wrestled with the question of how results of a clinical trial should be interpreted if the intervention’s anticipated efficacy is not achieved. Rather than rejecting the lipid hypothesis, he concluded that because clofibrate prescription did not achieve the cholesterol reduction anticipated in the original trial design, the Coronary Drug Project was unable to test its original hypothesis that lowering lipid levels would prevent myocardial infarction. Thus, one interpretation of the CANPAP study’s neutral results is that because the intervention administered did not achieve the anticipated therapeutic efficacy, they did not refute the hypothesis that suppressing CSA in HFrEF improves transplant-free survival. In a subsequent post-hoc analysis, it was discovered that the transplant-free survival of those with an AHI <15 events/h on treatment was significantly improved relative to the untreated control group (P=0.043).

In contrast to CPAP, ASV administers pressure continuously to maintain upper airway patency, senses hypopneas and apneas, and adjusts the pressure support accordingly using algorithms that target either tidal volume or airflow. ASV is thus capable of suppressing CSA to previous therapeutic options found ASV to be effective in reducing CSA. In HFrEF whose CSA was refractory to CPAP, 3 months' treatment with peak-flow ASV delivered by nasal mask effectively suppressed central apneas, reduced urinary NE excretion and increased LVEF. Thus, the innovation of ASV resolved the issue of efficacy and invigorated enthusi-
asm for large randomized outcome trials treating CSA in HFrEF.

**SAVE** Although not a HF trial, the Sleep Apnea Cardiovascular Endpoints Study (SAVE) is the largest randomized evaluation of CPAP for OSA to date and so its results are pertinent to the present discussion. The object of SAVE was to evaluate the effect of treatment on the occurrence of major cardiovascular events in a cohort with moderate-to-severe OSA and preexisting coronary or cerebrovascular disease. Potential trial participants were identified by home screening with oximetry, nasal pressure recordings, and automated signal analysis. Data were reviewed and confirmed at a core sleep laboratory. Trial entry criteria included age between 45 and 75 years and the detection of ≥2 episodes/h during which oxygen saturation fell by ≥8% from baseline. Important exclusion criteria were an Epworth Sleepiness Scale (≥15) signifying severe daytime sleepiness, severe hypoxemia (oxygen saturation <80% for >10% of the recording time) or a pattern of CSR. The SAVE investigators aspired to recruit 5,000 participants, but after screening 15,325 potential subjects only 2,717 were eligible and enrolled. After a mean follow-up of 3.7 years, data on 2,687 were considered sufficiently robust for analysis. The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, stroke or hospitalization for HF, an acute coronary syndrome, or a transient ischemic attack. CPAP was found to reduce snoring and daytime sleepiness and improve mood and health-related QOL, but the key finding in this study was the absence of any between-group difference with respect to the cumulative event curve for the primary endpoint or for any element of the composite or any other cardiovascular endpoints. Overall, the hazard ratio for CPAP use was 1.10 (95% confidence interval [CI] 0.91–1.32; P=0.34). The investigators concluded that adding CPAP therapy to usual care did not prevent cardiovascular events in patients with moderate-to-severe OSA and established cardiovascular disease.

**SERVE-HF** The Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure (SERVE-HF) trial represents the largest clinical experience to date of treating HFrEF patients with CSA within the context of a randomized clinical trial. Three investigators recruited 1,325 patients stable on contemporary guideline-based therapy, with LVEF ≤45%, New York Heart Association (NYHA) Class III or IV symptoms, or Class II symptoms with a hospital admission in the preceding 2 years, and identified by home polygraphy (and in some in-laboratory polysomnography [PSG]) to have predominately CSA with an AHI ≥15 events/h. Participants were assigned randomly in a 1:1 ratio to add minute volume of ventilation-triggered ASV (mv-ASV) or to continue with medical therapy alone. The former were advised to use the device every night for at least 5h. The primary study endpoint was a composite of death from any cause, cardiac transplantation, implantation of a LV assist device (LVAD), resuscitation after sudden cardiac death, appropriate implanted defibrillator discharge for ventricular arrhythmia, or an unplanned admission for worsening HF.

At recruitment, 69% of subjects reported NYHA Class III symptoms and 30% had NYHA Class 2 symptoms. After the first 3 months, subjects were evaluated only annually. The initial trial design was predicated on the occurrence of 651 events in 1,193 patients, but for logistical reasons recruitment required a longer time frame and involved more participants than initially anticipated. The trial’s Data and Safety Monitoring Committee, which performed 2 interim analyses over the course of 7 years, permitted the trial to continue without interruption.

Over a mean follow-up of 2.6 years, 695 primary events were recorded. Of participants allocated ASV, 60% used the device for a mean of 3 h per night or more over the course of the trial; 29% discontinued ASV. Of those randomized to the control group, 16% adopted at some point some mode of positive-pressure ventilation.

Data published thus far concern the intention-to-treat results of this allocation strategy. There was no difference between those allocated or not allocated mv-ASV with respect to the primary endpoint of all-cause mortality (hazard ratio 1.13, 95% CI, 0.97–1.31; P=0.10), but for those allocated ASV the risks of 2 secondary endpoints, all-cause and cardiovascular death, were increased significantly, with respective hazard ratios of 1.28 (95% CI, 1.06–1.55; P=0.01) and 1.34 (95% CI, 1.09–1.65; P=0.006). Although the effect of appropriate treatment, rather than an allocation strategy, on these endpoints was not reported, the SERVE-HF investigators concluded that the addition of mv-ASV to guideline-based medical therapy did not improve the outcome of HFrEF patients with predominately CSA, had no benefit with respect to HF symptoms or QOL, and increased the risk of cardiovascular death. They emphasized, in addition, that the SERVE-HF findings could not be extrapolated to HFrEF patients with predominantly OSA or to HF patients with preserved LVEF and might not pertain to treatment of CSA with other ASV algorithms.

**CAT-HF** The Cardiovascular Improvements with MV-ASV Therapy in Heart Failure (CAT-HF) trial aimed to determine whether mv-ASV improved cardiovascular outcomes of HF patients hospitalized for acute decompensation and detected by polysomnography to have an AHI ≥15 events/h. At each site, there was a prespecified stratification before randomization on the basis of LVEF (≥45% or ≤45%). Of the 126 patients recruited, 75% were classified as having CSA. The investigators intended to randomize 215 patients, but this trial was terminated when the SERVE-HF trial results were released. At 6 months the average daily adherence to ASV was 2.7 h. There was no between-group difference with respect to the primary endpoint, calculated as a global rank score comprising death, cardiovascular hospitalization, and percent change in 6-min walk distance at 6 months, but a prespecified subgroup analysis of the 24 with HFpEF suggested a positive effect of mv-ASV.

**Do These Reported Trial Results Clarify or Confuse?** Completion of SERVE-HF and SAVE was a remarkable achievement for which the trial investigators and their participating centers should be congratulated. The neutral or negative results of these 2 large clinical trials with cardiovascular endpoints in patients with and without HF suggest en face that SDB in non-sleepy HFrEF patients need not (for OSA) or should not (for CSA) be treated (Table). Can this conclusion be considered definitive?

Concerning OSA, SAVE recruited a non-HF cohort that may have been less susceptible to adverse hemodynamic, hypoxic and autonomic consequences of OSA and was a secondary, rather than primary prevention trial. Apneas were diagnosed by home screening relying on the
detection of desaturation, rather than by formal PSG. There were several important exclusion biases. Individuals with PaO2 <80% for >10% of the recording period or with an ESS >15 were deemed too severe to not treat. The intent, based on the original sample size calculation, was to enroll 5,000 participants; 2,717 were recruited. Of these, the majority (63%) was from China. The investigators acknowledged that many trial centers had little experience with respect to the diagnosis and long-term ambulatory management of SDB. Whether background cardiovascular therapies were optimal is unknown. CPAP adherence was on average only 3.3±2.3h and primarily during the early hours of sleep. Of note, it is towards the end of sleep that rapid eye movement sleep predominates, apneas and hypopneas lengthen, and oxygen desaturation is greatest.73 Greater adherence might have conferred benefit, as suggested by a post-hoc analysis of a randomized trial of 725 Spanish patients that illustrated a reduction in a composite of incident hypertension or cardiovascular events when CPAP was used for ≥4h nightly.49 Indeed, in a prespecified SAVE analysis involving participants who used CPAP ≥4h/night, the hazard ratio for the primary event was reduced by 20% (95% CI 0.60–1.07; P=0.13) and for cerebrovascular events by 46% (0.3–0.9; P=0.02). Thus, with respect to OSA in HFrEF there remains equipoise as to whether effective overnight therapy of OSA in HFpEF will reduce cardiovascular morbidity, hospitalizations, or death.

The SERVE-HF trial publication3 generated animated discussion (and within the sleep-HF community some existential introspection) as to: potential mechanisms for these neutral and in some respects adverse consequences of treatment; whether what transpired during CSA was of any consequence to the failing heart; and indeed whether central apnea was a protective compensatory mechanism in HF that did not oblige suppression.74,80 It was noted that a number of individuals with HFpEF slipped into this trial. In the majority of trial participants it was home polygraphy that was used to diagnose CSA. Because recording time rather than sleep time is used to calculate AHI, the latter likely was underestimated. Reliance on local sites rather than a core laboratory to determine the AHI may have led to inconsistent application of scoring criteria.

Unknown is whether the safety concerns reported indicate an adverse ‘class effect’ implicating all ASV devices or were specific to the technology used in this trial. SERVE-HF participants allocated treatment were provided a first-generation proprietary ASV device with an algorithm for treating CSA based on minute ventilation but no algorithm to address automatically any obstructive events (expiratory airway pressure could be increased manually). Data from device downloads indicated failure to control OSA or CSA or eliminate oxygen desaturation in many trial participants. Indeed, over the course of the trial a greater proportion of the recorded events were obstructive.

Initial default settings for both expiratory PAP (EPAP) and minimum inspiratory pressure support were relatively high (5 and 8 cmH2O, respectively). In prior work, there was an acute increase in cardiac output when HF patients with a pulmonary capillary wedge pressure ≥12 mmHg were exposed to 5 cmH2O of CPAP when awake but an acute drop if this was <12 mmHg.81 Thus, it has been suggested that high administered pressures may have inappropriately reduced cardiac output, particularly in trial participants with low cardiac filling pressures, compromising tissue perfusion and increasing lung-chemoreceptor circulatory delay.80 The SERVE-HF protocol called for use of a full face mask when initiating ASV. During chronic therapy 76% reported as continuing on a full face and 13% on a nasal mask (with 9% unknown). The predominant use of a full face rather than a nasal mask may have compromised adherence, which was, on average, only 3.7 h/night and also encouraged CO2 rebreathing.80 A second hypothesis is that by inducing hyperventilation the mv-ASV algorithm might have created an enhanced metabolic substrate for ventricular arrhythmias.

The principal source of present ambiguity with respect to interpretation and clinical translation of the SERVE-HF observations is that all findings published to date specifically describe results by treatment assignment but do not address the key question of efficacy: the effect of mv-ASV treatment itself and the timing of events with respect to actual ASV use have yet to be reported. Importantly, of those allocated ASV, 29% abandoned the therapy and of those not so allocated, 16% adopted some form of positive-pressure ventilation over the course of the trial.

A subsequent analysis sought to identify those patients at increased risk for hospital admission for HF, cardiovascular death without previous hospital admission for worsening HF or life-saving intervention (cardiac transplantation; LVAD implantation, resuscitation after sudden cardiac death, appropriate implanted defibrillator discharge for ventricular arrhythmia), or cardiovascular death after a life-saving intervention.82 There was no overall difference in the cumulative incidence of hospitalization in those allocated mv-ASV vs. those who were not but, more of the latter 2 categories of events were tabulated in those assigned treatment. Participants allocated mv-ASV with LVEF <30% or with a high CSR burden were identified as those at greatest risk for cardiac death or hospital admission for worsening HF. Such patients potentially are the most unstable medically and least likely to adhere to nightly positive-pressure therapy. In contrast, the cumulative incidence of hospital admission appeared reduced relative to participants allocated to the control arm if LVEF was >36% or if the CSR burden was low.

**ADVENT-HF: A Pivotal HF Trial**

The question as to whether the trajectory of HF can be improved by effective treatment of either OSA or CSA is therefore presently unanswered. ADVENT-HF (a multicenter, randomized study to assess the effects of ASV on survival and frequency of cardiovascular hospital admissions in patients with HF and sleep apnea) is a randomized, parallel-group, open-label trial engaging centers with precertified sleep and echocardiography laboratories located in Canada, the USA, Brazil, Spain, Germany, Italy, England, France and Japan, designed to assess the effect of treating SDB with a peak-airflow triggered ASV (pf-ASV) algorithm on morbidity and mortality of patients with HFpEF.83 The results of observational and short-term small-sized randomized trials with surrogate endpoints published by 2009, when ADVENT-HF was conceived, signaled the potential for reduced cardiovascular events and improved survival if HFpEF patients were provided effective treatment of both sleep-related breathing disorders. It was generally acknowledged, however, that clinically-indicated treatment should not be denied those patients describing excessive daytime sleepiness. Underway when the SAVE and SERVE-HF trial results were reported,
ADVENT-HF now may be the sole active trial capable of resolving this continuing clinical equipoise.

ADVENT-HF patients with chronic HFrEF (LVEF ≤45% by echocardiography, validated by the trial’s core laboratory) and sleep apnea (AHI ≥15 by overnight PSG, scored by the trial’s core sleep research laboratory) who are stable on optimal contemporary medical therapy, are stratified before randomization as having either predominantly OSA (≥50% of sleep-related events obstructive, but without excessive daytime sleepiness: Epworth Scale ≤10) or CSA (≥50% of events central). Trial participants are then allocated on a 1:1 basis to continue on optimal therapy alone or optimal therapy plus pf-ASV applied via a nasal interface with default expiratory and minimum inspiratory pressure support settings of 4 and 0 cmH₂O respectively. A sleep study is performed after 1 month. If the subject’s AHI remains >15 events/h an ASV re-titration PSG is scheduled. If the AHI cannot then be reduced below 15, ASV is withdrawn. Participants are followed at 3–6 monthly intervals (Figure 3) for up to 5 years.

The primary trial endpoint is a composite of death, transplantation, LVAD implantation, cardiovascular hospitalization, and out of hospital appropriate defibrillator discharge or new onset of atrial fibrillation with initiation of anticoagulation. The trial design calls for a total of 540 adjudicated trial events and a recruitment target of 860 participants. To date, 445 participants have been recruited from 42 sites in 9 countries. Of these, 60% describe NYHA Class II and 22% describe NYHA Class III HF symptoms. As anticipated from epidemiological prevalence data, the majority has OSA. Of those randomized to pf-ASV 78% continue to use a nasal mask. Average 1-year adherence to ASV thus far has been 4.8 h/night. The trial’s Data and Safety Monitoring Board (DSMB) meets every 6 months to review all reported serious adverse events and has examined these separately for the OSA and CSA cohorts on 3 occasions since the initial SERVE-HF trial announcement. The DSMB has expressed no safety concerns for either CSA or OSA subjects to date and has recommended continued enrolment of both as per protocol.

Important distinctions between SERVE-HF and ADVENT-HF include the following: enrolment of medically stable HFrEF patients with less severe symptoms, on average, with non-sleepy OSA in addition to CSA; laboratory-based PSG at enrollment and follow-up; prospective echocardiographic and sleep studies analyzed uniformly by core laboratories; application of a peak-airflow, rather than a minute-ventilation algorithm shown to suppress OSA in addition to CSA; lower expiratory and inspiratory default pressures; predominant use of a nasal rather than full face mask; nightly adherence to pf-ASV thus far that is 1.1 hour longer than adherence in SERVE-HF; and more frequent clinical follow-up and DSMB safety review.

Thus, ADVENT-HF is a unique and pivotal HF trial.
devised with sufficient power to resolve several important clinical questions; inform whether the SERVE-HF results predict an adverse class effect of ASV or are specific to a particular device and mode of delivery; yield novel data concerning the effects of treating HFrEF patients with asymptomatic OSA, whose intrathoracic structures are exposed to more negative pressure; document the natural history of OSA in HFrEF and its risk of progression to CSA; and help guide future therapy of both CSA and non-sleepy OSA in HF. ADVENT-HF has already yielded novel information concerning relationships between OSA, CSA and left atrial phasic function.84

Resolving Present Equipoise

Symptomatic HF, with its high rates of hospitalization, morbidity and mortality, continues to afflict a large swathe of the adult population despite impressive advances in evidence-based drug and device therapy.85–86 If unaddressed, the hemodynamic, autonomic, biochemical and inflammatory effects and after-effects of SDB add to this disease burden and foreshorten survival. However, there is as yet no evidence from large randomized clinical trials that either CPAP or ASV will reduce the risk of a cardiovascular event or prolong life. Thus, clinicians and patients are generally ambivalent as to the utility of either detecting or treating SDB in HF despite the availability of effective therapy for both OSA and CSA.

The 2 most recent large, event-driven clinical trials that sought to determine whether abolition or attenuation of SDB using non-invasive ventilation strategies would improve survival and reduce cardiovascular and cerebrovascular event rates bring to this clinical question neither closure nor clarity. CPAP prescription did not prevent events in the SAVE trial, involving a non-HF and primarily Asian population with moderate-to-severe OSA and established cardiovascular or cerebrovascular disease.9 Intriguingly, there was a signal, suggesting reduced cerebrovascular event rates, in those who used this intervention the most. Importantly, this trial excluded individuals perhaps most likely to benefit from the abolition of OSA, namely those with PaO2 <80% for >10% of the night-time recording period. The cardiovascular consequences of abolishing OSA in HFrEF have yet to be evaluated in an adequately powered randomized trial.

The SERVE-HF data published thus far describe only the effect of random assignment of niv-ASV with high default pressures to HFrEF patients with CSA. There was no between-group difference with respect to the primary endpoint, but those assigned ASV experienced heightened all-cause and cardiovascular mortality rates, raising safety as well as efficacy concerns.3 Importantly, the effect on these endpoints of effective treatment of CSA, as opposed to this allocation strategy, has yet to be reported.

Consequently, clinical equipoise persists as to whether treatment of SDB should be incorporated into contemporary HF practice. Resolving this present dilemma will require a commitment by cardiologists to support and enroll eligible HFrEF patients with coexisting OSA or CSA into adequately powered randomized trials evaluating other modes of pressure support, such as ADVENT-HF; emerging strategies such as hypoglossal87 or phrenic nerve stimulation;88 alternate targets, such as the magnitude and duration of oxygen desaturation during sleep;89 or involving different HF cohorts that also have high car-

diovascular event rates, such as those with preserved LVEF.

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