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EDITORIAL

Treatment of central sleep apnea in patients with heart failure: Now and future

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Abstract

Heart failure (HF) is known to be associated with sleep-disordered breathing (SDB). In addition to disturbing patients' sleep, SDB is also associated with a deterioration in the cardiac function and an increased mortality and morbidity. Central sleep apnea (CSA), typically characterized by Cheyne-Stokes breathing (CSB), is increasingly found in patients with HF compared to the general population. An important pathogenetic factor of CSA seen in HF patients is an instability in the control of the respiratory system, characterized by both hypocapnia and increased chemosensitivity. Sympathetic overactivation, pulmonary congestion and increased chemosensitivity associated with HF stimulate the pulmonary vagal irritant receptor, resulting in chronic hyperventilation and hypocapnia. Additionally, the repetitive apnea and arousal cycles induce cyclic sympathetic activation, which may worsen the cardiac prognosis. Correcting CSB may improve both patient's quality of life and HF syndrome itself. However, a treatment for HF in patients also experiencing CSA is yet to be found. In fact, conflicting results from numerous clinical studies investigating sleep apnea with HF guide to a troubling question, that is whether (or not) sleep apnea should be treated in patients with HF? This editorial attempts to both collect the current evidence about randomized control trials investigating CSA in patients with HF and highlight the effect of specific CSA treatments on cardiovascular endpoints.

Key words: Central sleep apnea; Obstructive sleep apnea; Heart failure; Positive airway pressure; Adaptive servo-ventilation

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Core tip: Central sleep apnea (CSA) is commonly comorbid with heart failure (HF). In fact, sleep apnea is associated with a worsening of the cardiac prognosis and an increasing mortality. However, treatment for CSA remains to be elucidated due to the numerous conflicting results of clinical trials. This review attempts to both clarify the current evidence from randomized control trials investigating CSA in patients with HF and highlight the effect of specific CSA treatments on cardiovascular endpoints.

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INTRODUCTION

Sleep apnea is one of the common complications in patients with heart failure (HF), with reported prevalence rates of 40%-60%[1]. There are two types of sleep apnea, namely obstructive sleep apnea (OSA) and central sleep apnea (CSA). OSA is caused by the partial or complete obstruction of the upper airway associated with an attenuation of the upper airway dilator muscle tone during sleep, which is a form of sleep apnea in the general population. In contrast, 25%-40% of patients with HF also experience CSA, with an equal or higher incidence than OSA[1].

CSA seems to be triggered by the hypocapnia associated with pulmonary congestion, by the enhanced chemosensitivity and by the delayed circulation associated with HF itself[2]. Other mechanisms, including overnight fluid shift from the legs to the upper body, may also play a role in the pathogenesis of CSA[3]. Repetitive arousals and episodes of intermittent hypoxia and their associated sympathetic overactivation may lead to further deterioration of the cardiac function, leading to fatal arrhythmia, therefore to poor prognosis. In addition, hemodynamic alterations, especially when occurring during hyperpnea following CSA, may also contribute to the deterioration of the cardiac function[4]. In contrast, considering that alterations in respiration associated with CSA (*i.e.*, repetitive episodes of central apnea and subsequent hyperpnea) were hypothesized to help impaired cardiac pumps and to work as a compensatory mechanism for severe HF, and considering that CSA suppression by either continuous positive airway pressure (CPAP) or adaptive servo-ventilation (ASV) failed to show long-term beneficial effects in clinical trials with patients with both HF and CSA, whether CSA is just an epiphenomenon of HF or a causality of HF is still under debate[5,6].

HF treatment (and its optimization) including beta blockers, angiotensin converting enzyme inhibitors, cardiac resynchronization therapy, left ventricular assist device, cardiac rehabilitation, and heart transplantation are able to alleviate CSA[1]. When CSA remained even under guideline-directed medication towards HF, positive airway pressure (PAP) therapy such as CPAP and ASV will be considered. Numerous observational and short-term randomized controlled trials reported these modalities to have positive effects, showing both an evident alleviation of CSA and a mild improvement of the cardiac function[1]. However, the long-term effects of specific CSA treatments on cardiovascular outcomes remain unclear.

This editorial aims at highlighting the effect of specific CSA treatments on some cardiovascular endpoints in patients with HF by summarizing the results of RCT.

SHORT-TERM EFFICACY OF THE CSA TREATMENT IN HF

In the 1990s and early 2000s, various small-scale randomized control studies identified an effect of the CSA treatment by CPAP on cardiovascular endpoints in patients with HF. In addition, several short-term (0-3 mo) studies reported that CSA treatment by CPAP caused a relative increase (30%) in the left ventricular ejection fraction (LVEF), a reduction in the mitral regurgitation, a decrease in both the overnight urinary norepinephrine (NE) excretion and the daytime NE concentration and an improved quality of life in patients with HF (Table 1)[7-9].

In contrast to CPAP, ASV automatically selects the appropriate support pressure based on the patient's ventilation volume, which is capable of suppressing CSA. In fact, Kasai *et al* performed a short-term analysis and showed that ASV is more capable

Table 1 Short term randomized control trial investigating the effects of continuous positive airway pressure treatment on cardiac functions in heart failure patients with central sleep apnea

Author, year	Duration	*n*	Design	Findings
Naughton, 1995[7]	1 mo	25	no-CSA *vs* CPAP *vs* CSA-control	Urine and plasma NE↓, LVEF↑, NYHA class↓
Naughton, 1995[8]	3 mo	29	no-CSA *vs* CPAP *vs* CSA-control	LVEF↑, improve symptoms
Granton, 1996[30]	3 mo	17	CPAP *vs* CSA-control	MIP↑, LVEF↑, improve symptoms
Tkacova, 1997[9]	3 mo	17	CPAP *vs* CSA-control	LVEF↑, Mitral regurgitant fraction↓, plasma ANP↓

RCT: Randomized control trial; CPAP: Continuous positive airway pressure; HF: Heart failure; CSA: Central sleep apnea; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; NE: Norepinephrine; MIP: Maximal inspiratory pressure; ANP: Atrial natriuretic peptide.

of suppressing CSA and that it improves the cardiac function when compared to CPAP[10]. In addition, Philippe *et al* reported an improvement in patients' quality of life and an increased compliance with ASV when compared to the CPAP treatment group in patients with stable HF (Table 2)[11].

Considering that these investigations suggested beneficial short-term effects on surrogate cardiovascular endpoints, longer follow-up data related to the effects of specific CSA treatments on cardiovascular outcomes are of great interest.

LONG-TERM EFFICACY OF THE CSA TREATMENT IN HF

Small scale RCT by Sin and colleagues (HFrEF, CPAP)

Sin and colleagues conducted a small scale RCT with 66 patients with HF together with or without CSA to investigate the effect of the CPAP therapy. They documented CPAP to both improve the LVEF after 3 mo and to show a trend towards a reduced event rate (P = 0.059, median follow-up period 2.2 years). In addition, CPAP significantly decreased the composite endpoints of death and cardiac transplantation in a subgroup of patients with CSA who were compliant with CPAP (Table 3)[12].

CANPAP (HFrEF, CPAP)

The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP) was a randomized, placebo-controlled clinical trial that involved 258 patients with HF with reduced EF (HFrEF) and CSA. All participants [mean LVEF: 24.5%; apnea-hypopnea index (AHI): 40], after being stabilized to the optimal medical therapy, were randomly allocated to either the control group, that continued the optimal HF therapy, or to the treatment group, that received the CPAP treatment in addition to the optimal HF therapy. They were finally followed for a median of 2.2 years. The treatment group experienced both a greater reduction in AHI (-21 *vs* -2 events/h; P = 0.002) and in daytime plasma NE concentrations (-1 *vs* 0 nmol/L; P = 0.009) and a greater increase in nocturnal oxygen saturation (1.6% *vs* 0.4%; P < 0.001) and LVEF (2.2% *vs* 0.4%; P = 0.016) when compared to the control group. However, the primary outcome related to the transplant-free survival was neutral between the two groups[13]. In contrast, post-hoc analysis of the data from the CANPAP trial showed that patients whose AHI was suppressed lower than 15 events/h by CPAP had a significant improvement in transplant-free survival and in LVEF when compared to the untreated control group (P = 0.043) (Table 3)[14].

These findings suggested that a better suppression of CSA in patients with HF may improve their cardiac outcomes, which increased the clinical demand of ASV (Table 3).

SERVE-HF (HFrEF, ASV)

The Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure (SERVE-HF) trial was the largest RCT that investigated the effect of the CSA treatment in patients with HFrEF. It involved 1325 patients with predominant CSA and an AHI higher than 15 events/h measured by home polygraphy. Participants were randomly allocated to either the minute volume of ventilation-triggered ASV (mv-ASV) group or to the medical therapy group. The primary endpoint was the composite of death from any cause, including cardiac transplantation, LV assist device (LVAD) implantation, resuscitation after sudden cardiac death, appropriate implanted defibrillator discharge for ventricular arrhythmia, or unplanted admission for worsening HF. Contrary to the expectations, the mv-ASV did not reduce the primary combined

Table 2 Short term randomized control trial investigating the effects of adaptive servo ventilation treatment on cardiac functions in heart failure patients with central sleep apnea

Author, year	Duration	*n*	Design	Findings
Pepperell, 2003[31]	1 mo	30	Therapeutic mv-ASV *vs* subtherapeutic mv-ASV	Plasma BNP↓, urinary metadrenaline↓
Philippe, 2006[11]	6 mo	25	CPAP *vs* mv-ASV	Significant increase in LVEF and improvement in QOL in ASV group
Fietze, 2008[32]	1.5 mo	37	bi-level PAP with standard S/T mode *vs* mv-ASV mode	LVEF increased more in the bi-level PAP group. Daytime blood pressure and heart rate did not change
Kasai, 2013[10]	3 mo	23	CPAP *vs* pf-ASV	LVEF increased more in the ASV group
O'Connor, 2017[21] (CAT-HF trial)[1]	6 mo	126	SDB-control *vs* mv-ASV	No significant cardiac improvement found

[1]CAT-HF trial includes patients with predominant OSA in addition to predominant CSA (> 70% patients had predominant CSA). RCT: Randomized control trial; ASV: Adaptive servo ventilation; CPAP: Continuous positive airway pressure; HF: Heart failure; CSA: Central sleep apnea; OSA: Obstructive sleep apnea; LVEF: Left ventricular ejection fraction; QOL: Quality of life; S/T mode: Spontaneous/timed mode; SDB: Sleep disordered breathing; mv-ASV: Minute volume of ventilation-targeted ASV; pf-ASV: Peak-airflow triggered ASV.

endpoints [hazard ratio (HR) = 1.13, 95%CI: 0.97-1.31; P = 0.10]; however, most importantly, the mv-ASV group showed a significantly increased risk of "all-causes" death (HR = 1.28, 95%CI: 1.06-1.55; P = 0.01) and cardiovascular mortality (HR = 1.34, 95%%CI: 1.09-1.65; P = 0.006) compared to the control group, even though they only represent secondary endpoints (Table 4)[15].

Various arguments were made to explain these unexpected results, including the relatively low usage of mv-ASV, which makes it difficult to interpret the results in an intention-to-treat analysis, and the concerns regarding the first-generation ASV device used in this study, which may have applied an excessive pressure that may reduce cardiac output in some instances.

As noted above, CSA was thought to be detrimental due to intermittent hypoxemia, arousals, and autonomic dysregulation. However, in the largest community-based study, CSA with non-HF conditions did not increase mortality, indicating that CSA itself is not detrimental[16]. Moreover, unexpected findings from the SERVE-HF trial renew the hypothesis stating that CSA may be a compensatory mechanism for HF because alterations in hyperventilation associated with CSA may both help impaired cardiac pumps and work as a compensatory mechanism for severe HF[5], such as increasing end-expiratory lung volume[17], intrinsic positive airway pressure[18], assistance of stroke volume[19], and attenuation of hypercapnic acidosis[20]. Although these effects are seen periodically during CSA, CPAP may provide the similar effects continuously. Nevertheless, although we should be aware that the results of the SERVE-HF trial cannot be applied to patients with different HF statuses, such as HF with preserved EF or predominant OSA, they did affect other RCTs and guidelines dealing with the treatment of patients with HFrEF with predominant CSA. In addition, the trial provided an insight into considering the mechanism underlying each individual HF with CSA, which will be determined in further investigations.

CAT-HF (HFpEF and HFrEF, mv-ASV)

The Cardiovascular Improvements with the mv-ASV Therapy in Heart Failure (CAT-HF) trial was one of the RCTs that was heavily affected by the findings reported by the SERVE-HF trial. This trial attempted to investigate the effects of the mv-ASV on relatively short-term cardiovascular outcomes (*i.e.*, 6 mo) in hospitalized patients with acute decompensated HF and an AHI higher than 15 events/h measured by the hospital polygraphy. The trial was terminated when the SERVE-HF trial results were reported. Interim analysis at the time of termination reported that the mv-ASV showed an absence of between-group difference in terms of the primary outcome (Table 2). However, a prespecified subgroup analysis showed that the mv-ASV can improve disease prognosis in patients with HFpEF[21].

ADVENT-HF (HFrEF, ASV)

Although the negative impact of the SERVE-HF led to the termination of the CAT-HF, further investigations on the effects of sleep apnea treatment by ASV on long-term clinical outcomes are underway. A multi-center RCT assessed the Effects of ASV on

Table 3 Long term randomized control trials investigating the effects of continuous positive airway pressure treatment on cardiovascular outcomes in heart failure patients with central sleep apnea

Author, year	Duration	*n*	Design	Findings
Sin, 2000[12]	2.2 yr (median)	66	No-CSA-control *vs* no-CSA-CPAP *vs* CSA-CPAP *vs* CSA-control	Mortality-cardiac transplantation rate↓ who complied with CPAP, LVEF↑ in CSA-CPAP group
Bradley, 2005[13] (CANPAP trial)	2 yr (mean)	258	CSA-control *vs* CPAP	Plasma NE↓, LVEF↑, distance in a 6-min walk test↑
Arzt, 2007[14] (Post hoc analysis of CANPAP trial)	23 mo (mean)	210	CSA-control *vs* CPAP	Patients whose AHI < 15 events/h by CPAP had significantly improved transplant-free survival and greater improvement in LVEF compared with control

RCT: Randomized control trial; CPAP: Continuous positive airway pressure; HF: Heart failure; CSA: Central sleep apnea; LVEF: Left ventricular ejection fraction; NE: Norepinephrine; AHI: Apnea hypopnea index.

both Survival and Frequency of Hospital Admissions of Patients with Heart Failure and Sleep Apnea (ADVENT-HF) and investigated the effects of the sleep apnea treatment by a peak-airflow-triggered ASV (pf-ASV) on long-term cardiovascular outcomes in patients with HFrEF. In the ADVENT-HF, patients with HFrEF (LVEF 45% or less) and sleep apnea with an AHI of 15 events/h or higher (either predominant OSA or predominant CSA) were enrolled. The primary 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.

What really distinguishes this study from the SERVE-HF trial is the enrolment and titration of patients using attended, overnight polysomnography. Each sleep study is analyzed at a central lab both to optimize the pressure settings and to ensure the control of sleep apnea. In order to continue the study, its protocol requires both the confirmation of the efficacy of ASV by formal polysomnography and the cessation of active treatment when CSA is not suppressed. In addition, it applies a different device through the nasal interface, providing lower pressure and presumably improving the compliance compared to full-face masks[22,23]. A unique feature of this trial is that either patients with predominant OSA or predominant CSA are enrolled. Despite their differing pathologies, patients with HF can have both types of sleep apnea, and the predominant type can shift from obstructive to central or vice versa[2,24]. OSA may induce CSA with a fall in arterial partial pressure of carbon dioxide and an increase in circulation time, in association with overnight declines in stroke volume and cardiac output[25]. In addition, CSA may lead to upper airway collapses due to inactivation of the upper airway dilatation muscles, in association with attenuation of central respiratory drive, or due to activation of the upper airway constrictor muscles[26]. Thus, in a patient with HF, CSA and OSA may coexist, and effects of treatments for either CSA and OSA, such as ASV on long-term outcome, are quite important. So far, the trial's Data and Safety Monitoring Board (DSMB) did not express ant safety concerns for either CSA or OSA subjects and recommended the continued enrolment of both as per protocol. The ADVENT-HF trial will be a pivotal trial to answer our clinical question, that is whether to treat (or not) sleep apnea in patients with HFrEF.

PERSPECTIVE

Treatment of OSA by CPAP did not show beneficial effects on long-term clinical outcomes in patients with cardiovascular disease. This is probably related to the poor adherence to the CPAP, such as CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea (SAVE) trial, where effects of OSA treatment with CPAP in patients with coronary and/or cerebrovascular disease and with moderate-to-severe OSA were investigated[27]. In addition, in patients with HF, there are no RCTs where effects of OSA treatments with CPAP on long-term clinical outcomes are investigated. Thus, treatment of OSA aiming for secondary prevention of cardiovascular disease remains unelucidated. Similarly, treatment of CSA aiming for the secondary prevention of HF is under debate. In particular, considering the negative results reported by the SERVE-HF trial[15], caution should be maintained when treating

Table 4 Long term randomized control trial investigating the effects of adaptive servo ventilation treatment on cardiovascular outcomes in heart failure patients with central sleep apnea

Author, year	Duration	*n*	Design	Findings
Cowie, 2015[15] (SERVE-HF trial)	31 mo (median)	1325	mv-ASV *vs* CSA-control	All-cause and cardiovascular mortality were both increased in ASV group

RCT: Randomized control trial; ASV: Adaptive servo ventilation; HF: Heart failure; CSA: Central sleep apnea; mv-ASV: Minute volume of ventilation-targeted ASV.

patients with CSA with a LVEF lower than 45%.

As presented in a post hoc analysis from the CANPAP trial, CPAP satisfactorily suppressed more than half of the events in patients with CSA and improved their cardiac prognosis[14]. Up to date, it would be tolerable to prescribe CPAP for CSA in patients with HFrEF and to consider their upgrading to ASV, case by case, when CPAP proves insufficient. In fact, previous short-term studies provided evidence of the positive effects of the ASV treatment for the improvement of the cardiac function or as a biomarker in patients with HF and CSA[26,28], and patients with CSA and HFpEF[29]. Although further investigation is required, the use of ASV should not be abandoned and determining which patients are appropriate and responsive to the ASV treatment should be a priority instead.

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