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Winfried Randerath, Oana Deleanu, Sofia Schiza, Jean-Louis Pepin. Central sleep apnoea and periodic breathing in heart failure: prognostic significance and treatment options. *European Respiratory Review*, 2019, 28 (153), pp.190084. 10.1183/16000617.0084-2019 . hal-03680738

HAL Id: hal-03680738

<https://hal.science/hal-03680738v1>

Submitted on 3 Jun 2022

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Central sleep apnoea and periodic breathing in heart failure: prognostic significance and treatment options

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CSA in heart failure impairs outcome, but optimal treatment is intensively debated. Increasing evidence may guide to differentiation and individualised therapy of phenotypes according to differences in pathophysiology and treatment response. <http://bit.ly/2kvTepX>

Cite this article as: Randerath W, Deleanu OC, Schiza S, *et al.* Central sleep apnoea and periodic breathing in heart failure: prognostic significance and treatment options. *Eur Respir Rev* 2019; 28: 190084 [<https://doi.org/10.1183/16000617.0084-2019>].

ABSTRACT Central sleep apnoea (CSA) including periodic breathing is prevalent in more than one-third of patients with heart failure and is highly and independently associated with poor outcomes. Optimal treatment is still debated and well-conducted studies regarding efficacy and impact on outcomes of available treatment options are limited, particularly in cardiac failure with preserved ejection fraction. While continuous positive airway pressure and oxygen reduce breathing disturbances by 50%, adaptive servoventilation (ASV) normalises breathing disturbances by controlling the underlying mechanism of CSA. Results are contradictory regarding impact of ASV on hard outcomes. Cohorts and registry studies show survival improvement under ASV, while secondary analyses of the large SERVE-HF randomised trial showed an excess mortality in cardiac failure with reduced ejection fraction. The current priority is to understand which phenotypes of cardiac failure patients may benefit from treatment guiding individualised and personalised management.

Introduction

Breathing disturbances during sleep are characterised by three main pathophysiological components: obstruction of the upper airways, disturbances of respiratory drive and reduction of tidal volume. Although these components are most clearly represented in the protagonist diseases of obstructive sleep apnoea (OSA), central sleep apnoea (CSA) and hyperventilation, they can variably contribute to the specific clinical situation of individual patients. The analysis of the underlying pathophysiology may guide the therapeutic approach (figure 1). Diagnosis and optimal treatment of the central component is a major challenge due to the complexity of comorbid diseases and the prognostic impact of therapeutic options.

CSA and periodic breathing: definition and characterisation

Chronic heart failure (CHF) with reduced (HFrEF) and preserved (HFpEF) left ventricular ejection fraction (LVEF) is a major public health problem. Its prevalence is estimated to be 1–2% of the adult

Provenance: Commissioned article, peer reviewed

Received: 09 July 2019 | Accepted after revision: 30 Aug 2019

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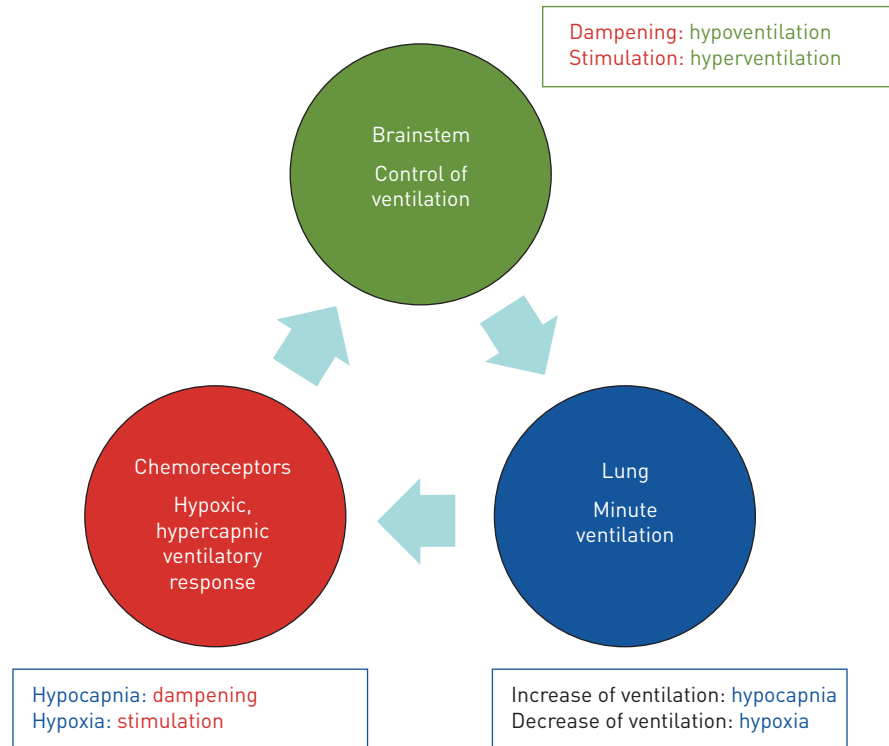


FIGURE 1 Illustration of the pathophysiological approach to treatment of sleep disordered breathing. Continuous positive airway pressure or expiratory positive airway pressure stabilise the obstructive component of the upper airways; variable pressure support or mandatory breaths counterbalance the overshoot and undershoot of ventilation due to brainstem disturbances; and reduction in tidal volume and minute ventilation require mechanical ventilation.

population in Western countries and increases with age [1]. Studies consistently demonstrated that $\geq 50\%$ of CHF patients present with OSA and/or CSA, including its subtype labelled “periodic breathing”. Data show a prevalence of 25–40% of periodic breathing in patients with HF_rEF, increasing with male sex, the severity of left ventricular impairment and the presence of atrial fibrillation. The European Respiratory Society (ERS) task force on CSA recommends replacing the historical term “Cheyne–Stokes respiration” with “periodic breathing in heart failure” [2].

The SchlaHF registry including >6500 HF_rEF patients reported a strong association between sleep disordered breathing (SDB), either OSA or CSA and body mass index. Age >60 years, atrial fibrillation, reduced LVEF and resting arterial carbon dioxide tension (P_{aCO_2}) <38 mmHg during wakefulness were the most important risk factors for CSA/periodic breathing as compared to OSA [3, 4]. CSA has been demonstrated to be independently associated with worse outcomes in patients with HF_rEF [2, 5, 6] and has a higher socioeconomic burden. The higher mortality rate in CHF with periodic breathing may be related to intermittent hypoxia, arousals, increased sympathetic activity and mechanical impact on the heart of intrathoracic pressure swings. As improvement of prognosis in CHF was plateauing, there was a growing interest to include SDB as an actionable risk factor to be targeted by positive airway pressure therapies. A prerequisite was the understanding of the pathophysiology of CSA/periodic breathing to anticipate the effects of currently available therapies [7, 8].

Pathophysiology

Heart failure is differentiated based on the LVEF. Current guidelines separate HF_rEF (<40%) from ejection fraction in the midrange (40–49%) and HF_pEF ($\geq 50\%$). Previous studies used a dichotomous separation of reduced and preserved ejection fraction. HF_pEF patients generally do not present with dilated left ventricle, but increased wall thickness and increased left atrial size as a sign of increased filling pressure. Impaired left ventricular filling or suction capacity is a likely cause of heart failure in these patients (diastolic heart failure). HF_rEF presents with dilation of the left ventricle. All phenotypes are characterised by symptoms of breathlessness, peripheral oedema and fatigue due to pulmonary congestion and reduced output. There is a bidirectional relationship between heart failure and SDB. SDB may exaggerate myocardial remodelling and function due to repetitive hypoxia, arousals and sympathetic activation [1].

Dysregulation of control of breathing plays the major role in the pathophysiology of CSA, with well-established differences compared to healthy individuals and heart failure patients free of SDB (figure 2). The term “loop gain” is used to describe the adaptation of ventilation to any disturbance reflecting the reactivity of the ventilatory system including the lungs (plant gain), the peripheral chemoreceptors (feedback gain) and the central chemoreceptors at the brainstem (controller gain). A high loop gain producing overshoot and undershoot of ventilation in responses to disturbances indicates instability of the system associated with overresponsiveness of the chemoreceptors and increased brainstem activity. While a high loop gain is typical in periodic breathing, a lower loop gain represents a dampening of the ventilatory system in hypoventilation disorders. A typical polysomnographic pattern of a high loop gain is represented by long-lasting apnoeic episodes followed by abrupt and sharp hyperventilation. SDB in the context of a low loop gain depicts prominent hypopnoeas or short apnoeas with limited hyperventilation ending the events [7].

A majority of CSA patients presents with chronic hyperventilation characterised by normocapnia or hypocapnia (increased plant gain). Pulmonary congestion in CHF activates vagal J-receptors in lung parenchyma, which in turn stimulate brainstem activity and generate hyperventilation [7]. The hypercapnic ventilatory responses, *i.e.* changes in minute ventilation to variations of carbon dioxide (CO_2) are elevated (increased feedback gain). Such an excessive chemosensitivity triggers ventilation instability with exaggerated hyperventilation in reaction to mild increases in CO_2 and hypoventilation or apnoeas in response to hypercapnia. These mechanisms are summarised by the typical polysomnographic pattern of overshoot and undershoot of ventilation, the crescendo–decrescendo variations in tidal volume and respiratory effort. The instability and increased reactivity of the control of ventilation is perpetuating a vicious circle: hyperventilation (overshoot) reduces the actual CO_2 tension below the apnoeic threshold, which dampens the neural drive and induces central apnoeas. Central apnoeas are associated with a rise in P_{aCO_2} and a decrease in arterial oxygen tension, stimulating ventilation and creating the next overshoot. Experimental data from animal studies and in clinical setting demonstrated that a prolonged circulation time between the alveoli and the brainstem amplifies this vicious circle. However, there is insufficient evidence to translate these data to humans [9].

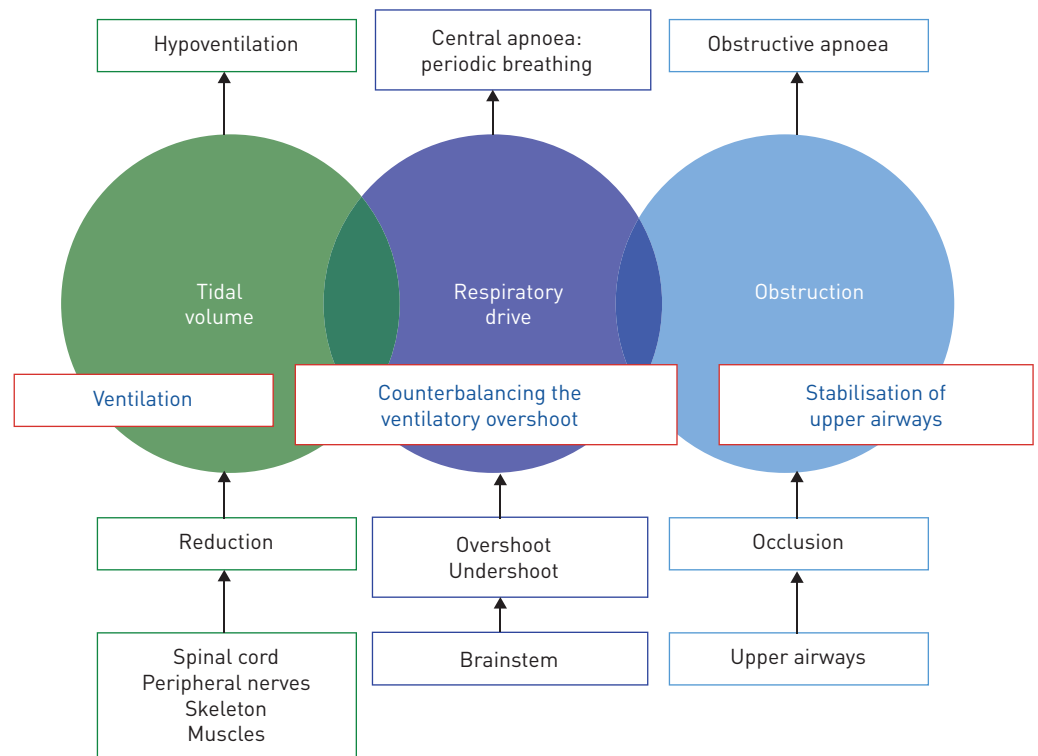


FIGURE 2 The respiratory system is composed of three components, which have been described as a loop gain. Imbalance of the loop gain may lead to a vicious circle of overshoot and undershoot of the ventilation: any inadequate increase of the ventilation induces hypocapnia; hypocapnia dampens the carbon dioxide-sensitive chemoreceptors, leading to a dampening of the inspiratory impulses of the brain stem. As a consequence, minute ventilation [generated from the plant gain] is reduced, leading to hypoxia; hypoxia stimulates the chemoreceptors and consecutively respiratory drive.

At the end stages of the disease, periodic breathing is not limited to sleep, but can also appear at rest or during exercise in advanced CHF [10–15]. Recently, it has been discussed that periodic breathing (although a marker of severity and poor prognosis) may represent a compensatory mechanism to limit the deleterious effects of heart failure. Periodic breathing-related large intrathoracic pressure swings, elevations of end-expiratory lung volume (EELV) and increased vagal tone from intrinsic positive end-expiratory airway pressure, improved ventilation/perfusion matching and reduced work of breathing might improve heart mechanics and stabilise left ventricular function [16]. However, this hypothesis is mainly supported by mathematical models and experimental studies in small sample size studies in healthy humans, making the translation to CHF patients difficult [17–21]. Moreover, it can be argued that this hypothesis rather supports the application of positive airway pressure therapies expected to have similar effects on lung volumes, cardiac mechanics and intrathoracic pressures.

Challenges in managing CSA/periodic breathing in CHF with reduced ejection fraction

The potential contribution of CSA/periodic breathing on decline in heart function and outcomes motivated clinicians and researchers to delineate optimal treatment strategies. Therapeutic goals include improvement in cardiac function, reduction of hospitalisations, morbidity and mortality and, if these are not possible, enhancement of quality of life (QoL) [22].

The ERS task force on CSA discussed the various treatment options [2] (figure 3). The first step of current practice is to optimise medical therapy of cardiac failure with diuretics to reduce pulmonary congestions and cardiac filling pressures, with angiotensin-converting enzyme inhibitors to reduce ventricular afterload [23] and with β -blockers to diminish excessive sympathetic activation [24, 25]. Physical activity, compression stockings, salt restriction and dialysis can also reduce fluid overload and accumulation in the

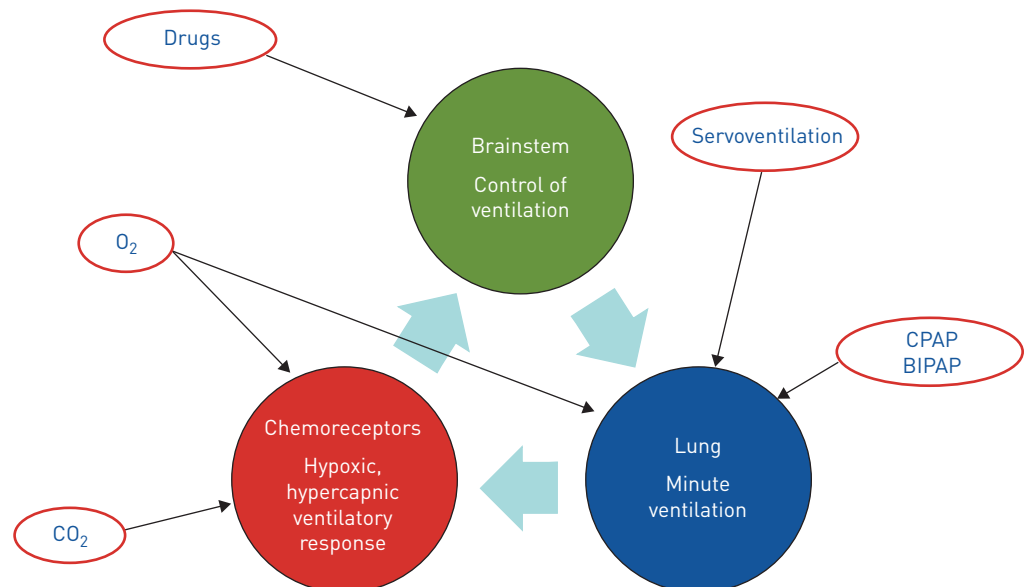


FIGURE 3 The figure shows the approaches of various treatment options on the loop gain. Oxygen (O_2) supply increases the alveolar O_2 concentration and avoids hypoxic stimulation of the chemoreceptors. In addition, it may influence myocardial function. Carbon dioxide (CO_2) plays a major role in the pathophysiology of periodic breathing. The application of CO_2 by rebreathing or external supply elevates the arterial CO_2 tension above the apnoea threshold and impedes central apnoeas. Drugs may influence respiratory drive in the brainstem. Some pharmaceutical influences on arousability, sleep stages and sleep efficiency can stabilise respiration or shift sleep stages from non-rapid eye movement (REM) stages I and II to slow-wave or REM sleep. CPAP: continuous positive airway pressure; BIPAP: bilevel positive airway pressure.

lower body compartment during the day and diminish nocturnal fluid shift to lungs and upper airways [26]. In addition, optimal cardiac treatment includes interventional or surgical therapies on cardiac vessels or valves. Resynchronisation therapy has been shown to decrease breathing disturbances [27], improve cardiac function, QoL and mortality in advanced heart failure.

In randomised controlled trials (RCTs) with small sample sizes, nocturnal oxygen therapy ameliorates CSA in heart failure patients, essentially by reducing hypoxic ventilatory drive and sympathetic activation. The apnoea–hypopnoea index (AHI) is reduced by 50% without significant change in the obstructive component [28]. Oxygen may improve physical activity and QoL [29]. Evidence is limited and large RCTs need to be conducted in this field.

Studies investigated the effect of added dead space and external CO₂ application for increasing P_{aCO_2} above the apnoeic threshold and thus stabilising ventilation. Although this approach is highly effective in experimental settings, the treatment cannot currently be recommended due to a lack of safety and long-term data [2, 30–32].

Theophylline has shown modest efficacy on improvement of periodic breathing, AHI and intermittent hypoxia. However, beneficial effects on cardiac function or sleep architecture were limited [33].

Most recently, unilateral phrenic nerve stimulation has been introduced in the treatment of CSA in CHF. Comparable to oxygen and continuous positive airway pressure (CPAP), it may reduce central AHI by 50%, but long-term and large-scale data are missing. Data regarding hard outcomes are lacking. Therefore, the treatment should be used very cautiously in selected populations participating in controlled trials [34, 35].

CPAP primarily re-opens and stabilises the upper airway, but may also influence left ventricular afterload and filling of the right heart, improve ventilation/perfusion mismatch and slightly increase P_{aCO_2} . Cohort and RCT studies have suggested that CPAP improves oxygenation and LVEF [36]. CPAP reduces central breathing disturbances by a mean of 50%. However, the CANPAP trial failed to show a survival benefit in patients with CSA and CHF with reduced LVEF [36]. Bilevel positive airway pressure (BPAP) with back-up mandatory breaths may abolish both obstructive and central SDB. However, data on the clinical use in patients with CHF and CSA/periodic breathing are scarce. DELLWEG *et al.* [37] showed that short-term beneficial effects of BPAP were lost over time. In addition, BPAP may even aggravate central events by inducing hypocapnia and facilitating glottis closures. Therefore, the ERS task force on CSA did not support the use of BPAP in CHF with CSA/periodic breathing outside clinical trials [2].

Adaptive servoventilation (ASV) adjusts the breath-after-breath level of inspiratory pressure support in order to counterbalance the overshoot and undershoot of ventilation. ASV devices increase pressure support during apnoeic/hypopnoeic periods and reduce it during hyperventilation. In addition, ASV devices provide fixed or variable expiratory pressure to suppress obstructive events and apply mandatory breaths to avoid central apnoeas [38]. Therefore, ASV normalises obstructive and central SDB and is superior to CPAP, oxygen or other therapeutic approaches [15, 37, 39–44] for suppressing sleep disturbances. However, the SERVE-HF trial, which compared optimum medical treatment for heart failure alone (control group) or in combination with adaptive servoventilation in severe CHF with reduced LVEF (<45%) and predominant CSA failed to show a prognostic benefit of ASV [45]. The primary end-point was neutral and secondary end-points analysis showed that all-cause and cardiovascular mortality were both increased [45]. To date, this is by far the largest RCT in the field and the results have led to contraindication of ASV in cardiac failure with reduced ejection fraction below 45% according to the SERVE-HF inclusion criteria.

However, the study results have been challenged owing to a high percentage (23%) of the study population switching from control to ASV or *vice versa*, low ASV adherence (40% of patients used the ASV device <3 h per day, 26.7% 0 h per day) and unbalanced use of antiarrhythmic drugs between the two arms [45, 46]. *Post hoc* analyses showed that ASV negative impact was mainly restricted to patients with the lowest LVEF (<30%) and those with the highest proportion of periodic breathing [22, 47]. Therefore, the contraindications of ASV should not be extended to the CHF population with preserved ejection fraction and/or to HFrEF >45%.

The unexpected results of SERVE-HF raised several questions on possible explanations for the higher mortality burden. JAVAHARI *et al.* [48] hypothesised that cardiac instability rather than effects of the treatment may be responsible for the mortality in SERVE-HF.

In fact, patients did not die from decompensation or progressive deterioration in heart failure, but from sudden cardiac death. The following hypothesis has been proposed: 1) the highest risk of sudden cardiac death occurred in the most severe patients (very low LVEF, <30%); 2) patients with poor outcomes were significantly more often treated with drugs which themselves induce cardiac instability (antiarrhythmics);

3) JAVAHERI *et al.* [48] discussed whether, against the background of these unfavourable preconditions, unnecessary pressure support and hyperventilation might have facilitated malignant arrhythmias.

Physiological studies suggest that algorithm might play a role. However, we do not have data to demonstrate that these acute physiological measurements translate into significant impact on outcomes [49].

Although more recent studies (non-RCT) showed beneficial effects of ASV (table 1), the results of another large, multicentre, multinational trial (ADVENT-HF) are required to truly evaluate the efficacy, benefits and potential harms of ASV treatment in cardiac failure with reduced ejection fraction. Similar to SERVE-HF, ADVENT-HF includes patients with CHF with an LVEF <45% under optimal medical therapy and with AHI ≥ 15 events-h⁻¹. However, ADVENT-HF includes OSA patients and uses an ASV device, which allows reduction of pressure support to zero. Most recently, preliminary results proved better treatment adherence in ADVENT-HF compared to SERVE-HF [57].

Is periodic breathing in CHF a unique entity?

The heterogeneous and contradictory results on ASV ask for new concepts in our understanding of CSA. The goal of tailoring of CSA/periodic breathing therapies in order to maximise the treatment response requires more accurate patient's phenomapping than reporting solely on AHI. CHF patients are particularly heterogeneous in terms of clinical, imaging and biological characteristics, but also concerning physiopathological traits underlying CSA/periodic breathing patterns during sleep. The overarching goal is to combine both standard clinical/biological parameters of CHF and the following complex polysomnographic patterns informing on mechanistic traits of SDB [58]. Recent studies indicate parameters possibly explaining heterogeneous response to treatment and survival, as follows.

Loop gain

A *post hoc* analysis of the CANPAP study demonstrated significant survival benefit in those patients with significant improvement of central breathing disturbances under CPAP (responders) [59]. On the one hand, it can be discussed that optimal suppression of breathing disturbances improves survival. On the other hand, treatment response and survival benefit can be a characteristic of a specific phenotype. SANDS *et al.* [18] analysed loop gain in CHF patients according to their CPAP response. They found that low loop gain was associated with better CPAP response, while high loop gain (high instability of the respiration) was associated with poor CPAP efficacy.

Exercise oscillatory ventilation

KAZIMIERCZAK *et al.* [15] assessed exercise oscillatory ventilation, a common pattern in heart failure patients characterised by significant variations in minute ventilation during increased workload. They studied 39 CHF patients with LVEF <45% and found that exercise oscillatory ventilation was associated with the severity of heart failure and can be reversed with ASV therapy.

Hypoxic burden

WATANABE *et al.* [60] measured the hypoxic burden as defined by the time with oxygen desaturation >4%. Survival was significantly impaired in those patients with higher total time with oxygen desaturation <4%, but did not depend on the number of oxygen desaturations.

Pattern of oxygen desaturation

GRANITZA *et al.* [61] used mathematical methods to analyse the pattern of oxygen desaturation. They differentiated a dynamic and a static desaturation pattern. Oxygen desaturation >8% was a strong predictor of fatal events. CHF patients who died had shown a bimodal distribution of oxygen desaturation with two peaks, one with a mean desaturation of 2% and one with a mean desaturation of 8%. In contrast, survivors showed a Gauss-like distribution of the oxygen desaturation with a maximum at 4%.

EELV

Based on previous findings of BRACK *et al.* [17], PERGER *et al.* [62] focused on the EELV in periodic breathing. They found two patterns, one with EELV higher than functional residual capacity (positive pattern), and one with negative EELV. The negative pattern was associated with longer hypopnoea and cycle time, higher N-terminal pro-brain natriuretic peptide and worse New York Heart Association classes.

Hypoxic and hypercapnic ventilator responses

GIANNONI *et al.* [63] measured the hypoxic and hypercapnic ventilatory responses in patients with HFrEF with a LVEF of $31 \pm 7\%$. During the mean follow-up period of 29 months, survival was best in patients with normal chemosensitivity, while it was reduced in patients with either increased hypoxic or

TABLE 1 Adaptive servoventilation (ASV) studies with mortality as primary outcome after SERVE-HF

Study/authors, year [reference]	Design	Population	Intervention	Primary outcome	Median or average follow-up	Results
FACE study, 2016 [50]	Prospective multicentre observational cohort France Up to January 31, 2013	CHF with reduced LVEF (HF _r EF <40%), mid-range (HF _m rEF 40–49%), preserved (HF _p EF >50%)	361 CHF patients with CSA eligible for ASV therapy (n=258) <i>versus</i> controls (n=133) refused/not compliant with ASV (<3 h per night) (ResMed, AutoSet CS) 66% compliant to ASV therapy	All-cause death, hospitalisation for worsening heart failure, heart transplant or ventricular assist device	21.6 months	ASV improved prognosis in HF _m rEF in non-ischaemic heart failure; trend to increase in event rate in HF _m rEF in ischaemic heart disease; improved prognosis in HF _p EF CHF with severe desaturations
CAT-HF study, 2017 [51]	Prospective, randomised, controlled, multicentre clinical trial United States and Germany 2013–2015	Hospitalised heart failure (HF _r EF >45% or HF _p EF ≥45%) and SDB (OSA or CSA) with AHI ≥15 events·h ⁻¹ <i>via</i> polygraphy	126 out of 215 patients assigned on ASV plus optimised medical therapy (n=65) <i>versus</i> optimised medical therapy alone (control) (n=61)	Composite global rank score (death, CV hospitalisations, and percentage changes in 6-min walk distance) Secondary end-points: sleep apnoea parameters, functional capacity, cardiovascular and all-cause death, days alive and out of the hospital, biomarkers, QoL, sleep parameters, imaging parameters and NYHA functional class	6 months	Neutral No improvement in 6-month cardiovascular outcomes; however, a positive effect of ASV in patients with HF _p EF Study was stopped after publication of SERVE-HF
IAMURA <i>et al.</i>, 2016 [52]	Case-control study Tokyo, Japan 2008–2014	Heart failure NYHA III or IV (71% NYHA IV, LVEF 33 ±17%) with ASV irrespective of SDB	85 patients receiving ASV 1 month <i>versus</i> guideline-directed medical therapies (AutoSet-CS; ResMed, Sydney, Australia) with full face mask (ResMed)	All-cause mortality and cardiac deaths	2-year follow-up	Continued ASV significantly lowered all-cause mortality and cardiac death rate
HETLAND <i>et al.</i>, 2016 [53]	Retrospective observational study Østfold, Norway 2007–2012	Heart failure NYHA class II–IV, LVEF ≤45%; CSR pattern ≥25% of sleeping time and dominant central sleeping pattern <i>via</i> polygraphy	75 patients treated with ASV (n=31 with ASV for >3–18 months <i>versus</i> n=44 control) (AutoSet-CS)	Mortality and hospital admission of any cause and number of days in hospital in total	18 months	ASV did not significantly affect CV death or combined CV death or hospital admissions after 18 months; trend toward better CV event-free survival for ASV usage
BORDIER and LATASTE, 2019 [54]	Retrospective study 2006–2018	Patient from the sleep unit of the CV department treated with ASV for sleep apnoea (C/M/O apnoeas <i>via</i> PG)	32 patients with ASV 8 deaths	CV mortality	Survival	CV deaths not predominant No relationship between sleep apnoea or ASV and death
MANSUKHANI <i>et al.</i>, 2019 [55]	Population-based study, using the Rochester Epidemiology Project database	CSA (AHI 41.6 ±26.5 events·h ⁻¹), with ASV therapy (65% ≥4 h per night on ≥70% nights in their first month), and had ≥1 month of clinical data before and after ASV initiation	309 CSA patients under ASV <i>versus</i> healthcare utilisation	Rates of hospitalisations, emergency department visits, outpatient visits and medications prescribed per year (mean±sd)	2 years pre- and post-ASV initiation	ASV did not change healthcare utilisation

Continued

TABLE 1 Continued

Study/authors, year [reference]	Design	Population	Intervention	Primary outcome	Median or average follow-up	Results
ADVENT-HF trial, recruiting [56]	Multicentre, multinational, randomised, parallel-group, open-label trial Canada	Chronic HFrEF ($\leq 45\%$) and SDB (OSA or CSA) with AHI ≥ 15 events·h ⁻¹ via PSG	Estimated n>800, still recruiting 524 patients (31% CSA, 69% OSA) randomised until February 2018 on medical therapy alone or ASV (AutoSet-CS) with nasal mask	All-cause mortality, first hospitalisation for CV diseases, new-onset atrial fibrillation/flutter requiring anticoagulation but not hospitalisation or implantable cardioverter-defibrillator shock not requiring hospitalisation	Every 6 months	Awaited

ASV studies with mortality as primary outcome. The table summarises the results of additional studies on ASV in heart failure and central sleep apnoea (CSA). Methodologies incompletely describe the types of masks and ASV devices used, sleep study, algorithm of titration and compliance to the device. Only one study (FACE) stratified patients in relation to the severity of heart failure with reduced ejection fraction (HFrEF). CHF: chronic heart failure; LVEF: left ventricular ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; SDB: sleep disordered breathing; OSA: obstructive sleep apnoea; AHI: apnoea-hypopnoea index; CV: cardiovascular; QoL: quality of life; NYHA: New York Heart Association; CSR: Cheyne–Stokes respiration.

hypercapnic ventilatory response and it was worst in patients with both increased hypoxic and hypercapnic ventilatory response.

Conclusion

These findings indicate that there are substantial differences within the group of heart failure patients with periodic breathing in terms of outcome. It is not a homogenous population with unique prognosis. Characteristics of potential phenotypes include the burden of hypoxaemia, variations of oxygen desaturation, chemoresponsiveness, ventilatory instability during wakefulness and sleep and lung volumes.

It is obvious that this hypothesis requires better definition, discrimination and prospective evaluation. However, it seems reasonable to include these parameters in the design and interpretation of future and, if possible, in published studies, by sharing open data to better understand survival and efficacy, benefits and harms under treatment. Including these parameters in future clinical routines will provide an appropriate classification to identify the CHF subgroup the most likely to respond to PAP therapies or alternatives.

Conflict of interest: W. Randerath reports grants and personal fees from Heinen & Löwenstein, ResMed, Philipps Respiromics, Inspire, Genzyme, Boehringer Ingelheim, Berlin Chemie and Roche Pharma, and personal fees from Vanda, outside the submitted work. O. Deleanu has nothing to disclose. S. Schiza has nothing to disclose. J-L. Pépin reports grants and personal fees from ResMed, Philips, Agiradom, AstraZeneca and SEFAM, grants from Fisher and Paykel, Mutualia, Vitalaire and Air Liquide Foundation, and personal fees from JAZZ and ITAMAR, during the conduct of the study.

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