Sleep-disordered Breathing in Heart Failure – Current State of the Art

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Abstract

Sleep-disordered breathing (SDB), either obstructive sleep apnoea (OSA) or central sleep apnoea (CSA)/Cheyne-Stokes respiration (CSR) and often a combination of the two, is highly prevalent in patients with heart failure (HF), is associated with reduced functional capacity and quality of life, and has a negative prognostic impact. European HF guidelines identify that sleep apnoea is of concern in patients with HF. Continuous positive airway pressure is the treatment of choice for OSA, and adaptive servoventilation (ASV) appears to be the most consistently effective therapy for CSA/CSR while also being able to treat concomitant obstructive events. There is a growing body of evidence that treating SDB in patients with HF, particularly using ASV for CSA/CSR, improves functional outcomes such as HF symptoms, cardiac function, cardiac disease markers, exercise tolerance and quality of life. However, conflicting results have been reported on 'hard' outcomes such as mortality and healthcare utilisation, and the influence of effectively treating SDB, including CSA/CSR, remains to be determined in randomised clinical trials. Two such trials (SERVE-HF and ADVENT-HF) in chronic stable HF and another in post-acute decompensated HF (CAT-HF) are currently underway.

Keywords

Obstructive sleep apnoea, central sleep apnoea, heart failure, adaptive servoventilation, continuous positive airway pressure

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Heart Failure

In developed countries, approximately 1–2 % of the adult population has heart failure (HF), and the prevalence of this cardiovascular disease increases with age.[1,2] HF can occur in the presence or absence of reduced left ventricular ejection fraction (LVEF), known as HF with reduced ejection fraction (HF-rEF) and HF with preserved ejection fraction (HF-pEF), respectively. The most widely studied of these is HF-rEF, which is particularly prevalent in men with ischaemic heart disease.[3] HF-pEF is present in 40–50 % of HF patients.[4,5] It is more prevalent in women and the underlying aetiology is more often non-ischaemic.[3,6] Despite these differences, the negative prognostic impact of both HF-rEF and HF-pEF appears to be similar.[6] The prevalence of renal disease and sleep-disordered breathing (SDB) is similar in patients with HF-rEF or HF-pEF, but the profile of other co-morbidities differs, with pulmonary disease, anaemia and obesity tending to be more prevalent in HF-pEF patients.[7] Even with the wide range of therapeutic options available for patients with HF-rEF and treatment being optimised according to current guideline recommendations, most HF-rEF patients will eventually die from progressive disease; for HF-pEF there are still no evidence-based treatments available, so the focus is mainly on treatment of co-morbidities and optimising risk factors.[3]

Sleep-disordered Breathing

There are two main types of breathing abnormalities seen during SDB: obstructive sleep apnoea (OSA) and central sleep apnoea (CSA), which may manifest as Cheyne-Stokes respiration (CSR), particularly in patients with HF. OSA is the most common type of SDB in the general population, and occurs secondary to recurrent collapse of the upper airway. The main features are repetitive complete (apnoea) or partial (hypopnoea) pauses in breathing during sleep, even in the presence of respiratory effort. CSA is characterised by a lack of drive to breathe during sleep, resulting in repetitive periods of reduced ventilation. CSR specifically consists of central apnoeas alternating with periods of crescendo–decrescendo respiratory tidal volume.

The severity of SDB is reported as the number of respiratory events per hour of (estimated) sleep time (apnoea–hypopnoea index, AHI), with mild disease defined as an AHI of 5–15/h, moderate as 15–30/h and severe as ≥30/h. In addition, parameters documenting the extent of intermittent hypoxaemia (the oxygen desaturation index, ODI), sleep time or estimated sleep time spent with oxygen saturation <90 % and mean and minimal oxygen saturation are being used for this purpose.

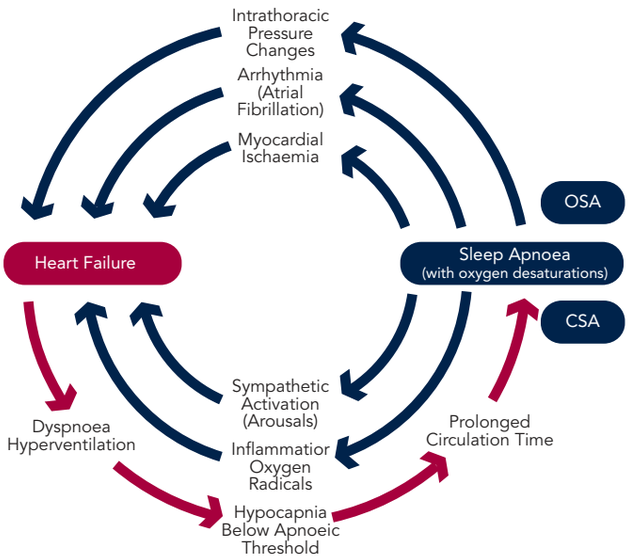
SDB is characterised by intermittent hypoxia, reoxygenation, hypercapnia, arousals and sleep deprivation, as well as increased negative intrathoracic pressure swings when an obstruction of the upper airway is present. SDB is both a cause and a consequence of HF (see *Figure 1*).[8] Potential mechanisms for increased cardiovascular risk in patients with OSA include sympathetic activation, changes in heart rate and blood pressure (BP) variability, vasoconstriction, oxidative stress, endothelial dysfunction, systemic inflammation, increased thrombotic risk, and functional problems including impaired diastolic function and increased wall stress, afterload and atrial size.[9] In terms of the cardiovascular effects of CSA, it is thought that this form of sleep apnoea is most likely to be a consequence, rather than a cause, of HF.[9,10] However, some of the physiologic effects of CSA are similar to those of OSA and therefore CSA also has the potential to initiate a cycle of events that lead to deterioration in cardiovascular function (see *Figure 2*).[10,11] This includes increased sympathetic nervous system activity, greater cardiac electrical instability and low-frequency oscillations in blood pressure and heart rate.[9,10] In contrast with OSA, CSA does not cause negative intrathoracic pressure swings, and the role of some of the other mechanisms contributing to increased cardiovascular risk in OSA, including inflammation, oxidative stress and endothelial dysfunction, remains to be determined.[9,10]

Sleep-disordered Breathing in Heart Failure

SDB is very common in patients with HF, much more common than in the general population, with prevalence rates of 50–75 %.[12,13] SDB has been documented in patients with both HF-rEF[14,15] or HF-pEF,[16–18] with no difference in prevalence between groups[19] and in patients with acute decompensated HF, where the prevalence can be even higher.[20–22] One of the interesting features of SDB in patients with HF compared with general SDB patients is a relative lack of symptoms, especially of daytime somnolence,[23–26] which could contribute to the lack of recognition and detection of SDB in HF patients.[27] One possible explanation for a lack of daytime sleepiness in HF patients with SDB is the increased sympathetic nervous system activity in HF patients compared with healthy subjects,[28,29] which is increased even further in the presence of OSA.[30,31] Increased sympathetic stimulation could stimulate alertness to counteract the effects of sleep fragmentation and sleep deprivation.[28] A significant inverse correlation between the degree of subjective daytime sleepiness and daytime muscle sympathetic nervous system activity has been documented in patients with HF and OSA.[32] A study conducted in severe OSA patients with and without HF used very low frequency heart rate variability (VLF-HRV) as a marker of sympathetic nervous system activity at night. The results showed that patients with severe OSA, that was not associated with excessive daytime sleepiness, had higher VLF-HRV (and therefore higher sympathetic activity) than those with excessive daytime sleepiness, and concluded that this was due to the alertness-inducing effects of excessive sympathetic nervous system activity.[33] Furthermore, patients with HF are often taking a variety of medications that cross the blood–brain barrier, and these could also impact on sleep and SDB.[34] One such group of agents is ß-blockers, which have been shown to reduce daytime sleepiness and the prevalence of CSA in HF patients.[35]

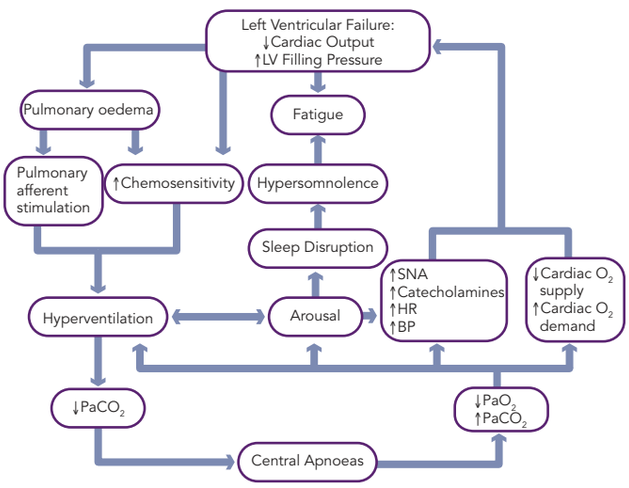
Approximately 20–45 % of patients with chronic HF have OSA.[14,15] European HF guidelines recognise that sleep apnoea is of concern in patients with HF.[3] OSA is independently associated with a worse prognosis in HF patients,[24] even in those who are receiving maximal and optimal HF therapy.[36] OSA is also highly prevalent in patients with HF-pEF, with a prevalence of 69–81 %.[16,18] The predominant type of SDB in HF-pEF appears to be OSA, which occurs more often than CSA in these patients.[16,18]

Figure 1: Links Between Sleep-disordered Breathing and Heart Failure



Reprinted from Brenner S et al.[8], copyright 2008, with permission from Elsevier. BP = blood pressure; CAS = central sleep apnoea; OSA = obstructive sleep apnoea.

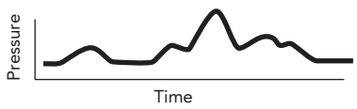
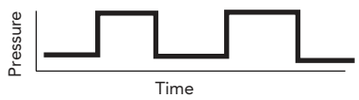
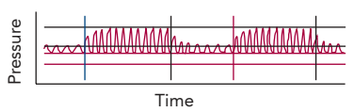
Figure 2: Mechanisms Linking Central Sleep Apnoea and Heart Failure



Reprinted from Hall and Bradley[11], copyright 1995, with permission from Wolters Kluwer Health. BP = blood pressure; HR = heart rate; LV = left ventricular; SNA = sympathetic nerve activity; PaO_2 = arterial oxygen pressure; $PaCO_2$ = arterial carbon dioxide pressure.

While rarely found in the general population, CSA/CSR is a common SDB pattern seen in patients with chronic HF, with a prevalence of 25–40 %.[15] The prevalence of CSA/CSR appears to increase as the severity of HF increases,[12,16] and the severity of CSA/CSR seems to mirror cardiac dysfunction.[37–39] Furthermore, CSA is independently associated with a worse prognosis in patients with HF, including increased mortality.[24,26,36,40–42] Even mild CSA, with an AHI of ≥5/h has been associated with increased mortality.[36] Although effective pharmacological[9,35,38,43,44] and device-based[45] treatment of HF may improve CSA/CSR, the negative impact of this form of SDB persists even in patients who are receiving maximal and optimal HF therapy, including cardiac resynchronisation.[26,46] For patients who have persistent CSA despite optimal medical therapy, it may be necessary to consider other interventions.

Table 1: Features of Different Types of Positive Airway Pressure Therapy

Theraphy	Aim	Features	Pressure Profile
CPAP	Maintain upper airways open	Fixed or automatically adjusted expiratory pressure	
APAP	Maintain upper airways open	Continually adjusting expiratory pressure to optimal level for specific patient needs	
BPAP	Support breathing in lung disease-related respiratory insufficiency	Fixed expiratory pressure and pressure support at inspiration, usually with fixed backup rate	
ASV	Stabilises breathing and maintains upper airway open	Continually adjusting inspiratory and expiratory pressure with variable, on-demand, back up rate	

APAP = auto-adjusting positive airway pressure; ASV = adaptive servoventilation; BPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure.

At 44–97 %, the prevalence of CSA in patients with acute decompensated HF is even greater than that in those with stable HF.[20–22] In addition, when present, CSA in acute decompensated HF patients is usually severe (AHI >30/h),[21] and has been shown to be a predictor of readmission and mortality.[47] It is interesting to note that optimal medical management, resolution of acute decompensation and return to baseline cardiopulmonary status are often not associated with a significant change in the severity of CSA.[21,43,48,49] Insertion of a left ventricular assist device (LVAD) has been associated with improvements in SDB in refractory patients.[50,51] These findings could indicate that severe CSA was present prior to the acute decompensation episode, and that more severe HF drives the higher prevalence and greater severity of CSA in these patients.[48]

Screening and Diagnosis of Sleep-disordered Breathing

SDB can be reliably diagnosed with cardio-respiratory polygraphy, which records nasal flow, respiratory effort, saturation, pulse and position. The technology can be used in both in- and outpatient settings. Polygraphy has been shown to be a valid alternative to the gold standard polysomnography (PSG) for SDB screening and diagnosis.[52–57] Attended PSG is currently the recommended option for assessing CSA in HF patients, but there is increasing evidence that polygraphy might be a valid alternative.[56] Polygraphy records the same respiratory signals as PSG (nasal/oronasal airflow, chest and abdominal movements, and oxygen saturation) but many devices do not incorporate electroencephalography (EEG), electrooculography (EOG) and electromyography (EMO) monitoring and therefore do not provide data on total sleep time, sleep staging and arousals.[56] As a result, polygraphy calculates SDB events per hour of monitoring time rather than per hour of actual sleep time like PSG, which may underestimate SDB severity in HF patients who have worse sleep quality and wake more times at night (known as lower sleep efficacy).[56,58] Therefore, newer polygraphy devices that also estimate sleep quality using actigraphy or PSG may be needed in more difficult cases. Important advantages of polygraphy are that it is well-accepted by patients, more accessible and less costly than PSG.[59,60]

Implantable cardiac electronic devices also have the ability to screen for SDB by analysing changes in intrathoracic impedance, and this feature is being built in to newer models.[61] Detection of SDB using implantable cardiac devices is not yet part of routine clinical practice, but there are devices currently available that are being used in clinical settings.

Questionnaires have not been useful in pre-screening patients with cardiovascular diseases including HF for SDB, because HF patients do not show the same symptoms and risk factors for SDB as patients without HF, and the screening questionnaires have only been validated for general OSA patients.[23] In addition, the overlap of some HF and SDB symptoms make questionnaires less useful in this group of patients. Furthermore, mild SDB may not be associated with obvious symptoms but can still have a negative impact on prognosis.

Treating Sleep-disordered Breathing in Heart Failure

Current Options and Interfaces

In addition to oxygen therapy, there are a number of positive airway pressure (PAP) treatment options available to clinicians managing SDB in patients with HF. These include continuous positive airway pressure (CPAP), auto-adjusting positive airway pressure (APAP), bilevel positive airway pressure (BPAP) and adaptive servoventilation (ASV) (see *Table 1*). Within these broad groups, there are a number of different devices utilising different algorithms to choose from. In addition to the selected PAP device, an important part of therapy is the choice of patient interface for delivery of treatment. These include nasal pillows, nasal mask and oronasal mask (sometimes known as full face mask); custom-made interfaces may be required in a small group of patients. The interface used for initiation of PAP therapy plays an important role in the acceptability of therapy and thus needs to be chosen carefully. For all therapies, the goal is to normalise breathing (AHI <5/h). An AHI of >5/h still meets criteria for diagnosis of SDB,[62] and the aim should be to eliminate this negative prognostic marker, if possible. Data from the Sleep Heart Health Study showed that men aged 40–70 years with an AHI of ≥30/h were 68 % more likely to develop CAD than those with an AHI <5/h.[63]

Table 2: Summary of Key Findings for Studies Investigating Adaptive Servoventilation Treatment in Heart Failure Patients with Sleep-disordered Breathing

					ASV Versus Control or Baseline	
Author (Date)	**N (ASV)**	**HF Characteristics**	**SDB Pattern**	**ASV Duration**	**SDB Outcomes**	**HF Outcomes**
Teschler (2001)[90]	14	Stable	CSA/CSR ODI 3 % >15/h	1 night	AHI 6.3/h versus 44.5/h (p<0.001)[b] ArI 14.7/h versus 65.1/h (p<0.01)[b] ↑ SWS; ↑ REM sleep	NR
Pepperell (2003)[94]	30	Stable, symptomatic NYHA class II–IV	CSR ODI >10/h AHI 19.8 ± 2.6	4 weeks	AHI 5.0/h versus 20.6/h (p<0.001)[a] ↑ objective wakefulness by 8.9 min (p=0.014)	↓ BNP by 56 pg/mL BNP (p=0.001) ↓ urinary metadrenaline release (p=0.019)
Schädlich (2004)[96]	20	LVEF 20–50 %	CSA/CSR AHI >15/h	1 year	AHI 3.4/h versus 44.3/h (p<0.0001)[b] ArI 12.0/h versus 29.8/h (p<0.01)[b] ODI 5.2/h versus 45.3/h (p<0.0001)[b] SpO_2 93 versus 92 % (p<0.05)[b] SWS 13.7 versus 4.5 % of TST (p<0.0001)[b]	LVEF 41.7 versus 37.1% (p<0.05) 6MWD 277 m versus 192 m (p<0.01)
Töpfer (2004)[95]	11	LVEF <40 %	CSR	6 weeks	AHI 6.4/h versus 48.2/h (p<0.001)[b] AI 18.4/h versus 33.9/h (p<0.05)[b]	Improved MLHFQ score (p=0.02)[b]
Phillipe (2006)[124]	12	Stable NYHA class II–IV LVEF ≤40 %	CSA/CSR AHI >15/h	6 months	↓ AHI to <10/h (p<0.05)[b]	↑ LVEF (p<0.05)[b]
Szollosi (2006)[125]	10	Stable NYHA class II–III LVEF <50 %	CSA AHI >5/h	1 night	AHI 14.0/h versus 30.0/h (p<0.05)[a] AI 5.5/h versus 17.0/h (p<0.05)[a] ArI 23.7/h versus 39.6/h (p<0.05)[a]	NR
Zhang (2006)[97]	14	Stable LVEF 30.8 ± 4.3 %	CSR	2 weeks	AHI 6.5/h versus 34.5/h (p<0.01)[bc] SpO_2 92.1 versus 84.3 % (p<0.01)[bc] ArI 18.2/h versus 30.4/h (p<0.01)[bc]	LVEF 37.2 versus 30.2 % (p<0.05)[bc] 6MWD 340.7 versus 226.2 m (p<0.01)[bc]
Oldenburg (2008)[39]	29	NYHA class ≥II LVEF ≤40 %	CSA/CSR AHI ≥15/h	5.8 ± 3.5 months	AHI 3.8/h versus 37.4/h (p<0.001)[b] AI 0.7/h versus 22.8/h (p<0.001)[b] Central AI 0.3/h versus 17.6/h (p<0.001)[b] ODI 5.2/h versus 6.8/h (p=0.001)[b] SpO_2 94.6 versus 92.9 % (p<0.001)[b]	NYHA 1.93 versus 2.43 (p<0.001)[b] LVEF 35.2 versus 28.2 % (p=0.001)[b] NT-proBNP 1,061 versus 2,285 pg/mL (p=0.012)[b]
Bitter (2010)[126]	39	NHYA class II–III LVEF normal	CSR AHI >15/h	11.6 ± 3 months	AHI 3.5/h versus 43.5/h (p<0.001)[b] ArI 17.5/h versus 30.7/h (p<0.01)[b] Maximum desaturation 88.1 versus 82.8 % (p<0.01)[b]	NT-proBNP 740 versus 1,480 pg/mL (p=0.1)[a] LAD 51.1 versus 49.8 mm (p<0.01)[a] ↑ exercise capacity (p<0.01)[a]
Hastings (2010)[93]	19	Stable NHYA class II or III LVEF <45 %	CSA AHI >15/h	6 months	AHI 8/h versus 49/h (p=0.001)[b] Central AI 5/h versus 9/h (p=0.04)[b] ArI 17/h versus 64/h (p=0.002)[b]	LVEF 36.9 versus 29.0 % (p=0.03)[b] Improved SF-36 energy vitality score (p=0.005)[b]
Kasai (2010)[108]	15	Stable NYHA class ≥II LVEF <45 %	CSA/CSR + OSA AHI ≥15/h	3 months	AHI 1.9/h versus 37.4/h (p<0.01)[b]	6MWD 428.3 versus 393.3 m (p<0.05)[b] BNP 245.5 versus 281.0 pg/mL (p<0.05)[b] LVESD 45.5 mm versus 49.3 m (p<0.05)[b]
Haruki (2011)[127]	15	Stable NYHA class ≥II LVEF <50 %	AHI >15/h	Mean 24 weeks	NR	NHYA class 1.5 versus 2.4 (p<0.01)[b] LVEF 43 versus 30 % (p<0.0001)[b] SV 56 versus 43 mL (p=0.001)[b] CO 3.83 versus 3.13 L/min (p=0.0037)[b]
Oldenburg (2011)[128]	56	Stable NYHA class ≥II LVEF ≤40 %	AHI >15/h >80 % central	6.7 ± 3.2 months	AHI 6.1/h versus 39.7/h (p<0.01)[b] Central AI 0.4/h versus 17.2/h (p<0.01)[b] Mean desaturation 4.8 versus 6.7 % (p<0.01)[b]	NHYA class 2.6 versus 1.9 (p<0.001)[b] LVEF 34.0 versus 29.9 % (p=0.003)[b] LVEDD 64.5 versus 67.2 mm (p=0.007)[b]
Koyama (2011)[98]	88	Stable NYHA class II or III LVEF <55 %	SDB	1 year	NR	Moderate–severe SDB (AHI ≥20/h) LVEF 50.2 % versus 45.5 % (p=0.012)[a] BNP 89.9 versus 150.9 (p=0.033)[a] ↑ CV event-free survival (p=0.032)[a] Non-severe SDB (AHI <20/h) No change in LVEF, BNP or CV event-free survival

Table 2. Cont.

					ASV Versus Control or Baseline	
Author (Date)	**N (ASV)**	**HF Characteristics**	**SDB Pattern**	**ASV Duration**	**SDB Outcomes**	**HF Outcomes**
Takama (2011)[99]	61	NYHA class II–IV	SDB	6 months	AHI improved to 19.9/h, 11.8/h and 2.4/h in pts with severe (AHI ≥40/h; p<0.0001), moderate (AHI ≥20/h; p<0.0001) or mild (AHI <20/h; p<0.05) SDB[b] Central AI and obstructive AI significantly improved in severe SDB pts, and obstructive AI in severe SDB pts (all p<0.005)[b]	↓ BNP in pts with severe (AHI ≥40/h; p<0.05), moderate (AHI ≥20/h; p<0.05) or mild (AHI <20/h; p<0.01) SDB[b] ↑ LVEF in pts with severe (AHI ≥40/h; p<0.01) or moderate (AHI ≥20/h; p<0.001)[b]
Yoshihisa (2011)[129]	23	Stable NYHA class ≥II	AHI >15/h >50 % central	6 months	AHI 9.0/h versus 38.8/h (p<0.01)[b] Central AI 1.6/h versus 19.5/h (p<0.01)[b] ArI 15.9/h versus 24.5/h (p<0.01)[b] ODI 3 % 5.3/h versus 30.1/h (p<0.01)[b] Sleep efficiency 72.3 versus 66.7 % (p=0.04)[b]	BNP 191.6 versus 499 pg/mL (p<0.05)[b] LVEF 46.4 versus 38.3 % (p<0.05)[b] LVEDVI 75.7 versus 84.7 mL/m^2 (p<0.05)[b] LVESVI 42.2 versus 56.3 mL/m^2 (p<0.05)[b]
Campbell (2012)[130]	7	Stable LVEF <50 %	CSA/CSR AHI >15/h	8 weeks	AHI 5.0/h versus 19.4/h (p=0.03)[a] AHI <10/h in 86 % of pts	LVEF 35.0 versus 32.5 % (p=0.24)[a]
Miyata (2012)[131]	11	Stable NHYA class ≥II	CSA/CSR AHI >15/h	6 months	AHI 5.9/h versus 39.0/h (p<0.01)[b] Central AI 0.6/h versus 14.8/h (p<0.01)[b] ArI 13.6/h versus 21.9/h (p<0.01)[b] ODI 3% 3.3/h versus 30.5/h (p<0.01)[b]	BNP 221 versus 482 pg/mL (p<0.05)[b] LVEF 36.0 versus 30.5 % (p=0.03)[b]
Randerath (2012)[132]	36	LVEF ≥20 %	AHI ≥15/h OSA & CSA	1 year	AHI 11.1/h versus 46.8/h (p<0.001)[b] Central AHI 6.1/h versus 23.1/h (p<0.001)[b] Central AI 1.5/h versus 6.3/h (p<0.001)[b] Minimum SpO_2 86.1 % versus 74.3 % (p<0.001)[b]	NT-proBNP 230.4 versus 537.3 ng/L (p<0.05)[b]
Arzt (2013)[100]	72	Stable LVEF ≤40 %	SDB AHI ≥20/h	12 weeks	AHI decreased by 39/h with ASV versus 1/h in controls (p<0.001)[a]	NT-proBNP reduced by 360 ng/mL with ASV versus 135 ng/mL increase in controls (p=0.01)[a] No significant differences in LVEF or QOL[a]
Kourouklis (2013)[102]	9	Stable NYHA class II–III LVEF <40 %	CSA AHI ≥15/h	6 months	AHI 3.5/h versus 43.2/h (p<0.05)[b] AI 2.8/h versus 34.1/h (p<0.05)[b] Central AI 0.2/h versus 2.4/h (p<0.05)[b] ODI 4.7/h versus 37.7/h (p<0.05)[b] SpO_2 95.4 versus 93.3 % (p<0.05)[b]	↑ LVEF (p<0.001)[b] ↑ NHYA class
Yoshihisa (2013)[92]	18	LVEF >50 %	SDB AHI >15/h	6 months	AHI 6.9/h versus 37.0/h (p<0.0125)[b] Central AI 0.1/h versus 11.9/h (p<0.125)[b] Obstructive AI 0.3/h versus 2.1/h (p<0.125)[b] Hypopnoea index 2.6/h versus 16.4/h (p<0.125)[b] ArI 14.1/h versus 21.4/h (p<0.125)[b] Lowest SpO_2 90.0 versus 77.9 % (p<0.125)[b] Mean SpO_2 96.6 versus 94.3 % (p<0.125)[b] Reductions in AHI and central AI also significant versus controls	NYHA class 1.5 versus 2.3 (p<0.125)[b] Systolic BP 112.4 versus 124.2 mmHg (p<0.125)[b] HR 63.8 versus 69.6 beats/min (p<0.125)[b] CAVI 7.7 versus 9.0 (p<0.125)[b] BNP 58.1 versus 121.5 pg/mL (p<0.125)[b] Reductions in NYHA class, HR and BNP also significant versus controls
Birner (2014)[101]	32	Stable NYHA class II or III LVEF ≤40 %	SDB AHI ≥20/h	12 weeks	AHI 11/h versus 43/h (p<0.001)[a]	LVEF 31 versus 32 % (p=0.75)[a] NT-proBNP 1,163 versus 1,042 ng/mL (p=0.92)[a]

[a] compared with control; [b] compared with baseline; [c] statistically significant differences also observed for ASV versus 14 days' oxygen therapy (data not shown). 6MWD = 6-minute walk distance; AHI = apnoea-hypopnoea index; AI = apnoea index; ArI = arousal index; ASV = adaptive servoventilation; BNP = brain natriuretic peptide; BP = blood pressure; CAVI = cardio-ankle vascular index; CO = cardiac output; CSA = central sleep apnoea; CSR = Cheyne–Stokes respiration; CV = cardiovascular; HF = heart failure; HR = heart rate; LAD = left atrial diameter; LVEDD = left ventricular end-diastolic diameter; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESVI = left ventricular end-systolic volume index; m = metres; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NR = not reported; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; ODI = oxygen desaturation index; pts = patients; QOL = quality of life; SDB = sleep-disordered breathing; SpO2, = oxygen saturation; SV = stroke volume; SWS = slow-wave sleep; TST = total sleep time.

Table 3: Summary of Ongoing Mortality Studies Investigating Adaptive Servoventilation in Patients with Heart Failure and Central Sleep Apnoea

	SERVE-HF[109]	ADVENT-HF[110]	CAT-HF[111]
Patient population	Chronic symptomatic HF NYHA class III or IV LVEF ≤45 % Predominant CSA AHI >15/h Central AHI ≥10/h	AHA stage B–D HF LVEF ≤45 % OSA or CSA AHI ≥15/h	Acute decompensated HF HF-rEF or HF-pEF Sleep apnoea AHI ≥15/h
Treatment arms	ASV* Control (no ASV)*	ASV* Control (no ASV)*	ASV* Control (no ASV)*
Design	Multicentre Randomised (1:1) Parallel Event-driven sequential	Multicentre Randomised Parallel Event-driven	Multicentre Randomised Parallel
Target enrolment, n	≈1200	860	215
Follow-up	≥2 years	≥2 years	
Primary outcome	Time to first event#	Time to first event¶	Global rank endpoint†
Secondary outcomes	Time to death Time to unplanned hospitalisation Pts alive and not hospitalised during f-up Quality of life HF symptoms Health economics Echocardiography substudy	Time to death Number of CV hospitalisations/year Number of days alive and not hospitalised LV function Plasma BNP level CRT or ICD implantation 6MWD % Pts with change in NYHA class AHI Quality of life	6MWD NT-proBNP Biomarkers Echocardiography Sleep parameters ESS PSQI Quality of life Health status Depression HF hospitalisation Death
Estimated completion	Mid-2015	Dec 2015	Sept 2016

*6MWD = 6-minute walk distance; AHA = American Heart Association; AHI = apnoea–hypopnoea index; ASV = adaptive servoventilation; BNP = brain natriuretic peptide; CRT = cardiac resynchronisation therapy; CSA = central sleep apnoea; CV = cardiovascular; ESS = Epworth Sleepiness Scale; f-up = follow-up; HF = heart failure; HF-pEF = HF with preserved ejection fraction; HF-rEF = HF with reduced ejection fraction; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OSA = obstructive sleep apnoea; PSQI = Pittsburgh Sleep Quality Index; pts = patients; *All patients are receiving optimal medical therapy. #Event = all-cause death, unplanned hospitalisation (or unplanned prolongation of a planned hospitalisation) for worsening chronic HF, cardiac transplantation, resuscitation of sudden cardiac arrest or appropriate life-saving shock for ventricular fibrillation and fast ventricular tachycardia in implantable cardioverter defibrillator (ICD) patients. ¶Death or first cardiovascular hospital admission or new onset atrial fibrillation/flutter requiring anti-coagulation but not hospitalisation or delivery of an appropriate shock from an ICD not resulting in hospitalisation. †Rank order response based on survival free from CV hospitalisation and improvement in functional capacity measured by 6MWD.*

Treatment of Obstructive Sleep Apnoea

CPAP maintains airway patency, enabling patients to breathe spontaneously and avoid intermittent hypoxia.[64] Other beneficial cardiac effects in patients with HF include decreases in preload and afterload,[65,66] a marked reduction in intrathoracic pressure swings[64] and reduced sympathetic activity.[67–69]

CPAP treatment for OSA lowers BP, improves cardiac function[69–71] as well as quality of life, can decrease the arrhythmic burden, and has been shown to improve survival in a cohort of HF patients, although this evidence does not come from randomised controlled clinical trials.[72]

There are potential treatment alternatives for specific OSA phenotypes, including weight loss, oral appliances, tonsillectomy and, most recently, implantable devices for upper airway stimulation. However, none of these have been tested in patients with concurrent HF.

Treatment of Central Sleep Apnoea

Although available information is limited, home oxygen therapy has been shown to have some beneficial effects in patients with CSA and HF, with significant reductions in AHI of about 50 %.[73,74] Data from two studies in Japanese patients with New York Heart Association (NYHA) class II or III HF-rEF and CSA/CSR were reported in three separate publications.[75–77] After 12 weeks home oxygen therapy, significant decreases were seen in the AHI (from 21/h at baseline to 10/h; p<0.001), the ODI (from 19.5/h to 5.9/h; p<0.001) and the Specific Anxiety scale score (from 4.0 to 5.0; p<0.001), and LVEF was significantly increased (from 34.7 % to 38.2 %; p=0.022).[75] In a separate study, continuing treatment for one year showed that home oxygen therapy was well-tolerated and that the benefits of treatment were maintained over the longer term.[76] A *post hoc* analysis of data from both trials showed that home oxygen therapy had no effect on the number of premature ventricular contractions, although there was evidence of benefit in the subgroup of patients with NYHA class >III and an AHI of >20/h.[77] A study conducted in France in a similar patient population also showed that nocturnal oxygen therapy significantly decreased the central AHI and ODI compared with baseline, with treatment effects evident within 12 hours of initiating therapy and persisting during the six-month treatment period.[78] In this study, oxygen therapy had no significant effects on the obstructive or mixed AHI values, quality of life or ventricular function.

The rationale for testing CPAP in patients with CSA and HF was that improving cardiac function by applying PAP would attenuate central SDB. Positive effects associated with CPAP therapy in patients with HF (usually HF-rEF) and CSR include improved LVEF and reduced AHI,[68,79–81]

but other studies have failed to document statistically significant improvement in outcomes when using CPAP to treat HF patients with CSA/CSR.[82–84] Given significant heterogeneity between studies in approaches to CPAP titration, it is possible that therapy failure may be due to inadequate titration and inadequate reductions in AHI during treatment. A good example of this is the Canadian Positive Airway Pressure Trial for Heart Failure Patients with Central Sleep Apnea (CANPAP) study, a randomised controlled trial that investigated mortality in patients with HF-rEF and CSA/CSR treated with CPAP. The study was stopped prematurely after enrolment of 258 of the planned 408 when analysis did not show a beneficial effect of CPAP treatment on survival.[85] However, a *post hoc* evaluation suggested that morbidity and mortality might be improved if there was an early and significant reduction in AHI to <15/h during CPAP therapy.[86] Other data suggest that even if CPAP therapy is appropriately titrated there may be a subgroup of patients who do not respond to this treatment option.[87,88] Meta-analysis showed a residual mean AHI of 15/h across eight included studies despite CPAP treatment.[79] This lack of efficacy may limit the utility of CPAP in some HF patients, while others may have issues with tolerability.[89] Recommendations vary, with some suggesting that the wide availability of, and familiarity with, CPAP means that this approach should be considered for initial treatment of CSA related to HF,[79] while others say that CPAP should not be considered as standard therapy for this indication.[9] Even if a CPAP trial is undertaken, an alternative treatment option needs to be considered when there is inadequate apnoea suppression.[79]

One such alternative for CSA/CSR in HF is ASV. A varying amount of inspiratory pressure (inspiratory positive airway pressure, IPAP) supports inspiration with decreasing breathing amplitude, and can also ensure sufficient inspiration when breathing efforts are absent.[90,91] Different technologies use different methods to stabilise the breathing pattern, with monitoring of minute ventilation being the most widely used. ASV also ensures upper airway patency by providing a fixed or variable amount of end-expiratory positive airway pressure (EPAP), so concomitant OSA will also be treated. Given the different ASV devices and algorithms on the market, it is not clear whether effects of one device can be extrapolated to another.

There is currently no consensus on whether treatment for CSA in HF should be initiated and what the optimal strategy might be. A number of smaller studies have documented improvements in symptoms, cardiac function, cardiac disease markers, exercise tolerance, short-term prognosis and quality of life when ASV treatment has been used in patients with HF and SDB, including CSR (see *Table 2*).[39,92–102] The majority of studies have been conducted in patients with HF-rEF, but beneficial effects of ASV on respiratory and cardiovascular parameters have also been documented in patients with HF-pEF.[92] Data from a recent meta-analysis showed that ASV significantly improved AHI, left ventricular function and exercise capacity compared with control in patients who had CSA and predominantly HF-rEF.[103] Beneficial changes in sympathetic nervous system activity assessed by microneurography have also been documented.[104] There were significant correlations between changes in the AHI and changes in both sympathetic nervous system activity and LVEF.[104]

Data from comparative studies provide some indication that ASV is a successful method for treating CSA/CSR in HF,[90,105–107] although evidence from randomised controlled parallel-group trials is currently lacking. ASV appears to be more effective than CPAP, BPAP and oxygen therapy for treating CSA/CSR in HF,[90,105,106] and it has been reported that patients prefer ASV over both CPAP and BPAP.[90] In one randomised, open-label study of HF-rEF patients, compliance with therapy (an important aspect of the effectiveness of treatment) was significantly better with ASV compared with CPAP (5.2 versus 4.4 h/night, respectively, p<0.05).[108]

The influence of effectively treating CSA/CSR in patients with HF-rEF on objective 'hard' outcomes such as mortality in randomised clinical trials remains to be determined. Data from the ongoing Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure (SERVE-HF) (NCT00733343),[109] Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure (ADVENT-HF) (NCT01128816)[110] and Cardiovascular Improvements With MV ASV Therapy in Heart Failure (CAT-HF) (NCT01953874)[111] trials (see *Table 3*) will help to answer these important questions.

A new treatment option for CSA currently under investigation is phrenic nerve stimulation. Preliminary data show that phrenic nerve stimulation with an implantable pacemaker can treat central apnoeas and thus attenuates respiratory abnormalities and reduces AHI by 50 %, but cannot treat hypopnoeas or other respiratory events.[112] Trials to evaluate the clinical effect of this method on HF outcomes are not yet available.

Compliance with Positive Airway Pressure Therapy

Compliance in the context of PAP therapy refers to the consistency with which a patient uses the prescribed treatment. A number of studies have investigated the level of compliance required by OSA patients for the beneficial effects of CPAP therapy to be achieved, be that improved survival,[113] decreases in BP,[114–117] or improvements in sleepiness[118–121] or memory.[122] For example, one study analysing the dose–response relationship between CPAP therapy and cardiovascular mortality found evidence that increased usage correlates with improved survival rates, with a significant difference in five-year survival between patients using CPAP for <1 h/day compared with those using CPAP for 1–6 or >6 h/day.[113] Similarly, a per-protocol analysis of randomised clinical trial data suggested that CPAP might reduce the incidence of hypertension or cardiovascular events in patients who were adherent to therapy for ≥4 h/night.[123] While these studies were not specifically conducted in HF patients, they suggest that a minimum duration of PAP therapy usage will be required for the beneficial effects of treatment to be realised in HF patients. In addition, the relative lack of SDB symptoms in patients with HF might make compliance with therapy more difficult to achieve, meaning that strategies to improve compliance are more important.

Conclusion

SDB is highly prevalent and associated with worse prognosis in all patients with HF, including those with HF-rEF, HF-pEF, chronic disease or acute decompensations. There are a number of treatment options, of which ASV appears to be the most consistently effective, particularly against CSA/CSR. Observational studies indicate that effective treatment of SDB improves functional parameters and surrogate endpoints and is well-tolerated in HF patients with SDB. Data from ongoing randomised clinical trials will further clarify the effects of treating SDB in HF on morbidity and mortality as well as healthcare utilisation. It is anticipated that treatment of co-morbidities such as SDB will become an important part of tailored HF therapy in the near future. ■

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