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Effect of cardiac pacing on sleep-related breathing disorders: a systematic review

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Abstract Sleep-related breathing disorders are commonly encountered in the middle-aged population, negatively affecting quality of life. Central sleep apnea is associated with congestive heart failure, whereas obstructive sleep apnea is related to different pathophysiologic mechanisms, such as the total or partial occlusion of upper airway tract. Both sleep-related disorders have been associated with increased morbidity, and hence, they have been a target of several treatment strategies. The aim of this systematic review is to evaluate the effect of different types of cardiac pacing on sleep-related breathing disorders in patients with or without heart failure. The PubMed and Cochrane Central Register of Controlled Trials were examined from April 2015 to January 2016. Of the initial 360 studies, 22 eligible trials were analyzed. The included studies were classified according to the type of sleep disorder and the intervention undertaken. The evidence shows that cardiac resynchronization therapy but not atrial overdrive pacing can reduce apneic events in central sleep apnea patients. However, their effect on obstructive sleep apnea is controversial. It can be assumed that pacing cannot be used alone as treatment of sleep-related breathing disorders. Further research is needed in order to elucidate the effect of these interventions in sleep apnea patients.

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Abbreviations

AHI	Apnea–hypopnea index
AOP	Atrial overdrive pacing
CPAP	Continuous positive airway pressure
CRT	Cardiac resynchronization therapy
CSA	Central sleep apnea
CSR	Cheyne–Stokes respiration
EF	Ejection fraction
HF	Heart failure
OSA	Obstructive sleep apnea
OVP	Overdrive ventricular pacing
PASP	Pulmonary artery systolic pressure
SAS	Sleep apnea syndrome
SRBD	Sleep-related breathing disorders

Introduction

Sleep apnea syndrome (SAS) constitutes a paucity of various disorders, referred as sleep-related breathing disorders (SRBD) [1]. It is characterized by repetitive episodes of total or partial breathing cessation during sleep, which cause sudden arousals and fragmentation of sleep [2]. SAS is diagnosed through night polysomnography study (gold standard) or nocturnal cardiorespiratory polygraphy, which both detect and measure multiple respiratory, cardiac and sleep parameters.

The syndrome is divided in two main categories according to the pathophysiological mechanism, the obstructive sleep apnea (OSA) and central sleep apnea (CSA). OSA is associated with total or partial occlusion of upper airway tract due to increased collapsibility of the

airway tissues during sleep, and it is characterized by the existence of thoraco-abdominal ventilatory efforts during apneic events. In contrast, CSA is characterized by the absence or decrease in thoraco-abdominal movements during apneic events [3].

It has been estimated that 4 % of middle-aged men and 2 % of middle-aged women suffer from SAS, although it is underdiagnosed [4, 5]. Epidemiological studies have shown an independent association between OSA and hypertension, coronary artery disease, heart failure, stroke and insulin resistance [5, 6]. Sleep-related breathing disorders, especially CSA, affect approximately 40 % of patients with chronic heart failure (HF) and seem to be a marker of HF severity and mortality [6–9]. In patients with congestive HF, CSA presents as a waxing and waning breathing pattern followed by apnea or hypopnea in >3 consecutive respiratory cycles, i.e., Cheyne–Stokes respiration (CSR) [3].

Numerous new pharmaceutical agents have been proposed during the last decades for treating HF, such as beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin II antagonists with substantially positive results [10, 11]. Moreover, biventricular pacing and, particularly, cardiac resynchronization therapy (CRT) have been recently proposed as an adjunctive to pharmaceutical treatment both for HF and for SAS [7–9, 12, 13]. Several studies have tried to implement atrial overdrive pacing (AOP) alone or with CRT or overdrive ventricular pacing (OVP) in the treatment of SRBD patients with or without HF with ambiguous results [3, 14, 15]. The aim of this systematic review is to investigate the effects of the aforementioned types of cardiac pacing in SRBD patients with or without HF.

Methods

Search strategy

Systematic literature review and critical synthesis of evidence according to the PRISMA statement for systematic reviews [16] and the Cochrane guidelines for reviewing non-randomized studies was performed [17].

The PubMed and Cochrane Central Register of Controlled Trials were searched from April 2015 to January 2016 using 'sleep apnea', 'sleep apnoea', 'sleep disordered breathing', 'Cheyne-Stokes respiration', 'cardiac pacing', 'resynchronization therapy' and 'cardiac resynchronization therapy' as keywords (MEDLINE search terms in "Appendix"). Only human studies and articles in English language were included. Cross-referencing was performed using the bibliographies from the articles obtained, while pediatric and neonatal studies were not included.

Selection process

Two independent reviewers (AD, CA) screened all potentially relevant titles and abstracts for eligibility. The remaining articles underwent full-text review; again, studies that that did not fit inclusion criteria were excluded. All trials evaluating the effect of different types of pacing (CRT, AOP and OVP) in patients with CSA and OSA were considered eligible. These types include CRT, which is characterized by biventricular pacing and atrial overdrive pacing.

The authors completed the literature search and selected by consensus the studies based on inclusion criteria as judged by title, abstract and complete manuscript. Each article with conflicting opinion from the two initial reviewers was discussed with another reviewer (XT) for a final resolution. Intrarater reliability was measured with a 10 % sample of citations, resulting in a kappa of 1, an absolute agreement.

The effect of each intervention on apnea–hypopnea index (AHI; baseline and post-intervention difference) was used as main outcome. AHI is the main parameter measured for SAS diagnosis during polysomnography study and is calculated as the total number of apneas (complete cessation of airflow $\geq$10 s) and hypopneas ($\geq$30 % decrease in airflow amplitude followed by $\geq$4 % decrease in oxygen saturation) divided by the number of sleeping hours recorded. Rates of AHI >5–15/h set the diagnosis of SAS [3]. In this study, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed to create a four-phase flow diagram (Fig. 1).

Data assessment

Because of the heterogeneity in outcome measures, quantitative synthesis of evidence was not feasible. The vast majority of studies did not mention a 95 % confidence interval of the difference. Evidence was critically synthesized in order to answer the review questions, taking into account study heterogeneity and validity. A p value <0.05 was considered to indicate statistical significance.

Search results

Initial search yielded 360 (208 PubMed and 152 Cochrane Library) references. After removing duplicates and exclusions based on title and/or abstract, 22 studies remained and underwent full-text review [3, 7–9, 12–14, 18–32] (Fig. 1).

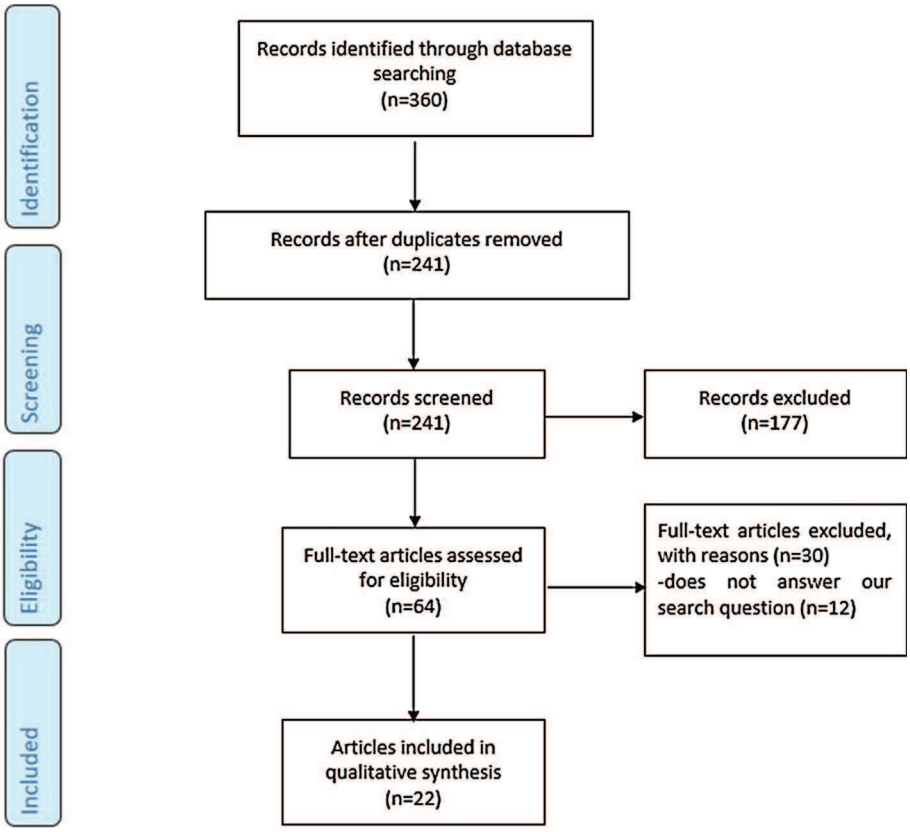

Fig. 1 Flow diagram of articles identified during the study selection process

Results

In order to clarify the effect of any of these pacing interventions in different types of SRBD, the studies and their results were classified as shown in Tables 1, 2, 3, 4. One study, in which OVP was used as an alternative treatment, was not classified in any of the previous subgroups. In this randomized, crossover study, in patients with either CSA or OSA, with or without HF, OVP resulted in modest improvements in central events [3].

In total, 128 patients participated in studies in which only CRT was undertaken in CSA individuals. All studies were not randomized, maximum duration of intervention was 6 months, and the intervention improved ejection fraction (EF), CSA symptoms and AHI in all participants (Table 1).

In the subgroup of studies of CRT with the participation of both CSA and OSA patients, 148 individuals took part, all studies were not randomized, maximum duration of intervention was 6 months, and CRT improved AHI, mainly regarding CSA, in all of the aforementioned studies (Table 2).

Moreover, regarding the studies where AOP with different other additional interventions (such as CRT or CPAP) was undertaken in patients diagnosed with OSA, eight out of nine studies were randomized and crossover. The total number of individuals was 137, while the maximal intervention period was 6 months. In most of the studies, there was no significant improvement in AHI (Table 3).

We found only one randomized, crossover study of CSA patients with HF who underwent CRT with or without AOP. Thirty individuals participated, the intervention lasted 3 months, and AOP achieved minor but statistically significant improvement in combination with CRT (Table 4).

Our search yielded three randomized, crossover, controlled studies and one not controlled, all of which examined the effect of AOP in both CSA and OSA individuals. In a total of 52 patients, most of them without HF, significant improvement in AHI either in CSA or in OSA patients was observed. The maximum intervention lasted 7 months (Table 4). Using populations of CSA and OSA patients with already implanted pacemakers, four randomized, crossover studies showed controversial results when compared AOP with pacing.

Discussion

This systematic review examined all studies related to pacing intervention in SRBD patients with or without HF. The results are controversial, and in order to obtain more

Table 1 CRT in patients with CSA

Author	Year	Type of study Control	N (sample)	SRBD type	Heart failure	Intervention Duration	EF (%)	AHI (pre–post or between interventions)	Conclusion
Skobel [8]	2005	Not randomized Controlled (patients without SRBD)	32	CSA	Yes	CRT 3–6 months	For both groups: 19 ± 5 (pre) versus 33 ± 8 (post)	18 ± 8 (pre) versus 3 ± 2 (post), $p < 0.0001$ (SS)	CRT reduced CSR
Hagenah [29]	2010	Not randomized Controlled (patients without CSA)	57	CSA	Yes	CRT 5 years	CSA patients: 25.9 ± 3.7 (pre) No CSA patients: 27.3 ± 5.1 (pre) No post-values	Baseline AHI: 22 ± 13 (only)	CRT improved mortality CRT improved CSR in patients with HF
Gabor [13]	2005	Not randomized Uncontrolled	10	Mainly CSA	Yes	CRT 6 months	19.0 ± 4.2 (pre) versus 24.2 ± 7.8 (post), $p < 0.05$ (SS)	Total AHI: 42.7 ± 9.1 (pre) versus 30.8 ± 18.7 (post), NS Central AHI: 30.6 ± 14 (pre) versus 15.3 ± 16.5 (post), SS Obstructive AHI: 9.7 ± 12.3 (pre) versus 11.8 ± 10.2 (post), NS	Improvement in CSA with CRT may contribute to good clinical outcome in patients treated with CRT
Sinha [9]	2004	Not randomized Controlled (patients without SRBD)	14	CSA	Yes	CRT 17 ± 7 weeks (4–6 months)	Total: 24 ± 6 (pre) versus 34 ± 10 (post), SS CSA patients: 25 ± 5 (pre) versus 35 ± 9 SS No SRBD patients: 23 ± 7 (pre) versus 33 ± 11 (post), SS	Total AHI: 11.9 ± 11.7 (pre) versus 3.3 ± 3.8 (post), SS Central AHI: 19.2 ± 10.3 (pre) versus 4.6 ± 4.4 (post), $p < 0.001$ (SS)	CRT improved CSA and sleep quality
Yiu [7]	2008	Not randomized Uncontrolled	15	Mainly CSA	Yes	CRT 3 months	28.8 ± 2.5 (pre) versus 38.1 ± 2.3 (post), $p < 0.01$ (SS)	Total AHI: 27.5 ± 4 (pre) 7 versus 18.1 ± 3 (post), $p = 0.05$ (SS) Central AHI: 7.8 ± 2.6 (pre) versus 3 ± 1.3 (post), $p = 0.03$ (SS)	CRT improved CSA

SRBD sleep-related breathing disorders, *AHI* apnea–hypopnea index, *CSA* central sleep apnea, *CRT* cardiac resynchronization therapy, *EF* ejection fraction, *pre* before intervention, *post* after intervention, *SS* statistically significant, *NS* nonsignificant

reliable conclusions about the effect of pacing on SRBD, the studies were categorized according to the intervention (type of pacing) and the type of SRBD of the participating individuals.

CRT in CSA patients

Biventricular pacing, known as CRT, has been used as an adjunctive treatment for HF patients in combination with

modern medical treatment and recent research efforts report encouraging results, with regard to the effect on CSA. Skobel et al. [8] studied 32 HF patients with CSA or no SRBD for 6 months and reported that CRT not only improves Cheyne–Stokes respiration, but it also improves sleep quality and symptomatic depression of these patients. Furthermore, Hagenah et al. [29], although they examined HF patients with or without CRT for a 5-year period, which resulted in mortality reduction in CSA patients with CRT, they did not obtain sleep investigation parameters after CRT implantation in order to exert more accurate results for its sleep-related effects. In a similar study, Gabor et al. was not able to identify which CHF patients can benefit from CRT. This study was uncontrolled and observational, used a small sample of individuals and resulted in an improvement in cardiac function with CRT and a reduction in frequency of Cheyne–Stokes respiration in some patients [13].

With the intention to explain the interventions on a pathophysiological basis, it is known that left ventricular pressures are increased in congestive heart failure, which result in pulmonary congestion and, possibly, activation of pulmonary J receptors. Subsequently, hyperventilation, hypocapnia and destabilization of ventilation control occur, referred as high loop gain [33], leading to CSA. CRT augments cardiac output, reduces pulmonary congestion and circulation delay and, finally, ameliorates hyperventilation and central events [13]. In a small cohort study, Yiu et al. reported CSA improvement with CRT. Left ventricular ejection fraction increased with the drop in pulmonary arterial systolic pressure (PASP), a possible mechanism of CRT function [7]. Finally, similar results after CRT intervention in HF patients with CSA were reported by Sinha et al. [9], although they used a non-validated method of single-night cardiorespiratory polygraphy instead of polysomnography for measuring AHI and other sleep parameters. Regardless of the variable limitations encountered in the aforementioned studies, there is an undoubted consistency regarding the positive effect of CRT on CSA.

CRT in CSA and OSA patients

Sredniawa et al. [19] concluded that abnormal baseline AHI identifies patients prone to death. In this study, however, Holter-derived AHI was used, which is limited to detect only obstructive events. Individuals were separated in AHI dippers and AHI non-dippers with the former presenting a >50 % reduction in their baseline AHI at the 6 months' follow-up and the latter no improvement or, even, deterioration of the sleep parameter. A higher mortality rate and more major adverse cardiac events occurred at AHI non-dippers. A possible pathophysiological explanation of these results is based on the observation that obstructive apneas reduce dramatically the intrathoracic pressure and left ventricular filling. This results in stroke volume reduction in HF patients in combination with a substantial increase in afterload, which is exacerbated by the increased sympathetic activity due to the intermittent hypoxia episodes during the night. These adverse effects predispose to tachyarrythmias, cardiac remodeling and fibrosis mediated by OSA, which activates angiotensin II and aldosterone axis with, chronically, negative results [19]. Of note, Oldenburg et al. [6] studying 77 individuals using cardiorespiratory polygraphy did not infer any influence of OSA by CRT, while improvement in CSA depended on positive clinical response to CRT.

AOP in OSA patients

An artificial increase in mean nocturnal heart rate, referred as AOP, has been applied alone or in combination with other different interventions in SRBD patients with controversial results. In this context, Pepin et al. [21] compared AOP with atrial synchronous ventricular pacemaker implanted in patients with spontaneous rhythm for 1 month in a randomized, crossover, single-blinded study and showed that it did not significantly change the incidence of obstructive events. These results were consistent with a similar cohort study by Krahn et al. [24] with the difference that participating individuals had no pacing indication. Small population and the absence of full sleep study are notable limitations and, based on the current evidence, permanent pacing in the OSA population does not seem to be justified.

In a randomized, crossover study, Simantirakis et al. [23] implemented continuous positive airway pressure (CPAP) intervention in pacemaker patients with spontaneous rhythm for 1 month and confirmed the high positive effect of CPAP compared with AOP alone. It should be pointed out that the major mechanisms related to obstructive events are the anatomical narrowing of the airway, increased collapsibility of the airway tissues, disturbance in the reflexes that affect the caliber of the upper airway and disturbance of pharyngeal muscle function [23], in all of which CPAP has major effects. Unterberg et al. [27] also used CPAP or AOP in patients with no indication for pacemaker implantation and concluded that AOP is not an alternative strategy to CPAP. Sharafkhaneh et al. [26] compared CPAP with AOP in HF patients and showed the same results, with the exception of the mild effect of AOP on respiratory events in patients younger than 74 years old in the current group. Additionally, in a small group of OSA patients with very low ejection fraction there was a benefit from AOP on respiratory parameters. It has been reported that beneficial effect of AOP can be mediated either by

Table 2 CRT in patients with CSA and OSA

Author	Year	Type of study Control	N (sample)	SRBD type	Heart failure	Intervention Duration	EF (%)	AHI (pre–post or between interventions)	Conclusion
Sredniawa [19]	2009	Not Randomized Controlled (patients with non-abnormal AHI)	71	CSA and OSA	Yes	CRT 6 months	Abnormal AHI group: 23.7 ± 6 (pre) Normal AHI group: 24.2 ± 6 (pre) AHI dippers: 35.6 ± 8.8 [post; ΔEF: 10.6 ± 5.7, $p = 0.02$(SS)] versus AHI non-dippers: 28.3 ± 6.5 [post; ΔEF: 6.6 ± 6.3, $p = 0.02$ (SS)], $p = 0.01$ (SS)	AHI dippers: 28.1 ± 2.1 (pre) versus 8.9 ± 7.9 (post), $p < 0.001$ (SS) AHI non-dippers: 28.1 ± 2.1 (pre) versus 11.6 ± 8.5 (post), $p < 0.001$ (SS) Mean AHI: 18.5 ± 4.4 (pre) versus 6.9 ± 6.9 (post), $p < 0.001$ (SS)	Abnormal baseline AHI identifies patients prone to death in midterm observation
Oldenburg [6]	2007	Not randomized Controlled (patients without SRBD)	77	CSA and OSA	Yes	CRT 6 months	All patients: 25.5 ± 5.9 (pre) versus 30.2 ± 7 (post), $p < 0.001$ (SS) CSA patients: 25.2 ± 6.1 (pre) versus 29.1 ± 7.3 (post), $p = 0.003$ (SS) OSA patients: 26.3 ± 5 (pre) versus 30.9 ± 6.7 (post). $p = 0.006$ (SS) No SRBD: 24.9 ± 5.9 (pre) versus 31.8 ± 6.1 (post), $p = 0.007$ (SS)	Total AHI: 21.2 ± 17 (pre) versus 13.7 ± 12.2 (post), $p < 0.001$ (SS) Central AHI: 31.2 ± 15.5 (pre) versus 17.3 ± 13.7 (post), $p < 0.001$ (SS) Obstructive AHI: 18.2 ± 13.3 (pre) versus 14.6 ± 9.8 (post),NS	Improvement in CSA with CRT depends on good clinical and hemodynamic response to CRT-OSA not influenced by CRT

SRBD sleep-related breathing disorders, *AHI* apnea–hypopnea index, *CSA* central sleep apnea, *OSA* obstructive sleep apnea, *CRT* cardiac resynchronization therapy, *EF* ejection fraction, *pre* before intervention, *post* after intervention, *SS* statistically significant, *NS* nonsignificant, *AHI dippers* ≥50 % relative AHI improvement, *AHI non-dippers* <50 % AHI improvement or change from baseline normal to borderline abnormal AHI after 6 months of CRT

counteracting nocturnal hypervagotonia or by improvement in cardiac function and stabilization of ventilatory control [26].

Furthermore, some studies have examined whether different levels of AOP could exert different, beneficial or not, effects. Luthje et al. reported no beneficial effect of two different AOP rates (7 beats/min and 15 beats/min more than mean nocturnal heart rate) compared with pacing in OSA individuals. Nevertheless, they used a non-validated calibrated respiratory inductive plethysmography instead of polysomnography [22]. A similar non-beneficial effect of two different levels of AOP (10 or 20 beats/min more than mean nocturnal heart rate) against pacing mode (50 beats/min) was also reported in OSA patients [25]. Also, a randomized, crossover study by the same group did not show significantly beneficial effects when HF patients with OSA were subjected to 3 months in either CRT alone or CRT with AOP [12]. Finally, using the same intervention for 6 months in HF patients, Stanchina et al. observed no additional impact on sleep architecture or daytime symptom scores, although CRT improved hemodynamic parameters and reduced AHI, which is consistent with aforementioned results of other studies. Improvement in AHI strongly correlated with change in circulatory time, an indirect measure of cardiac output [28].

CRT and AOP in CSA patients

Luthje et al. showed that AOP exerted a minor but significant additional benefit to CRT. However, they included a small

Table 3 AOP in patients with OSA

Author	Year	Type of study Control	N (sample)	SRBD type	Heart failure	Intervention Duration	EF (%)	AHI (pre–post or between interventions)	Conclusion
Pepin [21]	2005	Randomized crossover Controlled (used as control pacemaker patients)	15	OSA	No	No pacing or AOP 1 month	Baseline: 64 ± 13 No post-values	43.3 ± 27 (no pacing) versus 50.1 ± 24.1 (AOP), NS	No significant improvement in AOP on OSA
Luthje [22]	2005	Randomized crossover single blinded Controlled (used as control pacemaker patients)	20	OSA	Yes	No pacing or AOP (7 bpm and 15 bpm) 3 days	Baseline: 48, 6 ± 32 No post-values	20.9 ± 2.1 (no pacing) versus 19.5 ± 2.4 (AOP 7 bpm) versus 17.8 ± 1.9 (AOP 15 bpm), NS	AOP not appropriate for treatment of SRBD
Simantirakis [23]	2005	Randomized crossover single blinded Controlled [pacemaker patients only for the short term (1 day)]	16	OSA	No	AOP (15 bpm) versus pacing and CPAP 2 months	Baseline: 59 ± 4 No post-values	Short term (1 day, AOP): 55.8 (baseline) versus 56.1 (AOP; Dif.: +0.3–95 % CI: −3.4 to +4.1), $p = 0.82$ (NS) Long term (1 month, AOP) 49 (baseline) versus 49.2 (AOP; Dif: +0, 2–95 % CI: −2.7 to +2.3), $p = 0.87$ (NS) Short term (1 day, pacing) : 42.3 (baseline) versus 41.9 (pacing; Dif: −0.4, 95 % CI: −3.5 to +2.8), $p = 0.78$ (NS) Long term (1 month, pacing and n-CPAP): 49 (baseline) versus 2.7 (n-CPAP) Dif: −46.3, 95 % CI: −56.2 to −36.5), $p < 0.001$ (SS)	AOP has no significant effect on OSA, whereas n-CPAP is highly effective
Krahn [24]	2006	Randomized crossover single blinded Controlled (used as control patients with spontaneous rhythm)	15	OSA	No	AOP versus pacing off 2 days	Not mentioned	38.6 ± 20.5 (pacing 75 bpm) versus 42.1 ± 20.7 (pacing off), [Dif: −3.4, 95 % CI: −9.3 to +2.5, $p = 0.23$ (NS)]	Temporary atrial pacing does not appear to improve OSA
Shalaby [25]	2007	Randomized crossover single blinded Controlled	14	OSA	No	Pacing (50 bpm) versus AOP (2 levels of pacing: 10, 20 bpm more than mean nocturnal heart rate) <1 month	Baseline: 50 ± 14 No post-values	32 ± 22 (pacing) versus 34 ± 22 (AOP-10 bpm) versus 31 ± 17 (AOP-20 bpm), $p = 0.8$ (NS)	AOP demonstrated no benefit to obstructive SRBD of at least moderate severity

Table 3 continued

Author	Year	Type of study Control	N (sample)	SRBD type	Heart failure	Intervention Duration	EF (%)	AHI (pre–post or between interventions)	Conclusion
Sharafkhaneh [26]	2007	Randomized crossover single blinded Controlled (used as control pacemaker patients)	15	Mainly OSA	Yes	AOP (15 bpm) versus pacing versus CPAP 3 days	Baseline: 38 ± 14.4	36 (24, 6; no pacing-N) versus 31 (20; pacing-O) versus 7 ± 7, 9 (CPAP) and 41 (no pacing-N) versus 27 (pacing-O) in patients under 74 years old	AOP exerts a mild effect in some heart failure patients with OSA CPAP dramatically improved AHI
Unterberg [27]	2005	Randomized crossover single blinded Controlled (used as control CPAP only patients)	10	OSA	No	AOP versus CPAP 3 days	Baseline: 55(36–66)	41 (12–66.6; baseline) versus 39.1 (8.7–78.5; AOP), NS versus 2.2 (0.3–12.4; CPAP), $p = 0.002$ (SS)	AOP is no alternative therapeutic strategy to CPAP for the treatment of OSA
Shalaby [12]	2011	Randomized crossover single blinded Controlled (used as control patients with CRT)	19	Mainly OSA	Yes	CRT versus AOP + CRT 3 months	All patients: 33.3 ± 9.8 (pre) versus 34.8 ± 10.8 (FFU; NS) versus 36.1 ± 9.3 (LFU; NS) CRT: 35.7 ± 11.2 (pre) versus 37.5 ± 12.4 (FFU; NS) versus 38.6 ± 11.1 (LFU; NS) CRT + AOP: 30.2 ± 7.3 (pre) versus 31.6 ± 8.2 (FFU; NS) versus 33.5 ± 6.9 (LFU; NS)	21.5 ± 15.3 (CRT) versus 24.9 ± 21.9 (AOP + CRT), NS	CRT has no impact on obstructive SRBD with or without AOP
Stanchina [28]	2007	Not randomized Uncontrolled	13	OSA	Yes	CRT versus AOP + CRT 17 ± 7 weeks (4–6 months)	22 ± 17 (pre) versus 33.6 ± 2 (post), $p < 0.05$ (SS)	Baseline versus CRT: 40, 9 ± 6,4 versus 29, 5 ± 5, 2, $p = 0$, 04 (SS) CRT versus AOP + CRT 29, 5 ± 5, 2 versus 31,1 ± 7, 8, NS	CRT improved cardiac function and reduced AHI-AOP and CRT combination no impact on severity

SRBD sleep-related breathing disorders, *AHI* apnea–hypopnea index, *OSA* obstructive sleep apnea, *CRT* cardiac resynchronization therapy, *AOP* atrial overdrive pacing, *CPAP* continuous positive airway pressure, *EF* ejection fraction, *FFU* first follow-up, *LFU* last follow-up, *SS* statistically significant, *NS* nonsignificant, *Dif* difference, *95 % CI* 95 % confidence interval

Table 4 AOP in patients with CSA or both CSA and OSA

Author	Year	Type of study Control	N (sample)	SRBD type	Heart failure	Intervention Duration	EF (%)	AHI (pre–post or between interventions)	Conclusion
Luthje [15]	2009	Randomized crossover controlled (used as a control group no CSA patients)	30	CSA	Yes	CRT alone and CRT versus AOP + CRT 3 months	CRT alone: All patients: 22.2 ± 4.6 (pre) versus 29.8 ± 8.2 (post), $p < 0.0001$ (SS) CSA patients: 20.7 ± 4.6 (pre) versus 7.7 ± 5.8 change (SS) No CSA patients: 24.4 ± 3.6 (pre) versus 7.5 ± 7.8 change (SS) No measurement of hemodynamic effect of AOP	CRT alone: Central AHI: 33.6 ± 14.3 (pre) versus 23.8 ± 16.9 (post), $p < 0.01$ (SS) Total AHI: 37.1 ± 13.4 versus 25.7 ± 17.5, $p < 0.01$ (SS) CRT alone versus AOP + CRT: Central AHI: 23.8 ± 16.9 versus 21.5 ± 16.9, $p < 0.01$ (SS) Total AHI: 25.7 ± 17.5 versus 23.7 ± 17.9, NS	CRT improved CSA AOP + CRT minor but statistically significant additional improvement in CSA
Kato [30]	2001	Not randomized Controlled	6	OSA and CSA	Yes	Pacing (increased heart rate) 1 week	Baseline 73 ± 2 Not measured after cardiac pacemaker implantation	15.5 ± 20.7 (Control–no pacing) versus 9.8 ± 10.9 (pacemaker-increased heart rate) , $p < 0.05$ (SS)	The increase in cardiac output resulted in AHI reduction and/or CSR improvement
Sinha [31]	2009	Randomized crossover Controlled (used as a control group pacemaker or ICD patients)	12	OSA or mixed SRBD	Yes	Pacemaker/ ICD versus AOP 4 and 7 months	All patients: 38.3 ± 13.6 (pre) Group A: 31.5 ± 7.8 Group B: 41 ± 15.1 Not measured at follow-up	Group A: 26.5 ± 28.9 (baseline) versus 30.5 ± 23.8 (4-months AOP), NS Group B: 28.7 ± 15.4 (baseline) versus 43.5 ± 17.4 (7-months AOP), NS	Long-term dynamic AOP did not improve PSQI or SAS
Garrigue [14]	2002	Randomized crossover Controlled (used as a control group pacemaker patients)	15	CSA or OSA	No	Spontaneous rhythm versus AOP 3 days	Baseline: 54 ± 11 No post-values	Total AHI: 28 ± 22 (no pacing) versus 11 ± 14 (AOP), $p < 0.001$ (SS) Central AI: 13 ± 17 (no pacing) versus 6 ± 7 (AOP), $p = 0.007$ (SS) Obstructive AI: 6 ± 4 (no pacing) versus 3 ± 1 (AOP), $p = 0.03$ (SS)	AOP reduces episodes of OSA and CSA

Table 4 continued

Author	Year	Type of study Control	N (sample)	SRBD type	Heart failure	Intervention Duration	EF (%)	AHI (pre–post or between interventions)	Conclusion
Melzer [32]	2006	Randomized crossover single blinded Controlled (used as a control group pacemaker patients)	19	CSA or OSA	Yes	Pacemaker versus NOP (17 bpm) 2 weeks	All patients: 53.4 ± 11 (pre) Responders: 51.6 ± 9.8 Non-responders: 54.3 ± 12.1 No post-values	26.8 ± 17.1 (pacemaker) versus 23 ± 16.7 (NOP), $p = 0.49$ (NS)	Nocturnal overdrive pacing did not improve AHI in patients with SAS

SRBD sleep-related breathing disorders, *SAS* sleep apnea syndrome, *AHI* apnea–hypopnea index, *CSA* central sleep apnea, *OSA* obstructive sleep apnea, *CRT* cardiac resynchronization therapy, *AOP* atrial overdrive pacing, *EF* ejection fraction, *SS* statistically significant, *NS* nonsignificant

sample of CSA positive patients, while the study estimated only the acute effect of AOP and only for a single night [15].

AOP in CSA and OSA patients

Kato et al. [30] investigated the effect of pacemaker therapy in three patients with either OSA or CSA and bradydysrhythmias in comparison with three other patients without pacemaker (control group) and reported an increase in AHI simultaneously with the increase in heart rate or an improvement in CSR breathing in the former group. On the other hand, other groups did not report a significant beneficial effect of AOP in AHI or Pittsburgh Sleep Quality Index [31, 32]. However, the investigators of one of these two studies [32] observed a group of seven patients, referred as responders, in whom AHI was improved [control 29.3 ± 12.1 vs. nocturnal overdrive pacing (NOP): 12.3 ± 4.0, $p = 0.04$] predominantly due to improvement in hypopnea index [control 20.6 ± 5.9 vs. NOP: 8.6 ± 4.5, $p = 0.001$]. Moreover, these patients had increased duration of sleep, more extended stages 1 and 2 and shorter slow wave sleep stage. Furthermore, Garrigue et al. reported that AOP substantially reduced the number of episodes of CSA or OSA. They suggested that apnea induces hypoxemia, hypercapnia, bradycardia and hypotension which are associated with an increase in vagal tone and periodic variation in heart rate and may influence the incidence of CSA. Hence, the reduction in the variations in heart rate with AOP results to a decrease in apnea episodes. Another possible mechanism is that AOP may counteract the increases in vagal tone by maintaining sympathetic activity [14].

OVP in CSA and OSA patients

Bordier et al. investigated the effect of a different way of pacing named overdrive ventricular pacing (OVP) in OSA and CSA patients in a randomized, crossover study. They reported a modest alleviation of CSA in those with HF by a single overnight OVP. It should be mentioned that this study has some limitations, such as the small size of the entire population and the absence of baseline recording of nocturnal ventilatory polygraphy [3].

Of note, CRT in HF patients with CSA substantially improves their starting low EF, which is consistent with the simultaneous improvement in CSA in these patients [7–9, 13, 15]. Additionally, pacing in a group of OSA patients with low EF may improve both cardiac function and OSA [26, 28], although not always [6]. This is consistent with the recently reviewed bidirectional relationship of OSA and CSA in low EF patients [34]. In these patients, overnight fluid shifting out of the intravascular and interstitial compartment of the leg due to gravity determines SRBD type. In OSA patients, neck accumulation of fluids exists, which results in increase in peripharyngeal tissue pressure, reduction in upper airway size and exacerbation or pathogenesis of OSA. On the other hand, in CSA patients, overnight fluid shifting results in increase in venous return to the heart and thorax, increase in pulmonary capillary wedge pressure and accumulation of fluids to the lungs, which exacerbates or generates CSA. Optimization of HF therapy with pacing results in cardiac output augmentation, as previously mentioned, with the subsequent EF increase and the simultaneous SRBD improvement. Consistent with the previous mechanism, pacing in SA patients with no left ventricular dysfunction and normal EF was not beneficial, although EF data are incomplete [21–23, 25, 27].

Besides pacing, other interventions may benefit patients with low EF and CSA. Acetazolamide improves CSA by attenuating ventilatory sensitivity, which is increased in CSA [35], while beta-blockers, such as carvedilol [36] and metoprolol [37], may modulate ventilatory response in HF due to beneficial effects on myocardium and cardiac

function. Finally, left ventricular assist device has been shown to resolve CSA 10 months after implantation by increasing cardiac output, relieving symptoms and increase exercise tolerance [38].

Conclusions

The overall results show that CSA can be improved using CRT, but the use of AOP was not associated with similar positive results. Regarding OSA, the results using CRT or AOP are controversial. Definite conclusions cannot be drawn, since studies have many limitations, but based on the current evidence, it can be assumed that pacing cannot be used alone as treatment of SRBD. In any case, the studies that applied a same type of pacing may not be conclusive, but they can contribute to the understanding of pathophysiology of SAS in patients with or without HF. Future randomized controlled trials will elucidate the exact effect of the specific types of pacing in the treatment of SAS.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Appendix

("sleep apnoea"[All Fields] OR "sleep apnea syndromes"[MeSH Terms] OR ("sleep"[All Fields] AND "apnea"[All Fields] AND "syndromes"[All Fields]) OR "sleep apnea syndromes"[All Fields] OR ("sleep"[All Fields] AND "apnea"[All Fields]) OR "sleep apnea"[All Fields]) AND (("heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) AND pacing[All Fields]) AND (resynchronization[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])), ("cheyne-stokes respiration"[MeSH Terms] OR ("cheyne-stokes"[All Fields] AND "respiration"[All Fields]) OR "cheyne-stokes respiration"[All Fields] OR ("cheyne"[All Fields] AND "stokes"[All Fields] AND "respiration"[All Fields]) OR "cheyne stokes respiration"[All Fields]) AND (("heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) AND pacing[All Fields]) AND ("cardiac resynchronization therapy"[MeSH Terms] OR ("cardiac"[All Fields] AND "resynchronization"[All Fields] AND "therapy"[All Fields]) OR "cardiac resynchronization therapy"[All Fields]), (("heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) AND PACING[All Fields]) AND ("sleep apnoea"[All Fields] OR "sleep apnea syndromes"[MeSH Terms] OR ("sleep"[All Fields] AND "apnea"[All Fields] AND "syndromes"[All Fields]) OR "sleep apnea syndromes"[All Fields] OR ("sleep"[All Fields] AND "apnea"[All Fields]) OR "sleep apnea"[All Fields]), ("sleep apnea syndromes"[MeSH Terms] OR ("sleep"[All Fields] AND "apnea"[All Fields] AND "syndromes"[All Fields]) OR "sleep apnea syndromes"[All Fields] OR ("sleep"[All Fields] AND "disordered"[All Fields] AND "breathing"[All Fields]) OR "sleep disordered breathing"[All Fields]) AND (("heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) AND pacing[All Fields]) AND ("cardiac resynchronization therapy"[MeSH Terms] OR ("cardiac"[All Fields] AND "resynchronization"[All Fields] AND "therapy"[All Fields]) OR "cardiac resynchronization therapy"[All Fields]).

References

1. Roldan G, Ang RC (2006) Overview of sleep disorders. Respir care clin North America 12(1):31–54
2. Pashayan AG, Passannante AN, Rock P (2005) Pathophysiology of obstructive sleep apnea. Anesthesiol Clin North America 23(3):431–443. doi:10.1016/j.atc.2005.02.004
3. Bordier P, Maurice-Tison S, Ramana NK (2012) Overdrive ventricular pacing in pacemaker recipients with permanent atrial fibrillation and sleep apnea. J Clin Sleep Med 8(3):257–264. doi:10.5664/jcsm.1908
4. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S (1993) The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 328(17):1230–1235. doi:10.1056/NEJM199304293281704
5. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS (2002) Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 165(5):670–676. doi:10.1164/ajrccm.165.5.2103001
6. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V (2007) Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail 9(3):251–257. doi:10.1016/j.ejheart.2006.08.003
7. Yiu KH, Lee KL, Lau CP, Siu CW, Miu KM, Lam B, Lam J, Ip MS, Tse HF (2008) Alleviation of pulmonary hypertension by cardiac resynchronization therapy is associated with improvement in central sleep apnea. Pacing Clin Electrophysiol 31(12):1522–1527. doi:10.1111/j.1540-8159.2008.01222.x
8. Skobel EC, Sinha AM, Norra C, Randerath W, Breithardt OA, Breuer C, Hanrath P, Stellbrink C (2005) Effect of cardiac resynchronization therapy on sleep quality, quality of life, and symptomatic depression in patients with chronic heart failure and Cheyne-Stokes respiration. Sleep Breath 9(4):159–166. doi:10.1007/s11325-005-0030-1
9. Sinha AM, Skobel EC, Breithardt OA, Norra C, Markus KU, Breuer C, Hanrath P, Stellbrink C (2004) Cardiac resynchronization therapy improves central sleep apnea and Cheyne-Stokes respiration in patients with chronic heart failure. J Am Coll Cardiol 44(1):68–71. doi:10.1016/j.jacc.2004.03.040
10. Metra M, Giubbini R, Nodari S, Boldi E, Modena MG, Dei Cas L (2000) Differential effects of beta-blockers in patients with heart failure: a prospective, randomized, double-blind comparison of the long-term effects of metoprolol versus carvedilol. Circulation 102(5):546–551

11. McKelvie RS, Yusuf S, Pericak D, Avezum A, Burns RJ, Probstfield J, Tsuyuki RT, White M, Rouleau J, Latini R, Maggioni A, Young J, Pogue J (1999) Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD pilot study investigators. Circulation 100(10):1056–1064
12. Shalaby A, Atwood CW, Selzer F, Suffoletto M, Gorcsan Iii J, Strollo P (2011) Cardiac resynchronization therapy and obstructive sleep-related breathing disorder in patients with congestive heart failure. Pacing Clin Electrophysiol 34(5):593–603. doi:10.1111/j.1540-8159.2010.03015.x
13. Gabor JY, Newman DA, Barnard-Roberts V, Korley V, Mangat I, Dorian P, Hanly PJ (2005) Improvement in Cheyne-Stokes respiration following cardiac resynchronisation therapy. Eur Respir J 26(1):95–100. doi:10.1183/09031936.05.00093904
14. Garrigue S, Bordier P, Jais P, Shah DC, Hocini M, Raherison C, Tunon De Lara M, Haissaguerre M, Clementy J (2002) Benefit of atrial pacing in sleep apnea syndrome. N Engl J Med 346(6):404–412. doi:10.1056/NEJMoa011919
15. Luthje L, Renner B, Kessels R, Vollmann D, Raupach T, Gerritse B, Tasci S, Schwab JO, Zabel M, Zenker D, Schott P, Hasenfuss G, Unterberg-Buchwald C, Andreas S (2009) Cardiac resynchronization therapy and atrial overdrive pacing for the treatment of central sleep apnoea. Eur J Heart Fail 11(3):273–280. doi:10.1093/eurjhf/hfn042
16. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux P, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 151(4):W-65–W-94
17. Reeves BC, Deeks JJ, Higgins JP (2008) 13 Including non-randomized studies. Cochrane Handb Syst Rev Interv 1:391
18. Hagenah G, Beil D (2009) Prevalence of Cheyne-Stokes respiration in modern treated congestive heart failure. Sleep Breath 13(2):181–185. doi:10.1007/s11325-008-0218-2
19. Sredniawa B, Lenarczyk R, Kowalski O, Pruszkowska-Skrzep P, Kowalczyk J, Musialik-Lydka A, Cebula S, Kalarus Z (2009) Sleep apnoea as a predictor of mid- and long-term outcome in patients undergoing cardiac resynchronization therapy. Europace 11(1):106–114. doi:10.1093/europace/eun310
20. Oldenburg O, Faber L, Vogt J, Dorszewski A, Szabados F, Horstkotte D, Lamp B (2007) Influence of cardiac resynchronisation therapy on different types of sleep disordered breathing. Eur J Heart Fail 9(8):820–826. doi:10.1016/j.ejheart.2007.03.009
21. Pepin JL, Defaye P, Garrigue S, Poezevara Y, Levy P (2005) Overdrive atrial pacing does not improve obstructive sleep apnoea syndrome. Eur Respir J 25(2):343–347. doi:10.1183/09031936.05.00132703
22. Luthje L, Unterberg-Buchwald C, Dajani D, Vollmann D, Hasenfuss G, Andreas S (2005) Atrial overdrive pacing in patients with sleep apnea with implanted pacemaker. Am J Respir Crit Care Med 172(1):118–122. doi:10.1164/rccm.200409-1258OC
23. Simantirakis EN, Schiza SE, Chrysostomakis SI, Chlouverakis GI, Klapsinos NC, Siafakas NM, Vardas PE (2005) Atrial overdrive pacing for the obstructive sleep apnea-hypopnea syndrome. N Engl J Med 353(24):2568–2577. doi:10.1056/NEJMoa050610
24. Krahn AD, Yee R, Erickson MK, Markowitz T, Gula LJ, Klein GJ, Skanes AC, George CF, Ferguson KA (2006) Physiologic pacing in patients with obstructive sleep apnea: a prospective, randomized crossover trial. J Am Coll Cardiol 47(2):379–383. doi:10.1016/j.jacc.2005.09.026
25. Shalaby AA, Atwood CW, Hansen C, Konermann M, Freedman R, Fowler J, Simpson R, Bornemann MA, Kwok J, Pu Y, Lee K, Hartley J, Willems R, Neuzner J (2007) Analysis of interaction of acute atrial overdrive pacing with sleep-related breathing disorder. Am J Cardiol 99(4):573–578. doi:10.1016/j.amjcard.2006.09.101
26. Sharafkhaneh A, Sharafkhaneh H, Bredikus A, Guilleminault C, Bozkurt B, Hirshkowitz M (2007) Effect of atrial overdrive pacing on obstructive sleep apnea in patients with systolic heart failure. Sleep Med 8(1):31–36. doi:10.1016/j.sleep.2006.06.012
27. Unterberg C, Luthje L, Szych J, Vollmann D, Hasenfuss G, Andreas S (2005) Atrial overdrive pacing compared to CPAP in patients with obstructive sleep apnoea syndrome. Eur Heart J 26(23):2568–2575. doi:10.1093/eurheartj/ehi448
28. Stanchina ML, Ellison K, Malhotra A, Anderson M, Kirk M, Benser ME, Tosi C, Carlisle C, Millman RP, Buxton A (2007) The impact of cardiac resynchronization therapy on obstructive sleep apnea in heart failure patients: a pilot study. Chest 132(2):433–439. doi:10.1378/chest.06-2509
29. Hagenah G, Zapf A, Schuttert JB (2010) Cheyne-stokes respiration and prognosis in modern-treated congestive heart failure. Lung 188(4):309–313. doi:10.1007/s00408-009-9208-9
30. Kato I, Shiomi T, Sasanabe R, Hasegawa R, Otake K, Banno K, Yamakawa H, Mizutani N, Kobayashi T (2001) Effects of physiological cardiac pacing on sleep-disordered breathing in patients with chronic bradydysrhythmias. Psychiatry Clin Neurosci 55(3):257–258. doi:10.1046/j.1440-1819.2001.00849.x
31. Sinha AM, Bauer A, Skobel EC, Markus KU, Ritscher G, Noelker G, Breithardt OA, Brachmann J, Stellbrink C (2009) Long-term effects of dynamic atrial overdrive pacing on sleep-related breathing disorders in pacemaker or cardioverter defibrillator recipients. Pacing Clin Electrophysiol 32(Suppl 1):S219–S222. doi:10.1111/j.1540-8159.2008.02289.x
32. Melzer C, Fietze I, Duru F, Glos M, Lemola K, Bloch K, Erickson M, Cho Y, Markowitz T, Theres H (2006) Nocturnal overdrive pacing for the treatment of sleep apnea syndrome. Sleep 29(9):1197–1202
33. Simantirakis EN, Schiza SE, Siafakas NS, Vardas PE (2008) Sleep-disordered breathing in heart failure and the effect of cardiac resynchronization therapy. Europace 10(9):1029–1033. doi:10.1093/europace/eun190
34. Lyons OD, Bradley TD (2015) Heart Failure and Sleep Apnea. Can J Cardiol 31(7):898–908. doi:10.1016/j.cjca.2015.04.017
35. Javaheri S, Sands SA, Edwards BA (2014) Acetazolamide attenuates Hunter-Cheyne-Stokes breathing but augments the hypercapnic ventilatory response in patients with heart failure. Ann Am Thorac Soc 11(1):80–86. doi:10.1513/AnnalsATS.201306-201OC
36. Tamura A, Kawano Y, Kadota J (2009) Carvedilol reduces the severity of central sleep apnea in chronic heart failure. Circ J 73(2):295–298
37. Kohnlein T, Welte T (2007) Does beta-blocker treatment influence central sleep apnoea? Respir Med 101(4):850–853. doi:10.1016/j.rmed.2006.11.023
38. Vazir A, Hastings PC, Morrell MJ, Pepper J, Henein MY, Westaby S, Poole-Wilson PA, Cowie MR, Simonds AK (2010) Resolution of central sleep apnoea following implantation of a left ventricular assist device. Int J Cardiol 138(3):317–319. doi:10.1016/j.ijcard.2008.06.072