

Cardiac resynchronization therapy for the treatment of sleep apnoea: a meta-analysis

Jasmine Lamba¹, Christopher S. Simpson^{1,2}, Damian P. Redfearn^{1,2}, Kevin A. Michael^{1,2}, Michael Fitzpatrick^{1,2}, and Adrian Baranchuk^{1,2*}

¹Department of Medicine and Physiology, Cardiac Electrophysiology and Pacing, Kingston General Hospital, Queen's University, Kingston, K7L 2V7 Ontario, Canada; and
²Department of Medicine, Kingston General Hospital, Kingston, Ontario, Canada

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Aims

Sleep apnoea (SA) is a common problem among congestive heart failure (CHF) patients. Evidence has shown that cardiac resynchronization therapy (CRT) reduces morbidity and mortality associated with CHF. The aim of this paper was to review studies evaluating the reduction of the Apnoea–Hypopnoea Index (AHI) in patients with SA after treatment with CRT and to perform a meta-analysis to estimate the true effect of CRT on SA.

Methods and results

A systematic electronic literature search was conducted in Medline and Embase to identify studies reporting on the effects of CRT on SA. A hand search of five major cardiology societies was performed to identify any unpublished studies through structured abstracts submitted to conference proceedings. To be eligible for inclusion, studies had to include a comparison of CRT vs. no pacing and use AHI as an outcome. Non-English studies were excluded. Nine manuscripts and five abstracts were identified for review. Six manuscripts and three abstracts were included in meta-analysis, which included 170 patients. After treatment with CRT, a significant reduction in AHI was found in patients with central sleep apnoea (CSA) with a mean reduction of -13.05 (CI -16.74 to -9.36 ; $P < 0.00001$) but not in patients with obstructive sleep apnoea (13.32 ; CI -9.04 to 2.39 ; $P = 0.25$).

Conclusion

Cardiac resynchronization therapy reduces the severity of SA. Major effects are seen in patients with CSA. The presence of SA may be an additional consideration when deciding on which heart failure patients will receive CRT.

Keywords

Cardiac resynchronization therapy • Biventricular pacing • Sleep apnoea • Sleep breathing disorders • Meta-analysis

Introduction

Sleep apnoea (SA) is a common but under-diagnosed breathing disorder that is associated with increases in cardiovascular morbidity and mortality, cardiac arrhythmias, and daytime sleepiness.^{1–6} Both central sleep apnoea (CSA) and obstructive sleep apnoea (OSA) are common problems among symptomatic congestive heart failure (CHF) patients, which has caused some authors to propose that all CHF patients should undergo a sleep study.⁷ In this group of patients, SA increases overnight sympathetic activity, decreases oxygen delivery, and has a negative effect on physical mobility.^{8,9}

Evidence has shown that cardiac resynchronization therapy (CRT) reduces the morbidity and mortality associated with symptomatic CHF.¹⁰ Current guidelines^{10,11} recommend that CRT be offered to patients with a left ventricular ejection fraction (LVEF) of $\leq 35\%$, a wide QRS complex (≥ 120 ms) and left ventricular

dilatation. Many recent studies^{12–20} have demonstrated the positive effect that CRT has on the Apnoea–Hypopnoea Index (AHI—a measure of SA severity).

The goals of this study were to conduct a systematic review to identify all papers evaluating the reduction of the AHI in patients with SA after treatment with CRT and to perform a meta-analysis to estimate the true effect of CRT on SA.

Methods

An electronic search was conducted using Medline and Embase to identify all human studies of CRT in patients with SA that used the AHI as an outcome.

The search used Keywords, Emtree, and MeSH headings and included the following terms: 'cardiac pacing, artificial', 'defibrillators, implantable', 'pacemaker, artificial', 'cardiac resynchronization',

* Corresponding author. Tel: +613 549 6666x3801; fax: 613 548 1387, Email: barancha@kgh.kari.net

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'cardiac resynchronization therapy', 'biventricular pacing', 'sleep apnoea syndrome', 'sleep disordered breathing', and 'sleep apnoea'. In addition, a manual search was conducted of journal issues and abstracts from scientific sessions of the American College of Cardiology (*Journal of the American College of Cardiology*), American Heart Association (*Circulation*), Heart Rhythm Society (*Heart Rhythm*), Europace (*Europace*), and the European Society of Cardiology (*European Heart Journal*) since 2007.

Two researchers (A.B. and J.L.) independently reviewed titles and abstracts and retrieved any relevant articles for inclusion if they (i) compared CRT vs. no pacing in human subjects with SA and advanced symptomatic CHF and (ii) used AHI as an outcome. Articles were included in this study if both reviewers agreed on their relevance and any disagreements were resolved by consensus.

Only studies that were published in English were included in this review.

Data analysis was performed using Review Manager 5.0 using a fixed-effects model. Studies were weighted based on sample sizes and a mean effect size was calculated for the effect of CRT on AHI. A χ^2 test was performed to assess the heterogeneity between studies. Results are reported as mean (95% CI).

Study selection

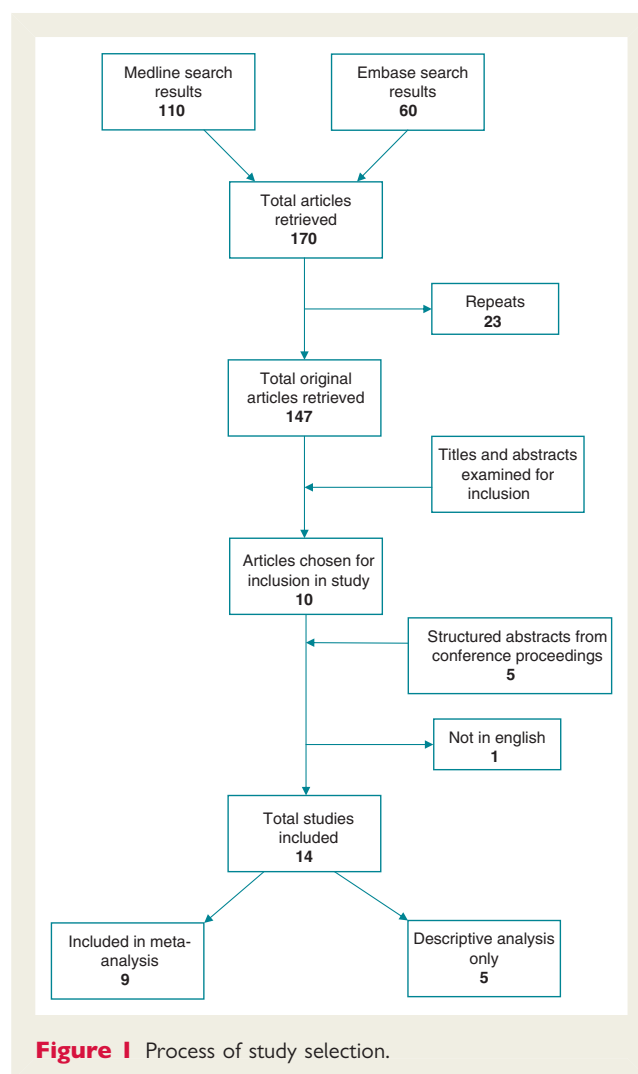
The process of study selection is outlined in *Figure 1*. Two reviewers (J.L. and A.B.) independently reviewed titles and abstracts and retrieved studies that they felt were relevant for inclusion. Their inter-rater reliability was found to be very good ($\kappa = 0.858$, 95% CI 0.701–1). A total of 10^{12–21} studies and 5^{22–26} abstracts were identified for inclusion but 1 study²¹ was excluded before analysis. Some authors were contacted for unpublished information and clarification of their results.^{17,23,26} Two^{23,26} of the three authors replied to our requests for further information.

Five of the 14 studies were not included in the meta-analysis for various reasons: 2 of the studies^{13,25} had very different study designs and follow-up times, 2 studies^{18,22} separated their follow-up results into 2 separate groups based on their response to CRT, and 1 study¹⁷ only reported results graphically and not numerically. Studies not included in the meta-analysis are described separately.

Results

A total of 14^{12–26} studies were included in this systematic review. Nine of the 14 studies^{12–20} were published in manuscript form while 5 studies^{22–26} were published as structured abstracts from international conference proceedings. Characteristics of included studies are described in *Table 1*. Most studies separated patients into groups depending on the predominant type of SA that they suffered from. However, one study¹⁸ included patients with OSA and Mixed SA ($n = 31$) without specifying how many patients had each type of SA. This study was not meta-analysed due to the method by which the results were reported. Two studies^{20,23} did not categorize patients into specific types of SA but rather combined all their results irrespective of the type of SA ($n = 27$). Their results were included in the meta-analysis under the subgroup 'All Types of Sleep Apnoea (CSA, OSA, and Mixed)' in *Figure 2*.

Six manuscripts^{12,14–16,19,20} and three structured abstracts^{23,24,26} were meta-analysed to determine the real effect of CRT on AHI in



patients with SA (*Figure 2*). Overall, CRT significantly reduced AHI scores by a mean of -9.63 (CI -11.66 to -7.61 , $P < 0.00001$). Subgroup analysis was conducted for five studies^{12,14–16,24} that involved patients with CSA, three studies^{15,19,26} that involved patients with OSA, and two studies^{20,23} that included all different types of SA. After treatment with CRT, a significant reduction in AHI was found in patients with CSA with a mean reduction of -13.05 (CI -16.74 to -9.36 ; $P < 0.00001$) but not in patients with OSA (-3.32 ; CI -9.04 to 2.39 ; $P = 0.25$).

Studies were statistically similar under all subgroups as well as overall and therefore, could be appropriately combined as determined by χ^2 tests (CSA $P = 0.84$, OSA $P = 0.25$, all types $P = 0.55$, overall $P = 0.18$). One study by Oldenburg *et al.*¹⁵ was included under the CSA subgroup as well as the OSA subgroup since the patients' results were appropriately separated into two groups. Olson *et al.*²⁴ reported AHI results from CSA and Mixed SA patients as one group. Their results were included under the CSA subgroup in the meta-analysis.

Two studies^{14,26} evaluated CRT with atrial overdrive pacing (AOP) compared with CRT alone as well as to baseline (*Table 2*). When comparing CRT + AOP with CRT alone, both

Table 1 Characteristics of included studies

Study name	Pre-post-design	Predominant type of SA (CSA, OSA, Mixed, and All)	Polysomnography	Blind (D, S, NR)	CRT vs. no CRT	CRT vs. no CRT vs. CRT + AOP
<i>Published studies</i>						
Sinha et al. ¹⁶	Yes	CSA (n = 14)	Yes	NR	Yes	No
Gabor et al. ¹²	Yes	CSA (n = 10)	Yes	S	Yes	No
Skobel et al. ¹⁷	Yes	CSA (n = 11)	Yes	NR	Yes	No
		Mixed (n = 7)				
Oldenburg et al. ¹⁵	Yes	CSA (n = 36)	Yes	S	Yes	No
		OSA (n = 26)				
Stanchina et al. ¹⁹	Yes	OSA (n = 13)	Yes	S	Yes	No
Kara et al. ¹³	No (Mixed design)	CSA (n = 11)	Yes	S	Yes	No
		OSA (n = 1)				
Yiu et al. ²⁰	Yes	All (n = 15)	Yes	S	Yes	No
Sredniawa et al. ¹⁸	Yes	OSA or Mixed (n = 31)	No (Holter monitor)	NR	Yes	No
Lüthje et al. ¹⁴	No (Mixed design)	CSA (n = 18)	Yes	S	Yes	Yes
<i>Abstracts</i>						
Magnano et al. ²²	Yes	CSA (n = 9)	Yes	NR	Yes	No
		OSA (n = 13)				
Matsushita et al. ²³	Yes	All (n = 12)	Yes	NR	Yes	No
Seidl et al. ²⁵	Yes	CSA (n = 15)	Yes	NR	Yes	No
		OSA (n = 6)				
Olson et al. ²⁴	Yes	CSA (n = 9)	Yes	NR	Yes	No
		OSA (n = 3)				
		Mixed (n = 7)				
Shalaby et al. ²⁶	No (RCT)	OSA (n = 19)	Yes	NR	Yes	Yes

All, all types; AOP, atrial overdrive pacing; CRT, cardiac resynchronization therapy; CSA, central sleep apnoea; D, double; Mixed, mixed sleep apnoea; NR, not reported; OSA, obstructive sleep apnoea; S, single; SA, sleep apnoea.

studies found that the addition of AOP did not significantly add to the reduction in AHI.

We calculated the mean LVEF (mean \pm SD) for studies under each subgroup that reported on this outcome to see if a reduction in AHI scores with CRT was associated with an improvement in LVEF. For studies under the CSA subgroup,^{12,15,16} LVEF significantly increased from 24.1 ± 5.5 at baseline to 29.7 ± 7.8 ($P < 0.0001$, $n = 60$) after treatment with CRT for a mean duration of 21.3 ± 10.7 weeks, which corresponds to the significant reduction in AHI ($P < 0.00001$) observed in this subgroup. Left ventricular ejection fraction also increased among studies in the OSA subgroup^{15,19} from 25.0 ± 4.4 at baseline to 31.8 ± 5.1 ($P < 0.00001$, $n = 39$) after treatment with CRT for a mean duration of 22.9 ± 10.7 weeks. However, the AHI in this group did not significantly decrease ($P = 0.25$).

Results of studies not included in meta-analysis

Three manuscripts^{13,17,18} and 2 structured abstracts^{22,25} of the 14 studies included in this systematic review were unable to be meta-analysed. Two studies were not included due to vastly different follow-up times. Kara et al.¹³ studied patients over 3 days

where the CRT device was left on for the first night, turned off for the second night, and turned back on for the third night. A similar design was used by Seidl et al.²⁵ over two nights. Kara et al.¹³ showed a significant reduction in CSA and hypopnea episodes per hour of sleep ($P < 0.001$) and Seidl et al.²⁵ found a significant reduction in overall AHI ($P = 0.01$) when the device was pacing (CRT) vs. non-pacing.

Two studies^{18,22} reported their results in a way that could not be included in the meta-analysis: Magnano et al.²² separated patients' results into 'CRT Responders' and 'CRT Non-responders' based on the change in peak oxygen consumption (ΔVO_{2max}). CRT responders ($\Delta VO_{2max} > 0$ mL/min/kg) did not have a significant reduction in obstructive AHI or overall AHI; however, there was a significant reduction in central AHI after 3 months of treatment with CRT. Sredniawa et al.¹⁸ reported on patients with abnormal and non-abnormal AHI and separated patients' results into two groups: 'AHI dippers' ($\geq 50\%$ reduction in AHI after 6 months) and 'AHI Non-dippers'. A total of 66% of patients were considered 'AHI dippers' and they had a significant reduction in AHI compared with baseline.

Skobel et al.¹⁷ found a significant reduction in AHI in CSA and Mixed SA patients. However, these results were not objectively quantified and therefore, could not be included in meta-analysis.

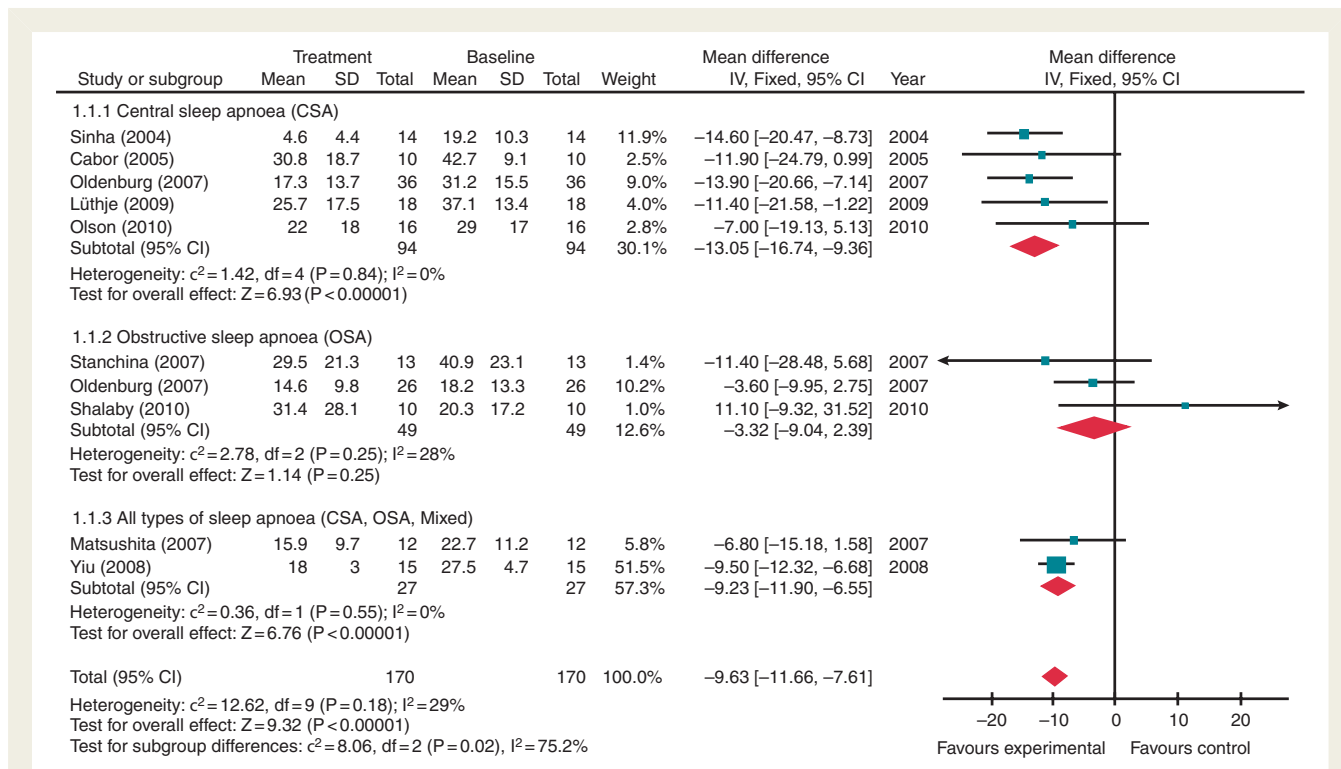


Figure 2 Reduction of sleep apnoea parameters with the use of cardiac resynchronization therapy. CI, confidence intervals; IV, inverse variance; SD, standard deviation.

Table 2 Studies that included a cardiac resynchronization therapy + atrial overdrive pacing arm

Study	Predominant type of SA	Baseline (AHI)	CRT (AHI)	CRT + AOP (AHI)	P value ^a
Lüthje <i>et al.</i> ¹⁴	CSA	37.1 ± 13.4	25.7 ± 17.5	23.7 ± 17.9	0.07
Shalaby <i>et al.</i> ²⁶	OSA	20.3 ± 17.2 ^b	31.4 ± 28.1	17.5 ± 28.8	NS
		22.9 ± 13.9 ^c			

Data are presented as mean ± SD.
 AHI, apnoea-hypopnoea index; CSA, central sleep apnoea; OSA, obstructive sleep apnoea.
^aComparison between patients treated with CRT only and those treated with CRT + AOP.
^bBaseline AHI for the CRT-only group.
^cBaseline AHI for the CRT+AOP group.

Discussion

Sleep apnoea is a problem frequently seen in patients with CHF. Severity of SA is based on AHI and grouped into mild (AHI 5–14.9), moderate (AHI 15–29.9), and severe (AHI ≥ 30) by the American Academy of Sleep Medicine.²⁷ A 10-point reduction in AHI could change the grade of a patient’s SA to one less severe and subsequently improve their functional status. Currently, the presence of SA is not among the selection criteria used by physicians to determine which CHF patients receive treatment with CRT.^{10,11}

In this study, we have shown that CRT reduces AHI scores by a mean of -9.63 ($P < 0.00001$) overall. However, a disparity in the effect of CRT on SA exists between OSA and CSA patients. Cardiac resynchronization therapy decreased AHI in CSA patients by a mean of -13.05 ($P < 0.00001$), which translates into being clinically significant. In contrast, however, CRT was unsuccessful in significantly reducing the AHI overall in patients with OSA (-3.32 , $P = 0.25$) and increased the AHI in the cohort examined by Shalaby *et al.*²⁶ This study actually demonstrated an increase in the severity of SA.

After calculating LVEF before and after implantation with CRT, we found that there was a substantial improvement in LVEF in both the CSA and OSA subgroups. However, a significant reduction in AHI was only seen in the CSA group and not in the OSA group. This suggests that the mechanism by which disease severity changes is different for OSA and CSA. There still remains no consensus on the exact mechanism by which CRT improves AHI scores in SA patients; however, based on the results of this meta-analysis, we can speculate on some possible explanations. A possible mechanism is that CRT improves LVEF, which increases cardiac output. This reduces pulmonary venous pressure and therefore reduces the tendency towards hyperventilation and hypoxaemia, and thus reduces AHI.²⁸

Floras and Bradley²⁹ provided another explanation to account for the benefits of CRT in patients with SA. Biventricular pacing improves cardiac output leading to a reduction of lung-chemoreceptor circulation time and left ventricular filling pressure, which may reduce the fluctuation in breathing patterns, preventing the hyperventilation that precedes an apnoea event. This could also explain the greater benefit, in terms of AHI reduction, observed with CRT over AOP.³⁰ However, this explanation is insufficient to determine why patients with OSA did not show a significant improvement in our study; given the fact that neck oedema may be, at least in part, responsible for the presence of OSA in patients with CHF. Previously, Bradley and co-workers concluded that the pathophysiology of the upper airway occlusion in patients with CHF and OSA share the same predisposing features of OSA than in patients with no CHF, including obesity, male gender, and middle age. Therefore, CRT may not be correcting the main factors that produce OSA in patients with CHF.³¹ More recently, the same group reviewed the impact of treating OSA in patients with CHF and stated that the lack of examination on the effect of interventions on nocturnal fluid displacement (from the legs to the neck), turn the results of those studies (including some of the meta-analysed studies here) inconclusive.³²

These explanations are speculative, but there is conclusive physiopathological research demonstrating that SA presents adverse cardiovascular effects and that the presence of SA reduces survival in patients with CHF; thus, further studies are required to better define the mechanism by which CRT benefits SA.

Limitations

Some limitations should be acknowledged. Most studies included in this systematic review had a pre-post study design while only one study was a randomized controlled trial. We found some differences in study design within the included studies; however, a test for heterogeneity showed that studies were comparable. Finally, there are a relatively small number of patients included in the meta-analysis due to a limited number of available studies and small study groups.

Conclusion

Cardiac resynchronization therapy is associated with a statistically as well as a clinically significant reduction in AHI in patients with CSA but not OSA. The presence of SA may be an additional

consideration when deciding on which heart failure patients will receive CRT.

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