Sleep Medicine 64 (2019) 106–111

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Sleep-disordered breathing and effectiveness of cardiac resynchronization therapy in heart failure patients: gender differences?

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ARTICLE INFO

Article history:
Received 18 December 2018
Received in revised form
17 March 2019
Accepted 12 June 2019
Available online 5 July 2019

Keywords:
Sleep apnoea
Heart failure
Cardiac resynchronization therapy
Pulmonary medicine

ABSTRACT

Objectives: This study evaluated heart failure (HF) patients who underwent cardiac resynchronization therapy (CRT) and who had device-documented sleep-disordered breathing (SDB). We found gender differences in acute changes in SDB due to CRT impact.
Background: SDB typically occurs in HF patients. However, the role of SDB and its response to CRT in HF patients, as well as the relation with gender are currently not fully researched.
Methods: Among 63 consecutive patients who received CRT with an SDB algorithm, 23 patients documented SDB at one-month cardiac device interrogation and represented our population. We defined a Sleep apnoea Severity SCore(SSSC), and consequently, patients were categorized to have mild, moderate, and severe sleep apnoea syndrome divided into two groups: Group-1: 18 males (78%); Group-2: 5 females (22%). We evaluated the variation of apnoea burden and CRT response based on gender differences.
Results: A significantly higher proportion of patients in the male group were non-responders to CRT at 12-months follow-up ($p = 0.076$) while in the female population 5/5 patients (100%) were responders to CRT at the same follow-up time ($p = 0.021$). Among Group-2 subjects, we documented a significant linear decrease in SSSC($p > 0,01$) while in Group-1 the CRT effect on SSSC was variable. At 12-months follow-up, the difference in SSSC between the two groups was statistically significant ($p < 0.001$).
Conclusions: Our study reports a correlation between CRT response and sleep apnoea burden considering gender differences. In particular, HF-women responders to CRT demonstrate a significant linear decrease in sleep apnoea burden determined through a device algorithm, when compared to a similar male population. Further research is needed to confirm these findings.

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1. Introduction

Sleep-disordered breathing (SDB) is common in cardiovascular patients, with a prevalence of 60%–75% [1]. SDB may be caused by mood disorders/psychological stress, medications (angiotensin-receptor blockers, loop diuretics, and β blockers), and nocturia; as well as by central sleep apnoea (CSA), obstructive sleep apnoea (OSA), or a mixed pattern of the two. In particular, CSA and OSA have been shown to be associated with a worse prognosis in heart failure (HF) [1]. Today, in HF patients with SDB, therapy focuses on different approaches with direct or indirect effects on abnormal sleep-related respiratory events. Among indirect therapeutic effects, we should consider the potential importance of cardiac resynchronization therapy (CRT). However, the role of SDB and its response to CRT in HF patients, as well as the relation with gender, are not well defined. Today, more than 30% of patients receiving CRT could have a sub-optimal therapy response, with a potential increase in the risk of HF progression [2–4]. Risk factors potentially linked to non-response

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https://doi.org/10.1016/j.sleep.2019.06.019
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(atrial fibrillation, gender, biventricular pacing percentage, left bundle branch block and QRS duration) are therefore extremely important, but sometimes not fully defined (eg, SDB) [4] promoting disease progression [5–9]. Today, few cardiac devices used for CRT are able to detect SDB through specific algorithms [10,11], although usually unvalidated. These algorithms could be, at first, a useful tool for long-term monitoring, reinforcing the diagnosis and improving therapeutic compliance. At the same time polysomnography (PSG), the gold standard for diagnosis, may be a cost/time-consuming strategy for sleep apnoea screening and is not routinely available; in particular, it may be available at a sleep disorders unit within few hospitals, or a sleep center [10–12]. Therefore, we developed a retrospective multicenter analysis involving a very selected population (HF patients who underwent CRT and who had documented SDB), evaluating acute changes in sleep apnoea burden due to CRT impact, while also considering gender differences.

2. Methods

Sixty-three consecutive patients who received CRT from January 2017 to December 2017 were reviewed. Strict inclusion criteria in three different Electrophysiology Units were: (1) advanced HF with a baseline left ventricular ejection fraction <35%; (2) QRS duration ≥130 ms; (3) New York Heart Association (NYHA) from class II to ambulatory class IV; and (4) a CRT device implantation with a sleep apnoea syndrome algorithm [10,11]. Only patients who fulfilled those criteria were included. Subjects' written informed consent was obtained. The study was approved by the relevant institutional review board. Only 23 patients (18 males, 78%) with documented SDB, one-month after device implantation, represented our patient population. We included both (a) patients who received a CRT device and (b) patients who received CRT in order to reduce right ventricular pacing with a previous indication for dual-chamber pacing. The percentage of biventricular pacing was assessed at the time of first follow-up as well as at last follow-up. We evaluated (a) electrocardiographic variables (presence of typical left bundle branch block, QRS complex duration, presence of atrial fibrillation); (b) the ejection fraction at the time of device implantation and after 3–6–12 months respectively (the assessment was performed using Simpson's biplane method); (c) sleep apnoea burden documented at cardiac device interrogation at 1–3–6–12 months respectively; and (d) demographic variables including sex differences. As discussed previously, sleep apnoea syndrome was the exposure of interest, and it was determined by sleep apnoea monitoring (SAM) [11]. The SAM algorithm available in Microport (formerly SORIN) derives minute ventilation from trans-thoracic impedance measurements [11]. Specifically, each respiratory cycle's amplitude and period were measured from the impedance signal; the minute ventilation value and the index were calculated as the ratio, or average of the ratio, of amplitude and period. Apnoea was considered as an absence of a significant respiratory cycle for >10 s, while hypopnoea was considered as a sustained (>10 s) reduction of the respiratory amplitude by at least 50% compared to the mean amplitude of preceding validated respiratory cycles. Therefore, at device interrogation, a respiratory disturbance index (RDI) evaluated by the SAM algorithm (SAM-RDI) corresponded to the mean number of detected events per hour of estimated sleep and was automatically computed [11]. We divided patients according to the percentage of their nights with a sleep apnoea burden, suggesting a potential difference in severity between patients, as previously described [13]. In particular we defined a Sleep apnoea Severity SCore (SSSC) considering: (1) low-burden apnoea patients: < 29% of nights with RDI >20; (2) medium-burden apnoea patients: 30–59% of nights with RDI > 20; and (3) high burden apnoea patients: > 60% of nights with RDI >20. Consequently, the study population was categorized to have mild, moderate, and severe sleep apnoea syndrome. Moreover, we evaluated: (1) the response to CRT considering ejection fraction values and (2) the variation of apnoea burden, considering gender differences.

2.1. Statistical analysis

Continuous data were expressed as mean ± standard deviation SD and categorical variables as counts and percentage. The Student's t-test was used to compare continuous variables for paired samples; categorical data were analyzed by the χ square test or by Fischer's exact test, as appropriate. All statistical analyses were performed using SPSS 17.0 software for Windows (SPSS Inc, Chicago IL, USA). Values of $P < 0.05$ were regarded as statistically significant.

3. Results

Over 63 consecutive patients who received CRT with a sleep apnoea syndrome algorithm, 23 patients (36,5%) documented SDB at one-month device interrogation and were included in the study. Among 23 patients we established two groups: Group-1: 18 males (78%); Group-2: 5 females (22%). Baseline patient characteristics were highly similar in both groups: in particular, no statistically significant differences among age, body mass index, and ejection fraction were documented (Table 1). Moreover, the SSSC at baseline did not differ between the two groups (N.S.), and both demonstrated a higher prevalence of non-ischemic cardiac diseases, although more pronounced in women (56% and 80% in Group 1 and Group 2 respectively, Table 1).

3.1. CRT effects: gender differences

When the two groups were compared, a significantly higher proportion of patients in the male group (22%) were non-responders to CRT at 12 months follow-up ($p = 0.076$) (Fig. 1) while in the female population 5/5 patients (100%) were responders to CRT at 12 month follow-up ($p = 0.021$) (Fig. 2). The mean percentage of biventricular pacing assessed at the time of last follow-up was >99% in both groups. We defined CRT responders as all patients with an ejection fraction improvement ≥10% compared to the baseline echocardiogram, using Simpson's biplane method; the end-systolic volume was considered in the Simpson's formula, while changes in exercise tolerance were not.

3.2. CRT effects on SSSC

Among the female Group-2, we documented a significant linear decrease in SSSC ($p > 0,01$, Fig. 3). On the other hand, in male

Table 1
Baseline patient characteristics.

Variables	Male (n = 18)	Female (n = 5)	p Value
Age (y)	82 ± 6	81 ± 2	N.S.
BMI (kg/m^2)	26 ± 4	24 ± 4	N.S.
LV ejection fraction (%)	33 ± 2	33 ± 2	N.S.
Atrial rhythm disorders			
Paroxysmal AF	8 (44%)	2 (40%)	N.S.
Persistent/Permanent AF	2 (11%)	1 (20%)	N.S.
Underlying cardiac diseases			
Ischemic	8 (44%)	1 (20%)	<0,05
Non-ischemic	10 (56%)	4 (80%)	<0,05
Other comorbidities			
Diabetes	6 (33%)	1 (20%)	N.S.
Hypertension	11 (61%)	3 (60%)	N.S.
Current smoker	2 (11%)	1 (20%)	N.S.

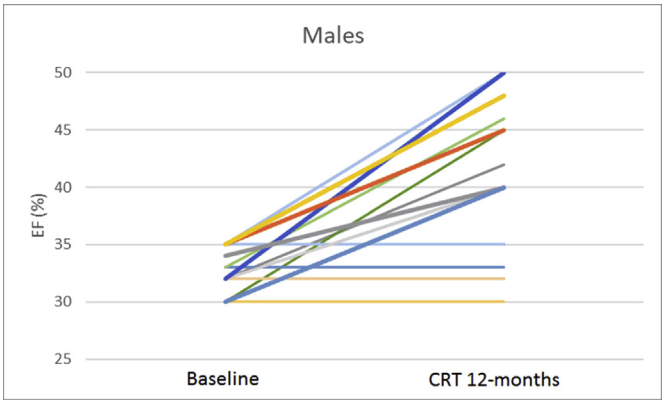

Fig. 1. Cardiac resynchronization therapy (CRT) in males: effects of CRT on ejection fraction (EF) in the male population ($p = 0.076$).

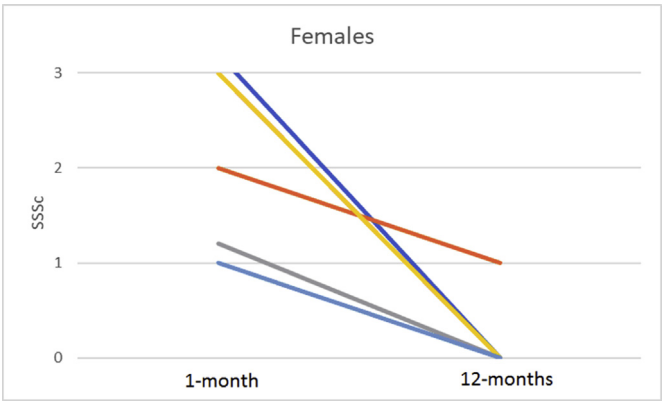

Fig. 3. Sleep apnoea syndrome in females with heart failure: effects of cardiac resynchronization therapy (CRT) on Sleep apnoea Severity SCore (SSSC) at 12-months follow-up in the female population (females vs. males $p < 0.001$).

Group-1, the CRT effect on SSSC was variable. In particular, among male patient non-responders to CRT, the SSSC was never modified. However, among responders to CRT in male patients, 11/14 showed a decrease in SSSC like the female population, while 3/14 showed a surprising increase in SSSC (Fig. 4). At 12 month follow-up, the difference in SSSC between the two groups was statistically significant ($p < 0.001$). Evidence of the SSSC decrease at cardiac device interrogation in a female patient is well represented in Fig. 5.

4. Discussion

Our study appears to be the first paper in the medical literature to report a correlation between CRT response and sleep apnoea burden considering gender differences. At first, in CRT patients with a sleep apnoea syndrome algorithm [11] and documented SDB, we defined a SSSC considering a low/medium/or high burden apnoea; we defined mild/moderate/and severe sleep apnoea syndrome by determining the percentage of nights with RDI. Our patient population included only 22% of females (Group 2) which is consistent with the medical literature. While current device guidelines are independent from gender, it is clear that women are underrepresented in these types of clinical trials. Furthermore, there is an underuse of defibrillator therapy in this particular patient population, representing 10–30% of patients enrolled in defibrillator trials [14–24], Moreover, the underrepresentation of women in trials of CRT [3,25–29] could make it difficult to determine the interaction between sex and therapy outcome. In addition, women have preserved or a mid-range left ventricular ejection fraction more often than men, and although some authors proposed that the benefit of CRT could extend to mildly reduced ejection fraction patients [30,31], there is no reference to this patient population in today's guidelines [32,33]. The proportion of women with HF and reduced ejection fraction is lower than men [34]. To date there is no RCT with the statistical power to reach a gender-specific outcome. However, in registry studies and subgroup analysis, women demonstrated a superior outcome from CRT compared to men [35–37] as in our study population (Fig. 2). The women in these trials with a similar age range as men, more often presented underlying non-ischemic cardiomyopathy and left bundle branch abnormality [38–40]. These findings may be linked to a greater extent of reverse remodeling by resynchronization therapy [41], potentially determining a greater clinical benefit. Today's guidelines [32,33] also stress that sub-studies indicate women have a greater benefit from CRT, and actual registry data show that the therapy response is greater in left bundle branch block woman-patients, compared with men [42,43]. Therefore, it has been suggested that indications could be different between women and men [44], with many potential reasons for why women could benefit more from CRT. In an individual-patient data meta-analysis, Linde et al., confirmed that women had reduced body size, documented smaller left ventricular dimensions, more often left bundle branch block and present with coronary heart disease less frequently than men [45]. In our study, an key outcome was the evidence of a

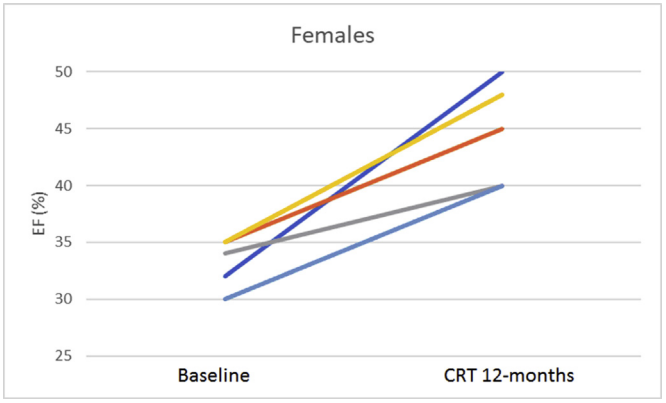

Fig. 2. Cardiac resynchronization therapy (CRT) in females: effects of CRT on ejection fraction (EF) in the female population ($p = 0.021$).

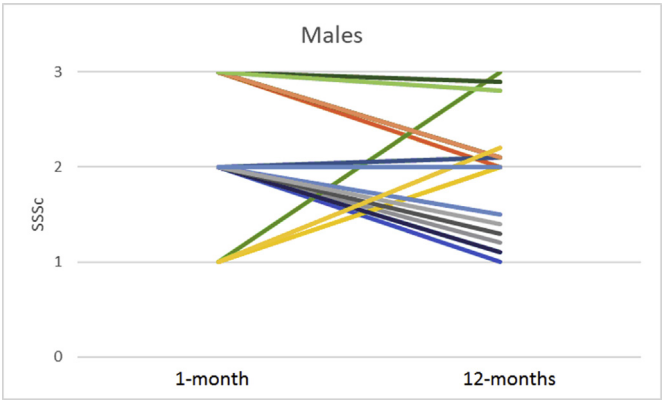

Fig. 4. Sleep apnoea syndrome in males with heart failure: effects of cardiac resynchronization therapy (CRT) on Sleep apnoea Severity SCore (SSSC) at 12-months follow-up in the male population (females vs. males $p < 0.001$).

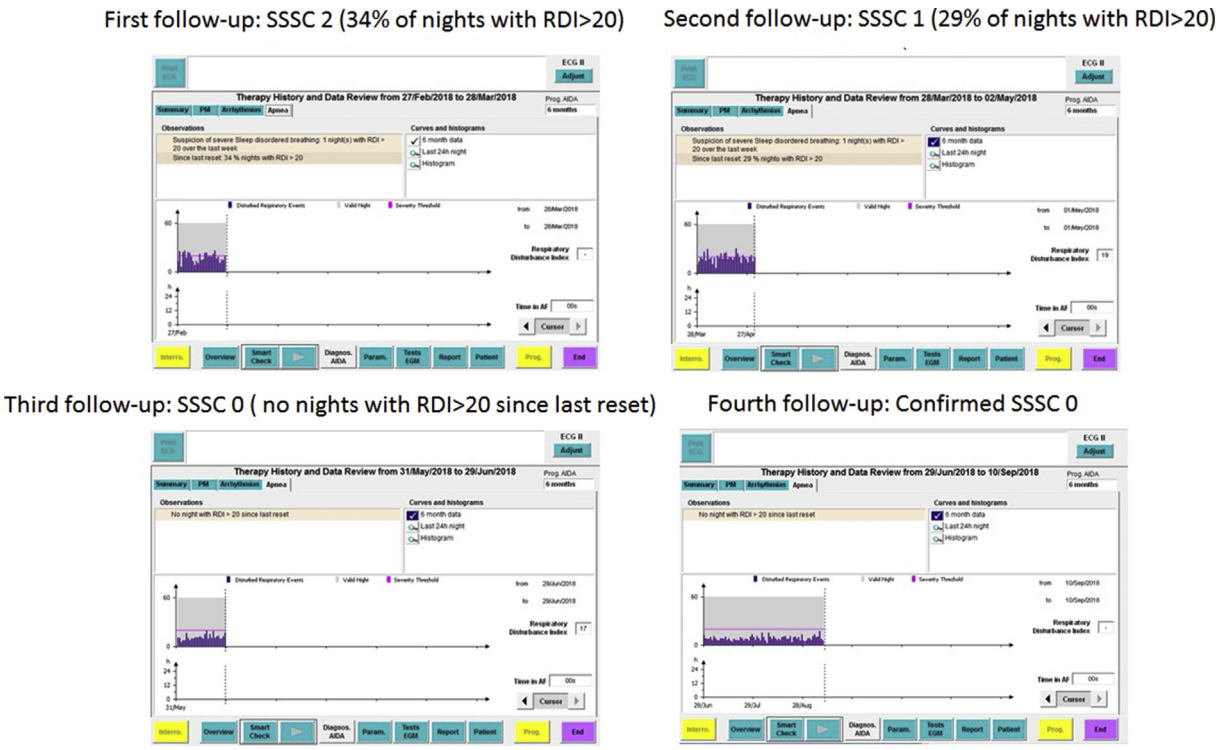

Fig. 5. Sleep apnoea syndrome evaluated at cardiac device interrogation during a 12-months follow-up: evidence of Sleep apnoea Severity SCore (SSSC) decrease at device interrogation in a female patient (RDI: respiratory disturbance index).

significant linear decrease in SSSC in the female Group-2 that documented 100% improvement of the ejection fraction at 12 month acute follow-up (Fig. 3). This trend was not documented in the male Group-1, where 3/14 patients showed a surprising increase in SSSC indicating interference from several factors that need further investigation. On the other hand, the CRT effect and the consequent unchanged SSSC in male non-responders may indirectly confirm the good effect of this therapy on sleep apnoea. Changes in SDB severity and its relationship with CRT have been previously reported [14,46] but with no sex correlation. In 77 HF patients eligible for CRT, Oldenburg et al., found that CSA was common and could be influenced by CRT, depending on good clinical and hemodynamic response to device therapy [46]. Currently, detecting SDB simply using cardiac devices algorithms is a valuable strategy reinforcing the diagnosis and improving therapeutic compliance. Defaye et al., in the DREAM study demonstrated that a transthoracic impedance sensor with the SAM algorithm currently available in Microport devices could be used in patients to identify SDB with a sensitivity of 88.9% and a specificity of 84.6% [11]. On the other hand, recent findings suggest that SDB in patients with cardiac devices is highly variable, while daily SDB severity may impact arrhythmia risk [47–49]. Therefore, the prominent link of heart failure, SDB, and cardiac arrhythmias should be carefully considered, and interactions of these diseases are variable and may be unclear in daily practice [50]. Omran et al., focused on the independence of daytime for cardiac arrhythmia occurrence in HF patients with SDB, also potentially explaining the response to CRT therapy [51]. Some authors demonstrated that, in SDB patients, an effective CRT could improve cardiac output with better perfusion or reduction in circulation time, and equivalent perfusion to the ventilator centers in the brain and chest muscles (the so-called “ventilator loop theory”) [52]. The apnea-hypopnea index (AHI) in the sleep study of these SDB patients improved [52]. Recently, Shanta et al., assessed the association between CRT response, SDB, and all-cause mortality in a heart failure patient population [53]; they reported SDB as a predictor of non-response to CRT [53]. However, it is apparent that an HF patient with SDB could have poorer cardiac output at the time of device implantation, entering a bad feedback loop with the sleep apnoea worsening cardiac perfusion and vice versa, regardless of sex, although these findings might be more noticeable in the male population. SDB may reduce stroke volume, increasing both ventricular afterload and preload and promoting hypertrophy and apoptosis [54]. Besides, it may lead to a higher neurohumoral activation due to sympathetic excess water and salt retention [55,56]. The HF population today has a changing profile, with a higher prevalence of co-morbidities and an increased mean age, which could influence the efficacy of diagnosis and the response to treatment.

4.1. Study limits

The principal study limitation is the patient population, considering both the number and percentage of women patients, but at the same time, this is consistent with female underrepresentation in cardiac devices clinical trials. Moreover, the percentage of responders to CRT in women is apparently not documented in the medical literature; however, this finding may simply corroborate the positive trend of HF women's response to CRT, confirming gender differences. It was not possible to develop useful predictive models due to the low number of patients. At the same time, the detection of SDB through cardiac devices compared to PSG is still not validated, despite the encouraging results in the medical literature [10,11]. Further studies are needed to confirm a significant linear decrease in sleep apnoea burden in HF-women responders to CRT. Further research, including an SDB prospective registry in HF patients and CRT is necessary. Finally, an apnoea severity score determined over months (and not daily, such as PSG) should also be developed and validated.

4.2. Clinical perspectives

Our study appears to report a correlation between CRT response and sleep apnoea burden in HF patients focusing on gender differences. In particular, the evidence of a significant linear decrease in sleep apnoea score in the HF-women group who underwent CRT may suggest a better response in this patients population, given that this trend was not documented in the male group. Further studies are needed to confirm these finding. As well, a prospective SDB registry in HF patients with CRT may help develop a future perspective. In a futuristic context, an apnoea severity score should also be developed and validated. Moreover in future studies of HF patients with CRT these algorithms may be both a useful instrument for long-term sleep apnoea monitoring with repeated SDB measurements every night, and also a tool to reinforce the diagnosis; at the same time, cardiac devices will help physicians optimize therapy in order to reduce risk factors and improve therapeutic compliance. Finally, an early sleep apnoea syndrome diagnosis may reduce many dangerous cardiovascular risk factors, and consequently lead to a decrease in medical costs.

5. Conclusion

Our study at first reports a correlation between CRT response and sleep apnoea burden considering gender differences. In particular, HF-women responders to CRT demonstrate a significant linear decrease in sleep apnoea burden determined through a device algorithm, when compared to a similar male population.

Disclosures

All eight authors report no relationships relevant to the contents of this paper to disclose. In particular, all authors have no forms of financial support to declare and no relationships with industry, no sources of funding.

Acknowledgments

No acknowledgments to report.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.06.019.

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