Mini Review

Interventional Cardiology

The impact of sleep-disordered breathing on the effectiveness of cardiac resynchronization therapy

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Received date: 14-Mar-2023, Manuscript No. FMIC-23-91550;
Editor assigned: 17-Mar-2023, PreQC No. FMIC-23-91550 (PQ);
Reviewed date: 03-Apr-2023, QC No. FMIC-23-91550;
Revised date: 10-Apr-2023, Manuscript No. FMIC-23-91550 (R);
Published date: 18-Apr-2023, DOI: 10.37532/1755-5310.2023.15(3).706

Abstract

Cardiac Resynchronization Therapy (CRT) offers survival benefits to patients with Heart Failure with Reduced Ejection Fraction (HFrEF) upon optimal medical treatment. It is ensured by Left Ventricular (LV) reverse remodeling with decreased LV systolic volume, improved LV ejection fraction, decreased mitral regurgitation severity, and reduced risk of life-threatening ventricular arrhythmias. However, in approximately 30% of patients, CRT does not have the expected hemodynamic or clinical effect. For some patients, this is because of the unfavorable influence of comorbidities. The review highlights one comorbidity that may interfere with CRT's beneficial effect: Sleep-Disordered Breathing (SDB). Central and obstructive sleep apnea is SDB subtypes found in nearly half of patients with HFrEF. SDB causes myocardial hypoxia and increases adrenergic activation and renin-angiotensin-aldosterone system activity. This may impair the volumetric response to CRT, inhibit the increase of the LV ejection fraction, and worsen long-term prognoses.

Keywords: Cardiac resynchronization therapy; Congestive heart failure; Central sleep apnea; Obstructive sleep apnea; Sleep-disordered breathing

Abbreviations: AHI: Apnea-Hypopnea Index; CRT: Cardiac Resynchronization Therapy; CSA: Central Sleep Apnea; HFrEF: Heart Failure with Reduced Ejection Fraction; LBBB: Left Bundle Branch Block; LV: Left Ventricle; LVEDV: Left Ventricular End Diastolic Volume; LVEF: Left Ventricular Ejection Fraction; LVESV: Left Ventricular End Systolic Volume; MADIT-CRT: Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy study; 6M-FU: Six-Month Follow-Up; OSA: Obstructive Sleep Apnea; RAAS: Renin-Angiotensin-Aldosterone System; SDB: Sleep-Disordered Breathing

Introduction

Cardiac Resynchronization Therapy (CRT) is an established, effective treatment for Heart Failure with Reduced Ejection Fraction (HFrEF) [1,2]. We have long known the factors in a good prognosis regarding CRT. The Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) [2] found that age under 65, female gender, and non-ischemic etiology were associated with higher benefits from CRT. A positive response was more common in patients with Left Bundle Branch Block (LBBB), and the longer the baseline QRS complex duration was, the better resynchronization's expected effect was [1,3].

Placing the Left Ventricular (LV) lead in the lateral or posterolateral region and avoiding the apical position are associated with increased positive responses to CRT [4,5]. Additionally, the LV lead's location in the highest intraventricular delay area seems important [6,7]. So are the target area's assessment and selection based on electrocardiographically detected abnormalities of intraventricular conduction, structural changes within the LV (fibrosis, scarring), and the heart veins' anatomical

condition [8]. However, in approximately 30% of patients, CRT does not produce the expected hemodynamic or clinical effect [9]. So, the reasons for CRT failure are still being sought.

According to the Scopus database, 5,054 articles and reports on CRT responses have been published in the last five years. A complex issue in response to CRT is the impact of comorbidities like renal dysfunction, hypertension, diabetes, coronary artery disease, cerebrovascular accidents, atrial arrhythmias, ventricular arrhythmias, and smoking [10]. In 1,214 MADIT-CRT participants analyzed by Zeitler et al. [10], an inverse relationship existed between comorbidity burden and improvements in Left Ventricular End-Systolic Volume (LVESV), Left Ventricular End-Diastolic Volume (LVEDV), Left Ventricular Ejection Fraction (LVEF), left atrial volume, and LV dyssynchrony in response to CRT. As the burden of comorbidities increased, so did the risk of death, hospitalization, and outpatient management for HFrEF. The highest risk was in patients with three or more comorbidities.

Sleep-Disordered Breathing (SDB) is underdiagnosed but common in patients with heart failure across a range of ejection fractions and New York Heart Association classes [11]. We highlight the SDB role as another comorbidity that may decrease the effectiveness of CRT.

Literature Review

Pathophysiology of central and obstructive sleep apnea in HFrEF patient–a quick look

SDB central (CSA) and obstructive (OSA) sleep apnea in patients with HFrEF is a common phenomenon. It is found in nearly half of patients with HFrEF [11,12]. Low cardiac output with prolonged circulatory delay (i.e., prolonged lung-to-chemoreceptor circulation time) and increased LV filling pressure with pulmonary congestion contributes to CSA, with cessation of airflow in the absence of respiratory effort [11,13,14]. The decreased tone of the oropharyngeal muscles during sleep, in combination with anatomical narrowing of the upper airways or a large mass of neck tissue in obese people, is the cause of OSA, characterized by transient upper airway collapse and inadequate ventilation despite the preserved activity of respiratory muscles [11,15]. Moreover, in HFrEF patients, the sodium and fluid retention arising from LV impairment and the Renin-Angiotensin-Aldosterone System (RAAS) overstimulation predispose to peripheral edema and the rostral fluid shift from the legs to central structures during sleep [13,16]. The overnight fluid shifting increases venous return and pulmonary congestion, stimulating pulmonary stretch receptors activity, hyperventilation, and hypocapnia predisposing to CSA [17,18]. Also, the rostral fluid shift increases the para-pharyngeal tissue pressure and reduces the upper airway size, which are specific risk factors for OSA in HFrEF [13,18].

SDB's role on the response to cardiac resynchronization therapy-pathogenetic background

In patients with HFrEF and LBBB, an insufficient response to optimal medical therapy is caused by a non-physiological sequence of stimulation and contraction of the opposing walls of LV (i.e., electromechanical dyssynchrony). Then it contributes to adverse LV remodeling, increasing LVESV, reducing LVEF, and resulting in functional mitral regurgitation [19]. CRT was developed for these patients, aimed at restoring the correct sequence of contractions of the heart chambers and improving their emptying without increasing the energy expenditure of the failing heart muscle. The increase in cardiac output contributes, inter alia, to the reduction of the sympathetic nervous system tone and decrease in the activity of RAAS. Moreover, reducing LVESV and LV filling pressure reduces pulmonary capillary wedge pressure and congestion. Other authors have extensively described the way CRT works [9].

In contrast, SDB causes myocardial hypoxia, an increase in LV afterload, adrenergic activation, and RAAS activity, possibly impairing the beneficial effect of CRT [11,13,14,16,19-21].

In OSA, inspiration against a closed airway produces excessive negative intrathoracic pressure as low as-80 cm H_2O and causes a rapid increase in LV transmural pressure and LV afterload. Simultaneously, increased venous return and hypoxia-induced vasoconstriction of pulmonary arteries increase right ventricular preload and afterload. The resulting distension of the right ventricle and leftward displacement of the interventricular septum during diastole impairs LV filling. The combination of increased afterload and decreased LV preload during obstructive apneas results in decreased LV stroke volume [21]. Moreover, this long-term, repeated increase in wall tension may stimulate further ventricular remodeling in ischemic HFrEF patients, leading to septal hypertrophy/concentric LV hypertrophy or dilatation of the heart chambers even in patients with mild OSA [16,22,23]. In addition, increased LV transmural pressure impairs coronary perfusion while increasing myocardial oxygen demand [14,21]. These mechanisms may accelerate myocardial ischemia in people with preexisting coronary artery disease and impair LV contractility and diastolic relaxation [14]. The intermittent hypoxia leads to oxidative stress, endothelial dysfunction, and systemic inflammation and promotes atherogenesis [24]. Moreover, myocardial hypoxia during obstructive or central apnea/hypopnea episodes provokes life-threatening ventricular arrhythmias [25,26].

OSA and CSA directly activate the sympathetic nervous system *via* apnea-induced hypoxia and carbon dioxide retention that stimulate, among others, central and peripheral chemoreceptors [11,14,27]. On the other hand, arousals from sleep caused by hypoxia and respiratory effort reduce cardiac vagal activity [11,14]. Both sympathetic overflow and parasympathetic withdrawal cause

tachycardia, peripheral vasoconstriction, resistant hypertension, and the progression of LV diastolic dysfunction [28]. Autonomic dysregulation and dynamic changes of left atrial volume in SDB patients increase the likelihood of refractory atrial fibrillation [29-31]. Meanwhile, insufficient biventricular pacing burden and atrioventricular synchrony loss increase the risk of tachycardia-induced cardiomyopathy and poorer CRT response [32,33]. In addition, increased activity of the sympathetic nervous system promotes sodium and water retention in the kidneys, directly and through the stimulation of RAAS, increasing the LV volume and pressure overload [16].

SDB's role on the response to cardiac resynchronization therapy (clinical investigations)

A cardiorespiratory fitness improvement is typically associated with an improvement in SDB severity, particularly CSA [34,35]. CRT has been previously assessed in this regard [36-41]. Most studies showed a median to high reduction in the Apnea/Hypopnea Index (AHI) or other respiratory parameters, with any improvement depending on the SDB type and CRT response [36-41]. However, the relationship between the LV volume and function and SDB severity in HFrEF patients with CRT is multidirectional [15]. Some data supports SDB influences the response to CRT and long-term prognosis [42-44].

Per Shantha et al. [42], OSA (mean baseline AHI of 26 ± 16 events/hour of sleep) predicted non-response to CRT and all-cause mortality in 548 cohorts of patients with HFrEF. LVEF remained unchanged (28 ± 5% vs. 27 ± 7%, p<0.71) in the OSA group but improved after a follow-up of 76 ± 17 months (27 ± 6% vs. 45 ± 7%, p<0.001) in the non-OSA group. Moreover, the LVESV index was higher in OSA than in the non-OSA group at the end of the follow-up period (42 ± 4 ml/m^2 vs. 33 ± 4 ml/m^2, respectively). In the group with severe preexistent OSA, the proportion of CRT responders (defined as LVEF improvement by ≥10%) was significantly lower (49%) than in the group with moderate (66%) and mild (78%) OSA (p=0.001). OSA diagnosis was associated with a 3.7-times-higher risk of all-cause mortality.

We conducted our study in patients with ischemic HFrEF in class I of indications for CRT (mean LVEF 26.37 ± 5.47% [43], LBBB with a median native QRS complex duration of 160.00 ms (IQR 155.00-160.00)). The preexisting severe SDB (77.8% CSA, mean AHI 43.22 ± 6.93 events/hour) negatively affected the volumetric response to CRT over six months of follow-up. Despite the optimal selection of CRT candidates and a high rate of CRT responders in the study group (67.6% of participants had a decrease in LVESV of ≥ 15%, 47.1% had an increase in the New York Heart Association's functional classification of at least one class, and 48.6% had a decrease in mitral regurgitation severity by at least one grade), in the subgroup of patients with severe SDB, there was no reduction in LV volumes and no increase in LVEF, in contrast to the group without severe SDB with similar baseline LV parameters. Therefore, at the end of the follow-up, the severely symptomatic SDB group had a 34.36 ml/m^2-higher mean LVESV index (98.26 ± 41.14 ml/m^2 vs. 63.90 ± 26.50 ml/m^2, p=0.002), 40.14 ml/m^2-higher LVEDV index (139.50 ± 54.61 ml/m^2 vs. 99.36 ± 31.21 ml/m^2, p=0.003) and 6.97%-lower LVEF (30.64 ± 9.94% vs. 37.61 ± 11.10%, p=0.046) than the non-SDB group. The linear relationship between AHI and the LVESV index (y=67.68+0.65x, p=0.004) and the LVEDV index (y=100.15+0.74x, p=0.006) was observed.

The influence of a significant SDB (OSA or mixed sleep apnea, the mean baseline AHI 18.5 ± 14.4 events/hour assessed based on the Holter digital recording) on long-term prognosis was described by Sredniawa et al. in 71 patients with HFrEF [44]. Non-significant differences were observed between the SDB and non-SDB groups concerning all-cause mortality rate (29.0% vs. 27.5%, p=0.89) and death due to HFrEF progression (12.9% vs. 15.0%, p=0.80) within 674 days of follow-up. However, the rate of sudden cardiac death was significantly higher in patients with a baseline AHI>20 events/hour than in the others (16.1% vs. 2.5%, p=0.04), and the trend toward more frequent adequate implantable cardioverter-defibrillator interventions was observed in the SDB group (16.1% vs. 5.0%, p=0.06). In addition, failure to reduce AHI by at least 50% after six months of follow-up was associated with worse LVEF improvement (Δ 6.6 ± 6.3% vs. Δ 10.6 ± 5.7%, p=0.02), less reduction in septal-to-lateral wall motion delay (Δ-19.3 ± 43.9 ms vs. Δ-50.7 ± 35.8 ms, p=0.005), and a higher risk of death due to end-stage HFrEF (hazard ratio 6.56, p=0.015).

Other results were reported by Scobel et al. [45], for 42 patients with HFrEF and moderate CSA (AHI 18 ± 8 events/hour) in this study, patients with and without CSA did not differ in exercise capacity or LVEF after CRT. Similarly, Barbieri et al. [40,41], found no effect of severe preexistent CSA (median AHI 39.1, interquartile range 32.1-54.0 events/hour, with follow-up for 2.8 years) or its severity on the effectiveness of CRT or CRT responders' rates in 54 patients with pacing-induced cardiomyopathy-a type of specific, non-ischemic HFrEF usually with a good response to CRT [46].

Notably, the hypothesis of SDB involvement in adverse LV remodeling in patients with HFrEF (with or without CRT) is supported by reports of reverse remodeling, clinical improvement, and reduction in rehospitalization for heart failure after successful therapy with positive airway pressure [47-50].

Discussion and Conclusion

Resynchronization therapy is an important and, in selected patients, effective treatment for heart failure with HFrEF. However, about 30% fail to achieve objective and subjective improvement

in the patient's clinical condition. Among the factors influencing the favorable effect of resynchronization therapy and limiting the percentage of non-responders are proper patient qualification, accuracy during the CRT implantation procedure, and proper programming of the implanted system on the one hand, and elimination of adverse factors and conditions that worsen heart failure and the patient's condition on the other. Many of these factors have been identified and documented in clinical trials. However, in order to further reduce the risk of non-beneficial response, we are constantly searching for new pathogenetic elements and phenomena that, through their mechanism, play an important role in inhibiting the beneficial remodeling induced by CRT. Evaluation of polysomnographic parameters, identification of sleep-disordered breathing is one of them. The cascade of adverse phenomena induced by SDB in patients with heart failure such as hemodynamic disturbances, oxidative stress, endothelial dysfunction, ischemia and activation of the sympathetic nervous system, proarrhythmia are underestimated factors limiting beneficial remodeling and consequently reducing the expected effect of CRT. The coexistence of severe SDB in patients with heart failure can also often be indicative of advanced LV damage. It reflects poor cardiac function, worsens the prognosis of patients with HFrEF and may be the reason for the lack of response to CRT.

Conflicts of Interest

The authors have no conflicts of interest directly relevant to the content of this article.

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