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Editorial

CSA Is Not Beneficial Long Term in Heart Failure Patients with Reduced Ejection Fraction

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ABSTRACT

Central sleep apnea (CSA) affects many patients, with heart failure and results in hypoxia and nor-epinephrine release and is associated with high morbidity and mortality. Recent trials in the treatment of CSA using positive airway pressure therapies have failed to demonstrate improvement in mortality and as a result, the compensatory nature of CSA has been questioned. The detrimental effects from CSA are clear. While there may be a short term compensatory effect, the long term effects cause chronic insult to the cardiovascular system indicating that CSA should be treated, but alternative treatment options need to be considered.

1. Introduction

Central sleep apnea (CSA) is highly prevalent in patients with heart failure and is strongly associated with poor outcomes [1,2]. CSA is a pattern of breathing in which periods of deep, rapid breathing are followed by periods of absent (apnea) or shallow breathing (hypopnea). Each cycle may result in periods of hypoxia and increased sympathetic activation causing recurrent insult to the cardiovascular system resulting in increased morbidity and mortality. These effects are driven by the toxic effects of hypoxia and nor-epinephrine on the cardiovascular system increasing ischemia and adverse cardiac remodeling [3]. CSA often presents in a rhythmic pattern termed Cheyne-Stokes Respiration (CSR) in patients with heart failure with reduced ejection fraction (HFrEF) [4]. Recent trials designed to look at the effect of treating CSA in HFrEF patients on outcomes have been disappointing [5]. In light of these studies, it has been questioned whether CSA in the form of CSR is a compensatory mechanism in HFrEF patients [6]. This manuscript will discuss the impact of CSA on patients with HFrEF and discuss the potential compensatory nature of CSA in patients with HFrEF including the possible beneficial effects.

2. CSA has devastating effects in heart failure patients

The diagnosis of CSA has an ominous prognosis. The 5-year survival in patients with CSA remains approximately 50% even with optimum heart failure management [7]. Multiple studies consistently have demonstrated that CSA patients with heart failure and low ejection fraction have increased mortality compared to patients without central sleep apnea. This could be driven, in part, by worsening heart failure driving an increased risk of recurrent hospitalizations compared to those without CSA [8]. In addition, ventricular arrhythmias appropriately treated by intracardiac cardioverter defibrillators are also more common in patients with CSA, putting these patients at risk for sudden cardiac death [9].

The increase in heart failure and death associated with CSA is understandable when looking at the pathophysiology of the disease. Each episode of CSA may result in both a drop and an increase in oxygenation around a mean level. At times, these changes can be quite dramatic with drops of oxygen saturation of over 10% followed by periods of hyperoxia similar to ischemia–reperfusion injury [3]. Hypoxia and oxidative stress are tied to increases in inflammation, plaque rupture, stroke, dementia, and sympathetic activation, although some benefit in the form of ischemic precondition has been hypothesized. In addition, each episode of CSA leads to an arousal (which moves a patient to a lighter stage of sleep) which is associated with a discrete burst of nor-epinephrine release. The combination of hypoxia and increased nor-epinephrine may lead to progressive left ventricular dysfunction, apoptosis, myocardial infarction, activation of the renin-angiotensin syndrome, systemic inflammation and renal dysfunction [3]. The combination of hypoxic myocytes and increased nor-epinephrine drive would also make serious ventricular arrhythmias and sudden death more likely.

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The adverse effects of increased nor-epinephrine levels in the setting of HF are well recognized [10]. In CSA, the increase of sympathoexcitation has been demonstrated in studies measuring muscle sympathetic nerve activity, overnight urinary excretion and early morning plasma concentrations of nor-epinephrine both of which are elevated in CSA patients [11,12]. Over time, elevations in catecholamines lead to tachycardia, peripheral vasoconstriction, sodium retention, and renin-angiotensin-aldosterone system activation. These effects, in combination with apoptosis, contribute to the adverse cardiac remodeling process [10].

The second clearly detrimental effect of CSA is recurrent episodes of intermittent hypoxia-reoxygenation. These episodes contribute to the progression of HF through a number of different mechanisms, including impairment of myocardial contractility, involvement in molecular signaling processes which lead to cardiac remodeling, and interference with nitric oxide metabolism, which is critically important to normal endothelial function [3].

A third reason for the detrimental effects of CSA in heart failure patients is the significant impact on sleep architecture. Heart failure patients with CSA have much less time in restorative sleep and spend much more time in lighter stages of sleep [13]. While it remains unclear if the disrupted sleep is due to heart failure or CSA, the disrupted sleep has a significant impact on cognition and increased fatigue [14]. In patients with baseline impairment in physical activities, CSA can have a major impact on quality of life. HFrEF patients with CSA have low quality of life scores, and periodic breathing on exercise tolerance testing is associated with lower peak VO_2 [15].

It is important to understand that CSA can present in multiple forms. The most common form in patients with HFrEF is a Cheyne-Stokes respiration (CSR) pattern in which there is a gradual increase in the speed and depth of breathing followed by slow, shallow breathing pattern ultimately resulting in an apneic period. These cycles are at a consistent frequency usually occurring between 15 and 40 episodes per hour. The cycles are linked to cardiac output, with longer ventilation and apneas associated with lower ejection fractions [16]. Many studies have assumed that all patients with HFrEF have CSA in the CSR form (CSA-CSR) and these names unfortunately are used often interchangeably. However, patients with HFrEF may present with other forms of CSA including a pattern more associated with brain injury in which apneas are of different length and shorter duration [4]. While the detrimental effects of both diseases are similar, only the CSR form of the disease has been questioned regarding possible beneficial effects [6]. CSR is closely tied to periodic breathing found during exercise testing termed exercise oscillatory ventilation (EOV). Ninety-three percent of patients with EOV have CSA-CSR. Only 16% of patients with CSR however have EOV indicating that EOV may be a later stage form of CSA-CSR [17,18].

While the pathophysiology of the disease has been summarized well in several recent articles, there still seems to be some question as to whether CSA in the form of CSR could actually be compensatory and perhaps beneficial to patients [3,19,20].

3. Could CSA-CSR be a compensatory mechanism in the presence of HFrEF?

It has been hypothesized that CSA in the form of CSR could be a compensatory mechanism in systolic heart failure [20]. There are certainly other compensatory mechanisms in heart failure. For example, tachycardia is often noted in patients with untreated heart failure and may preserve cardiac output for a limited time. Long-term elevated heart rate however has been clearly associated with worse prognosis in patients with heart failure, and multiple therapies to reduce the heart rate have demonstrated improved outcomes [21]. Thus, while an effect may initially confer some modest initial benefit in patients with heart failure, long term these effects are detrimental and cause progressive left ventricular dysfunction.

A number of the theoretical benefits of CSA-CSR have been described in the literature. During hyperventilatory episodes, large tidal volumes are generated. Hyperventilation could result in increased oxygen or decreased restrictive airway deficit. However, these benefits are removed during the apneic periods. Stimulation of juxtacapillary receptors in the lungs improves vagal tone and improves sympathetic-parasympathetic balance. Several studies however have demonstrated that patients with CSA-CSR have higher levels of nor-epinephrine during CSR periods while they are asleep [20].

Decreased intrathoracic pressure may increase cardiac output due to afterload reduction. However, similar to the other discussions above, this benefit would reverse during apneic phases. In patients with a marginal cardiac output at baseline, this decrease could result in a cardiac output insufficient to maintain adequate blood flow resulting in organ damage and death [22].

Hyperventilation may improve cardiac output; however, this is driven by a substantial increase in heart rate with only an insignificant increase in stroke volume. Since tachycardia itself is an independent risk factor for mortality, no long-term benefit would be seen by hyperventilation [23].

Any benefits from CSA-CSR are temporary and linked only to the hyperpneic phase of the cyclical breathing pattern. Thus, long-term benefit is doubtful. In addition, all of the positive effects caused by hyperventilation would be augmented by positive airway pressure due to the full tidal volumes delivered by the therapy. Thus, positive airway pressure therapies should have resulted in strongly positive clinical trials, which have not been seen to date [24].

While it has been proposed that CSA-CSR could be compensatory, over time any short- term benefit would be overtaken by the significant detrimental effects of CSA. Specifically, hypoxia and increased sympathetic tone are clearly linked to cellular damage and progressive heart failure [6,10]. Potential benefits from hyperventilation are reversed during the apneic periods, especially with the long apneic periods seen in patients with HFrEF. Patients with HFrEF and CSA-CSR have elevated sympathetic drive compared with HFrEF patients without CSA-CSR [12]. From a physiologic sense, it is clear that CSA is detrimental [3].

4. Possible reasons for worse outcomes in the CSA trials if CSA is not compensatory

If CSA-CSR has no long term benefit, why have the current randomized trials to date not been able to demonstrate an improvement in morbidity and mortality? To date, only two randomized, controlled studies evaluated the changes in morbidity and mortality of patients with CSA (with or without CSR) and heart failure [5,25]. Both of these studies were conducted in patients with HFrEF, and both utilized positive airway pressure therapies. It is probable that the worse outcomes were due to the therapeutic modality utilized in these studies. [24].

The initial study, the Canadian Positive Airway Pressure Trial (CANPAP) was stopped early due to trends in survival in favor of the control arm at the interim analysis, slow recruitment, and low event rates. On the final intention-to-treat analysis, the study did not show any mortality benefit for continuous positive airway pressure treated patients with HFrEF. However, a post-hoc analysis of this study suggested that there was the cardiac and survival benefit in a subgroup of patients who were compliant with therapy and reached an apnea hypopnea index (AHI) < 15 events/h. If CSA were compensatory, then it would be expected that patients treated longer would have a higher mortality and not result in reduced mortality as suggested by this analysis. It has been pointed out that this finding argues strongly against CSA being a compensatory mechanism, if out of those treated only those in whom it is suppressed appeared to benefit [26]. Overall, there was a reported low adherence to CPAP (mean usage 3.6 h/night) and a lack of adequate titration of positive airway pressure therapy. In addition, it was hypothesized that increased pressure on the right heart in patients with reduced right ventricular function could have led to the early increase in mortality in the therapy group [6].

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