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Review

Future of Sleep-Disordered Breathing Therapy Using a Mechanistic Approach

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ABSTRACT

Sleep disordered breathing (SDB) is highly prevalent among patients with cardiovascular disease (CVD), and the relationship between SDB and CVD may be bidirectional. However, SDB remains underdiagnosed and undertreated. One of the major barriers identified by cardiologists is lack of satisfaction with SDB therapy. This situation could be the result of the discordance between treatment and the pathophysiological characteristics of SDB. This condition is caused by multiple pathophysiological mechanisms, which could be classified into upper airway anatomic compromise, pharyngeal dilator muscle dysfunction, and ventilatory control instability. However, the effective treatment of SDB remains limited, and positive airway pressure therapy is still the mainstay of the treatment. Therefore, we review the pathophysiological characteristics of SDB in this article, and we propose to provide individualized treatment of SDB based on the underlying mechanism. This approach requires further study but could potentially improve adherence and success of therapy.

RÉSUMÉ

Les troubles respiratoires du sommeil (TRS) sont très répandus chez les patients souffrant de maladies cardiovasculaires (MCV). Par conséquent, les TRS et les MCV montreraient un lien bidirectionnel. Cependant, les TRS demeurent sous-diagnostiqués et sous-traités. L'un des obstacles majeurs déterminés par les cardiologues est l'insatisfaction concernant le traitement des TRS. Cette situation pourrait résulter de la discordance entre le traitement et les caractéristiques physiopathologiques des TRS. Cette affection est causée par de multiples mécanismes physiopathologiques, qui pourraient être classifiés comme suit : le compromis anatomique des voies aériennes supérieures, la dysfonction des muscles dilatateurs du pharynx et l'instabilité de la maîtrise ventilatoire. Cependant, le traitement efficace des TRS étant limité, leur traitement repose encore sur la thérapie par pression positive expiratoire continue. Par conséquent, dans cet article, nous passons en revue les caractéristiques physiopathologiques des TRS et nous proposons d'offrir un traitement individualisé des TRS reposant sur le mécanisme sous-jacent. Cette approche nécessite des études plus approfondies, mais pourrait favoriser l'observance et le succès du traitement.

Sleep disordered breathing (SDB) with daytime sleepiness was previously estimated to affect 4% of men and 2% of women in North America.[1] However, recent data suggest that SDB is considerably more common at present, affecting approximately 13% of men and 6% of women. This increase is likely the result of increasing rates of obesity, an aging population, and improvements in technology to detect subtle respiratory events.[2-4]

The increasing prevalence is alarming, given the existing knowledge about the role of SDB as a cardiometabolic risk factor. SDB contributes to the development and progression of cardiovascular and cerebrovascular diseases, including heart failure, atrial fibrillation, myocardial infarction, stroke, and mortality.[5-8] These associations have been explained by multiple proposed mechanisms, although intermittent hypoxemia in SDB has emerged as the most prominent. Specifically, recurrent hypoxemia followed by reoxygenation resembles repetitive ischemia and reperfusion injury, which leads to sympathetic nervous system overactivity, systemic inflammation, metabolic dysfunction, and subsequent endothelial dysfunction.[9-12] During an obstructive apnea event, strenuous inspiratory effort against an occluded upper airway leads to sympathetic overactivity, and the resultant negative intrathoracic pressure increases left ventricular afterload and right ventricular preload, which chronically increases myocardial oxygen demand and causes ventricular remodelling.[13-15] Arousal at the end of an apneic episode also increases sympathetic activity and suppresses vagal tone, triggering the surge in blood pressure and heart rate.[16]

Emerging evidence suggests a reciprocal relationship in which cardiovascular disease (CVD) also leads to SDB (Fig. 1). Fluid redistributes from the extremities to the neck region

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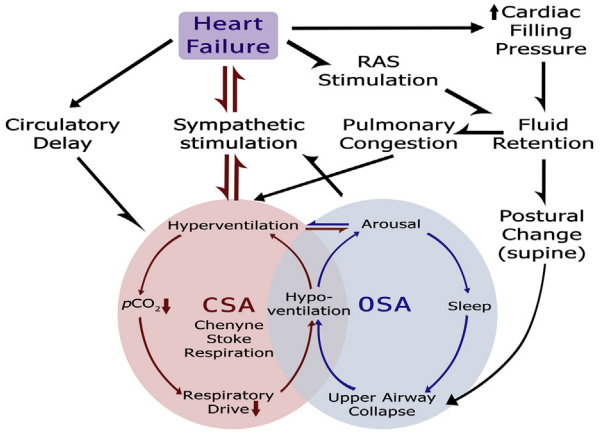

Figure 1. Schematic representation of the bidirectional relationship between sleep disordered breathing and congestive heart failure. RAS, renin-angiotensin system; CSA, central sleep apnea; OSA, obstructive sleep apnea; P_{CO_2}, partial pressure of carbon dioxide.

because of the gravity effect of positional change from upright to supine during sleep and may contribute to upper airway edema and increased neck circumference, thus leading to upper airway mechanical obstruction.[17] Optimization of diuresis and congestive heart failure (CHF) management should be the first-line treatment for these patients, because diuresis with furosemide and spironolactone in a nonrandomized trial demonstrated enlarged upper airway diameter and reduction in the apnea-hypopnea index (AHI).[18] Furthermore, cardiac dysfunction may lead to ventilatory control instability, which is well known to cause central sleep apnea (CSA) and Cheyne-Stokes respiration (CSR), but may also result in obstructive sleep apnea (OSA) (Fig. 2).[19,20] Also, pulmonary congestion enhances chemoreflex sensitivity and pulmonary irritant receptors, which result in unstable ventilatory control.[21-23] Therefore, there seems to be at least a bidirectional relationship between SDB and CVD,[24] if not a vicious cycle. Moreover, treatment of OSA has been associated with improved cardiovascular outcomes.[25-27] Studies have demonstrated that treating OSA decreases recurrence of atrial fibrillation after ablation and cardioversion.[28,29] The most recent 2013 American College of Cardiology Foundation/American Heart Association guidelines also made class IIa recommendations on the treatment of OSA in patients with heart failure.[30]

Despite the large burden of disease and the close association with CVD, SDB continues to be under-recognized and thus undertreated. Based on a 2011 American College of Cardiology Foundation survey among cardiologists, the major barriers to referring patients to sleep centres are lack of satisfaction with the effectiveness of sleep apnea therapy, the cost of a sleep study, and concerns over managing continuous positive airway pressure (CPAP) therapy.[31] Here, we focus on reviewing potential future SDB treatment with a new approach based on pathophysiological mechanisms of SDB (Fig. 3).

Behavioral Intervention for CPAP Adherence

Despite the large burden of disease, therapy for SDB remains unsatisfactory. CPAP is the treatment of choice, especially for OSA.[32] Although CPAP therapy can be transformative for many patients, tolerance and adherence to CPAP have been a major hindrance for proper treatment of SDB for a major portion of patients.[33-35] As many as 83% of patients who begin CPAP therapy are not optimally treated in that they do not use their CPAP device for even a minimum threshold of 4 hours per night on at least 70% of nights.[34,36] This problem has led to studies testing interventions that include patient education,[37,38] intensive support,[39-41] behavioral therapies based on motivational interviewing,[42] and cognitive behavioral therapy.[43]

Several studies have shown that intervention for treatment adherence needs to start as early as possible. Adherence in the first weeks predicts adherence at 6 months, which predicts long-term adherence.[44] Further, those who have been able to maintain adherence tend to see greater symptom reductions.[45] Despite this knowledge, adherence still remains poor, and behavioral approaches remain underused. Despite mounting evidence that these approaches can be helpful, efficacy of these interventions is suboptimal when they are available, and, in many cases patients do not have access to these interventions.[35]

A more mechanistic approach to SDB therapy may aid in this regard by more properly aligning patients with treatments and obviating the need for CPAP when an alternative can be provided. It should be noted, however, that alternative treatments also require adherence, and thus further study is clearly required.

Mechanistic Approach to SDB Therapy

Although CPAP has emerged as the first line of treatment, the problems associated with adherence have led to the exploration of alternative therapies such as oral appliances and upper airway surgery.[32] These alternative therapies have variable efficacy, however, and it is difficult to reliably predict the rates or degree of response to these therapies based solely on clinical examination or baseline polysomnographic results.[32,46] Thus, new therapeutic approaches and targets are greatly needed.

To improve treatment, the emerging concept is to provide individualized therapy for patients with SDB based on underlying pathophysiological mechanisms. Key causes of SDB could be classified into upper airway anatomical compromise, pharyngeal dilator muscle dysfunction, and ventilatory control instability. If we could accurately classify patients based on the primary causes of their SDB, targeted and individualized therapy could be offered to improve long-term therapeutic effectiveness.

Upper Airway Narrowing and Obstruction

Anatomic compromise

OSA is characterized by recurrent upper airway narrowing and closure. Traditionally, a narrowed upper airway resulting from various anatomic causes, such as thickened lateral pharyngeal walls from obesity, or from genetic predisposition, have been proposed to be the major mechanism for OSA.[47-49] If anatomic narrowing is the predominant factor, it is plausible to suggest that surgical procedures to correct the anatomic narrowing could be effective treatment. In practice,