Sleep-disordered breathing and heart failure: a vicious cycle of cardiovascular risk

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Abstract

Sleep-disordered breathing (SDB) represents an important cardiovascular risk factor that is still often underestimated and not always optimally treated. Such breathing disorders can induce several harmful effects on the heart, also favoring the development of arrhythmias, ischemic heart disease, and left ventricular remodeling. Obstructive sleep apnea syndrome (OSA) is more frequent in heart failure patients than in the general population, promoting the worsening of left ventricular dysfunction. Both sleep apnea and heart failure have common clinical manifestations but also similar neurohormonal characteristics, contributing to the development and progression of heart failure and resulting in increased mortality. The pathophysiological mechanisms underlying left ventricular dysfunction associated with SDB will be analyzed, and the potential therapeutic effects of gliflozins on OSA in heart failure patients will be discussed.

Introduction

Sleep-disordered breathing significantly affects cardiovascular risk, contributing to the development of hypertension, arrhythmias, ischemic heart disease, and left ventricular remodeling, which can evolve into heart failure. Because of their potential implications for cardiac morbidity and mortality, sleep-related breathing disorders are now considered among the main modifiable cardiovascular risk factors [1]. Among these, obstructive sleep apnea syndrome (OSA), characterized by a cyclical reduction or interruption of breathing during sleep, is more frequent in patients with heart failure, especially if obese and hypertensive, favoring the progression of left ventricular dysfunction [2]. Obesity, hypertension, advanced age, and male sex are the main predisposing factors for the onset of both OSA and heart failure, making it difficult to recognize the border between these conditions. It should also be remembered that among patients with heart failure and reduced ejection fraction (HFrEF), a percentage between 12 and 25% is affected by OSA, while up to 50% suffer from central apnea (CSA) [3,4]. In view of the close correlation between the progression of heart failure and sleep apnea, it is essential to early recognize and treat this class of sleep-breathing disorders to reduce cardiovascular morbidity and mortality.

Sleep apneas and heart failure

Sleep apnea and heart failure share similar clinical manifestations, such as paroxysmal nocturnal dyspnea, fluid retention, and

fatigue. They also have overlapping neuro-hormonal characteristics, including reduced availability of nitric oxide and increased inflammatory indices. These conditions contribute to the development and progression of heart failure, starting with the form of preserved ejection fraction (HFpEF), which may subsequently lead to impaired left ventricular compliance, eventually causing HFrEF [5].

Previous studies have shown that nocturnal continuous positive airway pressure (CPAP) treatment at night improves the cardiovascular outcome of patients with HFrEF and OSA [6], whereas it is less effective in reducing the mortality of patients with CSA [7,8]. Traditional drug therapies for heart failure have no substantial effect on OSA except for diuretics, which may have a potential negative impact on renal function indices. However, angiotensin-neprilysin receptor inhibitors have demonstrated a favorable impact on patients with heart failure and sleep apnea, reducing the apnea-hypopnea index (AHI) [9].

The recent introduction of sodium-glucose co-transporter inhibitors (SGLT2i) in heart failure treatment has improved the quality of life by reducing hospitalizations for heart failure-related symptoms [10]. This class of drugs has also shown promise in reducing the incidence of OSA in patients with type 2 diabetes mellitus, suggesting a potential new therapeutic approach to reducing global cardiovascular risk [11].

Pathophysiology of obstructive sleep apnea syndrome and cardiovascular involvement

Patients with OSA experience continuous cycles of hypoxia and re-oxygenation within a general framework of autonomic nervous system dysfunction and changes in intrathoracic pressures [12]. In the long run, this leads to a pro-inflammatory and pro-fibrotic state characterized by increased circulating cytokine levels, endothelial dysfunction, and hypercoagulability. These changes cause left atrial dilatation and reduced diastolic compliance of the left ventricle, which clinically favor the onset of both cardio- and cerebrovascular events.

The repetitive episodes of airway obstruction and disrupted sleep patterns characteristic of OSA induce an imbalance in the functioning of the autonomic nervous system. As a consequence, a number of physiological changes occur, including sympathetic overactivity, baroreflex dysfunction, alterations in heart rate variability, and metabolic changes. These lead to cardiovascular consequences such as hypertension, arrhythmias, and heart failure [13].

The cardiac effects of intrathoracic pressure changes and cyclic desaturation and re-oxygenation occur at both atrial and ventricular levels, in both the right and left sections of the heart. In the acute phase, OSA can be responsible for atrial arrhythmic events due to a reduction in the refractory period and conduction rate. It can also induce ventricular events resulting from increased QT dispersion and the activation of arrhythmic triggers. The long-term effects of OSA include left atrial dilatation, fibrosis, and left ventricular hypertrophy, thus favoring the onset and progression of heart failure [14].

Regarding the effects on ventricular compliance, increased intramural pressures in the left ventricle led to increased oxygen consumption and reduced coronary flow, which, in the context of hypoxia caused by apnea, can induce ischemia and consequent unfavorable ventricular remodeling. Conversely, in the right sections, increased pressures in the pulmonary circle cause a reversal of the pressure and the volumetric relationship between the right and left chambers, resulting in a "leftward shift" of the interventricular septum, tricuspid insufficiency, and reduction of the longitudinal systolic function of the right ventricle (Figure 1). The mechanisms described so far are more pronounced in obese patients, those suffering from metabolic syndrome, and those with HFpEF, where chronic deficiency of atrial natriuretic peptide (BNP), increased representation of epicardial adipose tissue (EAT) (Figure 2), and constant inflammation indices are more prominent [15]. All these factors contribute to the progression of OSA.

From heart failure with reduced ejection fraction to central apnea

CSAs are forms of sleep disorders related to higher mortality rates and represent an independent risk factor for morbidity and mortality in HFrEF patients. These consist of an interruption of the respiratory nervous stimulus in the absence of mechanical obstruction and, unlike obstructive forms, do not benefit from the use of CPAP. In these patients, the use of adaptive servoventilation improved the AHI; however, it was ineffective in correcting sympathetic nervous system activity and was associated with an increased risk of cardiac and all-cause mortality [16].

To summarize, in advanced forms of HFrEF, congestion in the pulmonary circulation leads to hyperstimulation of pulmonary vagal receptors, causing hyperventilation and subsequent hypocapnia. Simultaneously, awakenings caused by activation of the autonomic nervous system (the so-called "fight-or-flight" response) result in abrupt increases in ventilation, lowering the partial pressure of carbon dioxide values below the ventilation threshold, and triggering CSA (Figure 3) [17]. HFrEF patients, who typically have lower than normal expiratory volume and consistently elevated plasma concentrations of the N-terminal fragment of the protein precursor BNP, often present with CSA forms that are associated with Cheyne-Stokes breathing. It is believed that the fluid accumulated during the day in the intravascular and interstitial spaces of the lower limbs is redistributed to the upper respiratory tract during the night, leading to a state of edema that creates an ideal condition for sleep apnea [14].

Effects of sodium-glucose co-transporter type 2 inhibitors on sleep apnea syndromes

Previous research has shown a significant effect of SGLT2i in improving AHI in diabetic patients with OSA, reducing the incidence of cardiovascular and renal complications [18,19]. In particular, the positive effect of gliflozins on OSAs is achieved through weight loss [20], and a reduction in plasma volume due to osmotic diuresis, resulting in a decrease in preload [21]. In obese patients, gliflozins not only reduce fat mass in the abdomen but also mainly in visceral fat. This reduction in visceral fat leads to a decrease in the expression of EAT, which acts as an endocrine organ and significantly contributes to left ventricular remodeling and progression to heart failure in the HFpEF form through the production of pro-inflammatory adipokines [22].

The natriuretic effect of SGLT2i reduces blood pressure and volume overload, which is more prominent in heart failure patients. Unlike traditional diuretics, the diuretic action of SGLT2i induces an euvolemic state, reducing excess fluid. However, this function is limited by the action of vasopressin, which prevents hypotension, dehydration, and consequent renal damage [23]. Furthermore, the cardioprotective effects of SGLT2i include the reduction of oxidative stress and fibrosis, along with an increase in hemoglobin and hematocrit levels [24,25].

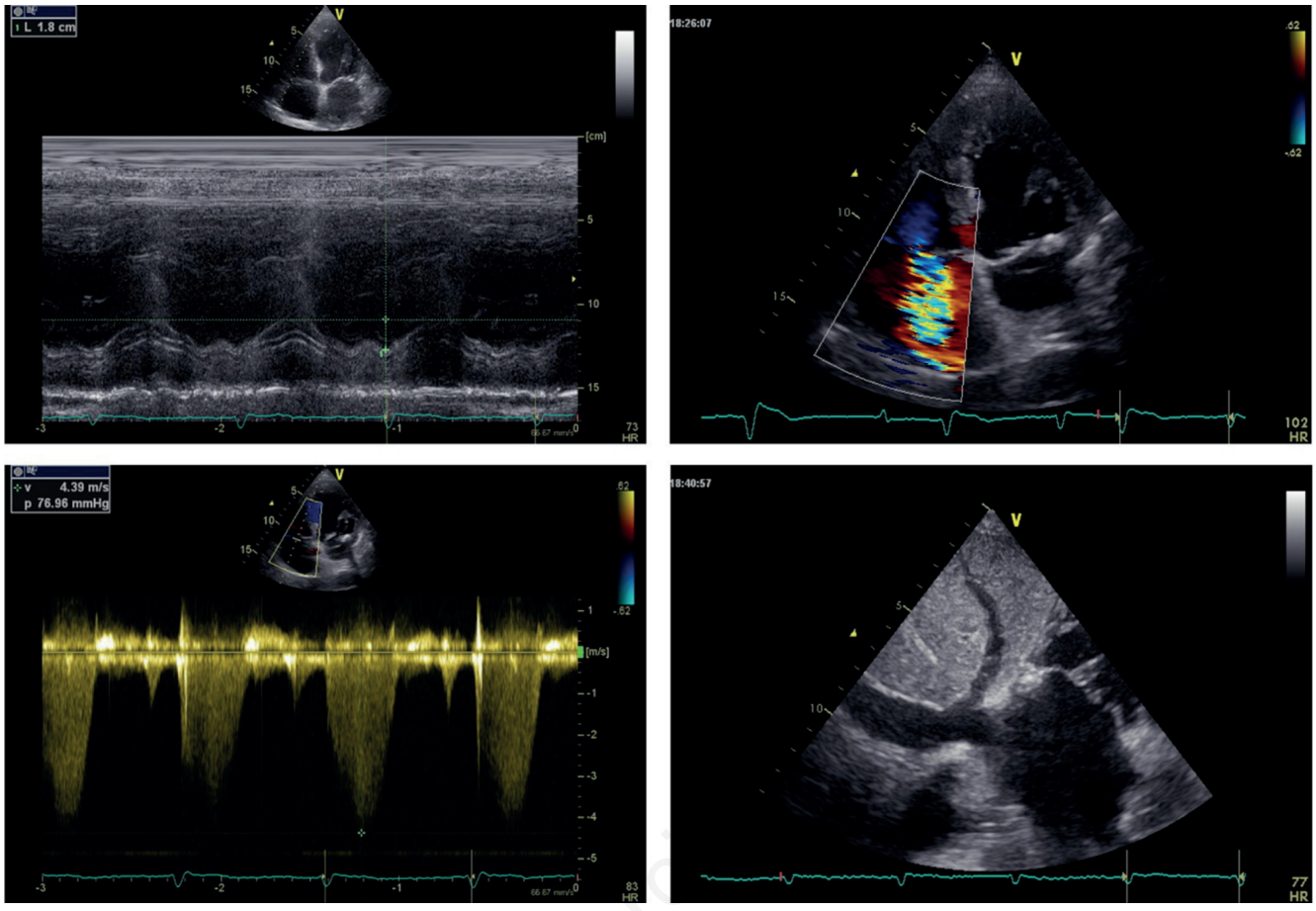

Figure 1. Echocardiographic evaluation of the effects of obstructive sleep apnea syndrome on pressure variations of the pulmonary circulation and right ventricle.

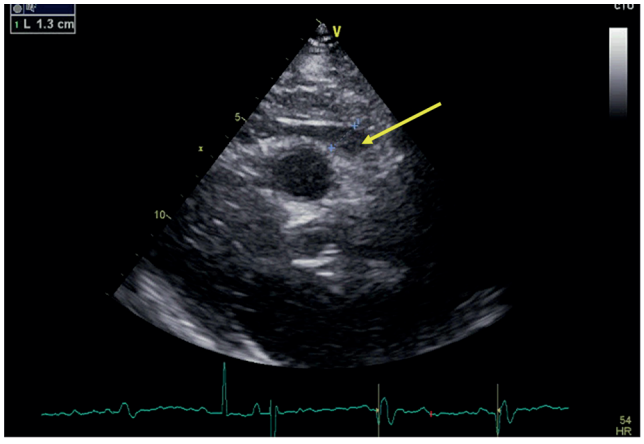

Figure 2. Parasternal long axis view. Epicardial adipose tissue (arrow).

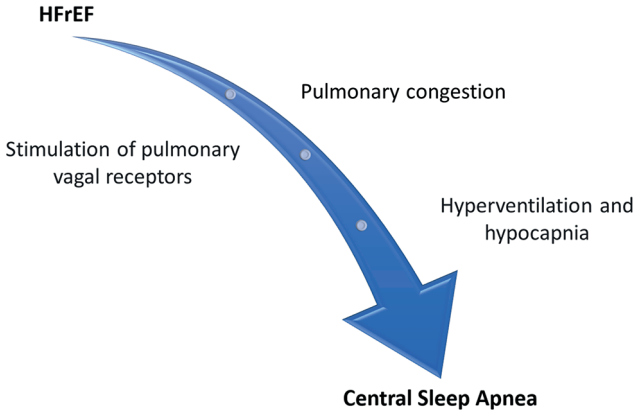

Figure 3. Mechanisms leading from heart failure with reduced ejection fraction to central sleep apnea. HFrEF, heart failure and reduced ejection fraction.

Conclusions

There is a close correlation between sleep apnea and heart failure. The two conditions tend to aggravate each other in a vicious circle, progressing from obstructive apnea to refractory central forms, which are resistant to treatment and associated with high mortality.

The addition of SGLT2i on top of maximal therapy for heart failure, especially in patients with HFpEF, particularly if obese, could have a positive effect on AHI, desaturation indices, and mean nocturnal SO_2 values. This could lead to a reduction in the incidence of sleep apnea phenomena and significantly influence both the progression and prognosis of heart failure, even in patients without type 2 diabetes mellitus. This provides a new therapeutic target in the pharmacological management of these patients.

The natriuretic action of SGLT2i reduces the need for high doses of diuretics, thereby limiting their harmful effects on renal function.

Only a few studies have explored the effects of SGLT2i on OSA in patients with HFpEF, highlighting their potential benefits [26]. Further prospective studies on larger populations would be essential to gain a better understanding of the cardioprotective mechanisms of gliflozins and validate their use in clinical practice.

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