Review

Same heart and different sleep? A brief review of the association between sleep apnea syndrome and heart failure based on two clinical cases

ABSTRACT

The research in the field of sleep medicine has increased during the whole twentieth century, principally for the involvement of sleep-related disordered breathing (SDB) in cardiovascular disease. If sleep encompasses about a third of one's life, the reasons are mostly linked to its effects on the cardiovascular and respiratory systems. Sleep is a physiological phenomenon characterized by changes in the human body leading to a state of quiescence of the cardiovascular, respiratory and metabolic systems [1]. The importance of these events becomes more evident if we consider what happens in their absence, that is, during SDB syndromes. These syndromes include habitual snoring, sleep apnea, Cheyne-Stokes breathing syndrome and sleep hypoventilation syndrome [2]. Sleep apnea syndromes are characterized by several apneic events during the night, which consist in absence of the airflow or its reduction by more than 90% lasting more than 10 seconds, with consequent oxyhemoglobin desaturation and arousal [2]. These events provoke microawakening and sleep fragmentation that represent, along with hypoxemia, important harmful triggers on the cardiovascular system. In fact, SDB presents as a highly prevalent comorbidity in patients with heart failure (HF); both diseases are related to each other in a bidirectional way through multiple mechanisms: apneic events raise cardiac afterload, and at the same time impaired cardiac function itself may contribute to the development sleep apnea. HF is a clinical syndrome characterized by signs or symptoms due to the inability of the heart to provide a normal tissue perfusion: the failing cardiac pump is not able to maintain an adequate output for this task. Typical features of HF are represented by shortness of breath, resting or exertion dyspnea, fatigue, fluid retention leading to

pulmonary congestion or ankle swelling, and objective evidence of a structurally or functionally abnormal heart at rest [1,3].

Keywords: sleep apnea syndrome, obstructive sleep apnea, central sleep apnea, heart failure, continuous positive airway pressure.

INTRODUCTION

In this report we describe two cases of 38 years old men sharing a similar medical history characterized by recent onset asthenia and mild effort dyspnea with a subsequent diagnosis of non-ischemic dilated cardiomyopathy. Based on the high prevalence of SDB in patients with cardiovascular disease and the well established relationship between SDB and HF in terms of risk factors and comorbidities, we decided to perform a cardio-respiratory sleep study in both patients. This examination established a diagnosis of sleep-related disordered breathing with prevalent obstructive apnea in only one of these patients, thus giving rise to a brief discussion about the complex pathophysiological relationships between HF and SDB.

Clinical case 1

A 38-years-old man with no previous cardiovascular events and no risk factors presented to the Emergency Department of our hospital for new onset mild effort dyspnea. Physical examination revealed protodiastolic gallop rhythm and pulmonary basal crackles. A twelve lead ECG was recorded, showing sinus tachycardia (HR: 100 bpm), possible left atrial enlargement, left anterior fascicular block and some supraventricular ectopic beats (Figure 1.A). The chest X-rays showed widened heart silhouette and Kerley's B lines. An echocardiogram revealed significant enlargement and severe dysfunction of the left ventricle (end diastolic diameter: 70 mm; LVEF < 20%), moderate mitral valve regurgitation due to annulus dilation, significant left atrial enlargement (258 ml). The patient was admitted to the Cardiology Unit and underwent blood sample ruling out the presence of acute viral infections. The coronary angiography showed normal coronary arteries. A cardiac magnetic resonance evidenced severe biventricular dysfunction and enlargement and ruled out the presence of areas of edema and delayed enhancement (Figure 1.B). Beta-blockers, ARBs (up-titrated to the highest tolerated doses) and diuretics were administered with clinical benefit and a primary prevention single-chamber implantable cardioverter-defibrillator was implanted three months later because of persistent low ejection fraction despite optimal medical therapy.

Clinical case 2

A 38-years-old man with recent onset hypertension came to our Emergency Department for paroxysmal nocturnal dyspnea and chest oppression. The chest-X rays showed interstitial pulmonary edema and cardiac dilation, twelve lead ECG showed new onset left bundle branch block and atrial flutter with 2:1

atrioventricular ratio (Figure 2.A) (the left bundle branch regressed after treatment of supraventricular tachycardia and rate control). The patient was then recovered into the Cardiac Intensive Care Unit. The echocardiogram showed severe left ventricular dysfunction (LVEF < 20%), global left ventricular hypokinesis, bi-atrial enlargement and slightly enlarged right ventricle; severe pulmonary hypertension was also found (PAPS 65 mmHg). Blood samples ruled out the presence of acute viral infections. The coronary angiography found no signs of atherosclerosis. During the hospitalization beta-blockers, ACE-inhibitors (up-titrated to the highest tolerated doses) and diuretics were administered with improvement of the patient's clinical conditions. A cardiac magnetic resonance evidenced severe reduction of the systolic left ventricular function, normal right ventricular function and few areas of intramyocardial interventricular septal delayed enhancement which were, however, inconsistent with prior myocarditis (Figure 2.B). A single-chamber implantable cardioverter defibrillator was then implanted in primary prevention three months later because of persistent low ejection fraction despite optimal medical therapy.

Cardiorespiratory sleep study

Since both patients complained nocturnal snoring, dryness of mouth at the awakening and daytime sleepiness, we decided to perform a cardiorespiratory sleep study to detect the presence of SDB. Patient 1 presented obstructive sleep apnea (OSA) and a large number of central sleep apneas (CSA), with an Apnea-Hypopnea Index (AHI) of 56/hour and moderate hypoxemia, pointing out severe sleep apnea syndrome. Patient 2 only showed rare short phases of hypopnea with an AHI of 4/hour, thus not matching the diagnostic criteria for sleep apnea syndrome (Figure 1.C-D, 2.C-D).

SLEEP APNEA SYNDROME AND HEART FAILURE

SDB affects 2 to 5% of the general population, but its prevalence is much higher among HF patients. Those patients are reported to have a prevalence of OSA ranging from 12 to 53% in polysomnography studies [4,5,6]. In addition, more than 55% of patients with OSA have diastolic dysfunction [7]. Numerous studies investigated the prevalence of SDB in the context of HF, reporting inhomogeneous results because of the use of different cutoffs of AHI, variable heart failure severity, dissimilar comorbidities and risk factors between studies.

OSA was found in approximately 11% of 81 ambulatory male patients with systolic HF and a mean EF of 25% [8]. Few years later, the same group prospectively analyzed 100 ambulatory male patients with HF and mean EF of 24% and found a 12% prevalence of OSA. [9] In a similar way Vazir et al [6] found the prevalence of OSA to be 15% among male patients with mild symptomatic HF, and in another prospective study including female patients Wang et al [10] reported a 26% prevalence among 218 heart failure patients with a LVEF lower than 45%. A retrospective study conducted by Sin et al on a larger population of 450 patients with systolic HF showed that 37% of the study population suffered from OSA [11]. In a similar fashion, Ferrier et al found the prevalence of OSA to be 53% in 53 stable HF outpatients [5]. However, the two latter studies used a AHI cutoff of 10/h and included patients with higher EF (anyway remaining below 45%). Further data supported a high OSA prevalence in HF, in fact Oldenburg et al [12] studying 700 HF patients with NYHA Class ≥ II, found that 36% were affected by OSA based on a AHI cutoff of ≥ 5/h.

The same studies also described the prevalence of central sleep apnea (CSA) in patients with chronic HF. Jahaveri et al found CSA prevalence of 40% and 37% in subsequent studies enrolling ambulatory male patients with HF [8,9]. The studies by Vazir and Wang showed the prevalence of CSA in HF patients to be 38% and 21%, respectively, with the second study also including female patients [6,10]. In their retrospective study on 450 consecutive patients with systolic HF, Sin et al found a 33% prevalence of CSA [11], and in a similar way Ferrier et al found a CSA prevalence of 15% [5]. In another study using the minimum AHI cutoff (5/h), CSA prevalence was as high as 40 % (12)). Table 1 provides an overview of the prevalence of OSA and CSA in various studies which enrolled patients with HF.

Those findings altogether point out the importance of SDB in HF patients, despite a dissimilar prevalence in different studies. The basis of such discrepancy might be represented by the use of different cutoff values, dissimilar patient populations in terms of ethnicity and gender prevalence, concomitant presence of both

types of apnea and their different classification according to the relative percentage of one of the two types of SDB. Besides, since CSA seems to be associated to more advanced HF, the presence of patients with more severe HF might play an important role as a selection bias in some studies. Recent investigations also showed a high prevalence of SDB, predominantly OSA, among patients with stable HF with NYHA class II-IV and preserved ejection fraction [13].

PATHOPHYSIOLOGY OF SLEEP APNEA IN THE PRESENCE OF HEART FAILURE

Patients with HF show increased fluid retention and a higher prevalence of both obstructive and central sleep apnea, which can coexist in the same subject. A recent study suggested that there may be a common pathophysiological pathway underlying both types of apnea in patients with systolic HF. In these patients, a nocturnal rostral fluid shift from the legs has been documented by a reduction in the leg fluid volume and calf circumference. At the same time, an increased neck circumference has been observed, which can be related to soft tissues congestion, loss of dilator pharyngeal muscles tone and pharyngeal obstruction, thus explaining the occurrence of obstructive apnea events. On the other hand, in patients experiencing central apnea events there is a more pronounced reduction of leg fluid volume which is only partially explained by the increase of neck circumference, suggesting that part of these fluids may be responsible of augmented pulmonary congestion and filling pressures in these patients. Pulmonary congestion is directly related to the pathogenesis of central apnea events through an imbalance of pulmonary gas exchange, characterized by a progressive reduction of PaO2 below the threshold of the physiological nocturnal reduction of 4-10 mmHg and an increase of PaCO2 above the 3-7 mmHg usually observed in a normal sleep, and stimulation of pulmonary J receptors. The combination of these alterations triggers hyperventilation, subsequently leading to PaCO2 reduction below the so-called apnea threshold, thus suppressing stimulation of the respiratory muscles and causing phases of apnea. This imbalance of PO2 and PCO2 concentration stimulates the central nervous system, thus increasing the ventilation rate and provoking arousals with sleep fragmentation and respiratory fatigue that further worsen the underlying cardiac condition (Figure 3). The interaction between CSA and HF is therefore complex; fluid retention seems to be a key mechanism linking these two conditions, as also suggested by the recently proven association between excessive sodium intake (with subsequent intra- and extra-vascular plasma volume expansion) and sleep apnea in patients with HF [14-19].

TREATMENT OF SLEEP APNEA SYNDROME IN THE SETTING OF HEART FAILURE

Despite continuous treatment advancements, patients with HF have a poor prognosis. Worsening clinical conditions often require progressive therapeutic adjustments. The therapeutic options for HF encompass both pharmacological and electrical treatment: beta-blockers, renin-angiotenin-aldosterone system antagonists and diuretics, cardiac resynchronization therapy and implantable cardioverter-defibrillators. At the same time it is important to treat all the other conditions that might contribute to worsen HF such as sleep apnea syndrome. The primary choice in the treatment of sleep apnea syndrome is characterized by the nightly use of continuous positive airpressure of ventilatory support, such as APAP, CPAP, bi-PAP or bi-level, or adaptive servo-ventilation, depending on the type and the amount of the apneic events and on the underlying cardiac and respiratory conditions. Several studies have shown the advantages of this therapeutic option for patient with sleep apnea also in terms of blood pressure [20,21] and improved glucose tolerance [22]. The left ventricular ejection fraction is improved in HF patients when OSA is treated with CPAP [23,24]. Although the CANPAP trial failed to show any impact of CPAP on heart transplant-free survival, a post-hoc analysis demonstrated that if CSA is suppressed soon through the use of CPAP, this results in an improvement of both left ventricular ejection fraction and heart transplant-free survival. [25] In patients with chronic HF, OSA and CSA often co-exist; adaptive servoventilation effectively reduced all forms of SDB and improved left ventricular ejection fraction at six-months follow-up in a small study[26].

CONCLUSIONS

In spite of the currently available knowledge about SDB and heart failure, several aspects of the relationship between these two conditions remain unknown. The clinical cases reported herein underline the complexity of such connections, that are at times not as straightforward as one might expect. Although SDB are likely to affect patients with severe HF, thus mandating further investigations such as polysomnography in this subpopulation, some of these patients might not show apneic events during the night, as observed in the second clinical case. The exact relationship between SDB and HF is still under investigation, and nowadays many questions are still unanswered. Should be every patient with HF screened for the presence of SDB? Are there any clinical or pathological features that are able to strongly suggest the presence of SDB in HF patients? Are patients with HF associated to SDB subject to a different degree of severity of nightly desaturations or apneic events than the remainder of SDB patients? Do they respond in a significantly different manner to ventilation therapy, either better or worse? As shown in our reports, every clinical case could present different characteristics. Probably, further pathophysiogical pathways in addition to the ones described in this brief review act in the complex cascade of events that in the setting of HF eventually provoke apneic events thus contributing to worsen this condition. Several other topics are still under debate. For example, the contribution of the right ventricle to pulmonary congestion through fluid retention and its rostral nightly distribution is currently unclear. At the same time, a different impact on the presence of SDB might be determined by the underlying cardiomyopahty, with different etiologies leading to a different risk of developing SDB due to their diverse involvement of cardiac wall areas and autonomic system receptors. The role of the sympathetic autonomic system also remains incompletely explained as well as the role played by autonomic triggers in different cardiac diseases. Further studies are warranted to better understand the reciprocal interplay of HF and SDB and the specific role of the apnea treatment by ventilatory support in the armamentarium of HF therapies.

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Study	Patients, n	Age, mean ± SD	Gender M/F (n)	Mean LVEF	NYHA functional class	AHI Cutoff	SDB, %	OSA prevalence (%)	CSA Prevalence (%)
Javaheri, 1998	81	64±10,5	81/0	25	I-III	≥15	51	11	40
Sin, 1999	450	60±13,6	382/68	27,3	II-IV	≥ 10	70	37	33
Ferrier, 2005	53	60,1±9,8	41/12	34	I-II	≥ 10	68	53	15
Javaheri, 2006	100	64± 10	100/0	24	I-III	≥ 15	49	12	37
Vazir, 2007	55	61± 12	55/0	30,6	II	> 15	53	15	38
Wang, 2007	218	55±11,7	120/44	25	II-IV	≥ 15	47	26	21
Oldenburg, 2007	700	64,5±10,4	561/139	28,3	II-IV	> 5	76	36	40
Herrscher, 2011	71	61.4 ± 9.5	60/11	29,6	II-IV	≥ 5	81	49	32

Table 1

Figure 1: A twelve lead ECG showed sinus tachycardia (HR: 100 bpm), left anterior fascicular block and some supraventricular ectopic beats (Figure 1.A). A cardiac magnetic resonance evidenced severe biventricular dysfunction and enlargement and ruled out the presence of areas of edema and delayed enhancement (Figure 1.B). A cardiorespiratory sleep study to detect the presence of SDB revealed obstructive sleep apnea (OSA) pointed out in light violet, infact in the apneic events there is the absence of airflow and at the same time a thorax and abdominal effort (Figure 1.C-D)

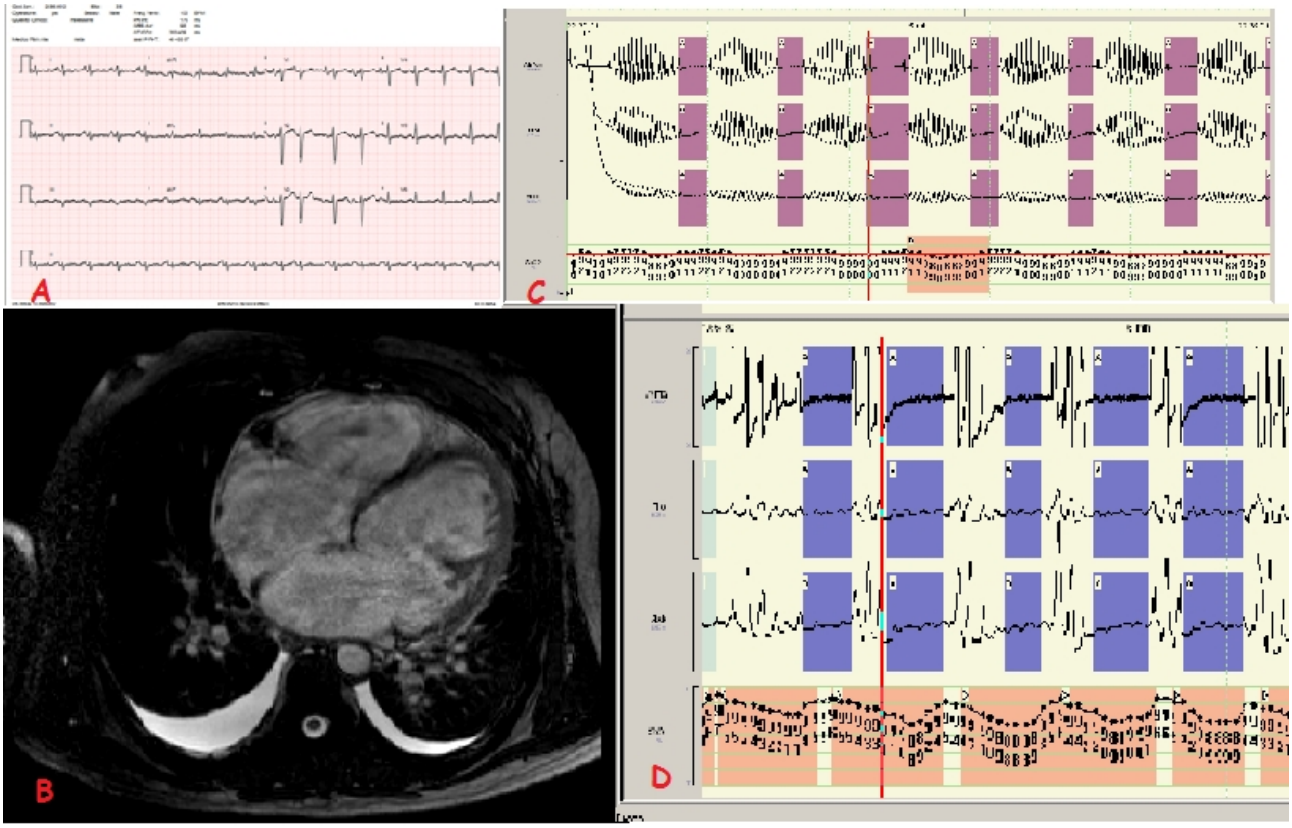

Figure 2: A twelve lead ECG showed new onset left bundle branch block and atrial flutter with 2:1 atrioventricular ratio (Figure 2.A). A cardiac magnetic resonance evidenced severe reduction of the systolic left ventricular function, normal right ventricular function (Figure 2.B). A cardiorespiratory sleep study does not show apneic events, but only short phases of hypopnea with the mild reduction of airflow during nightly breath (2.C)

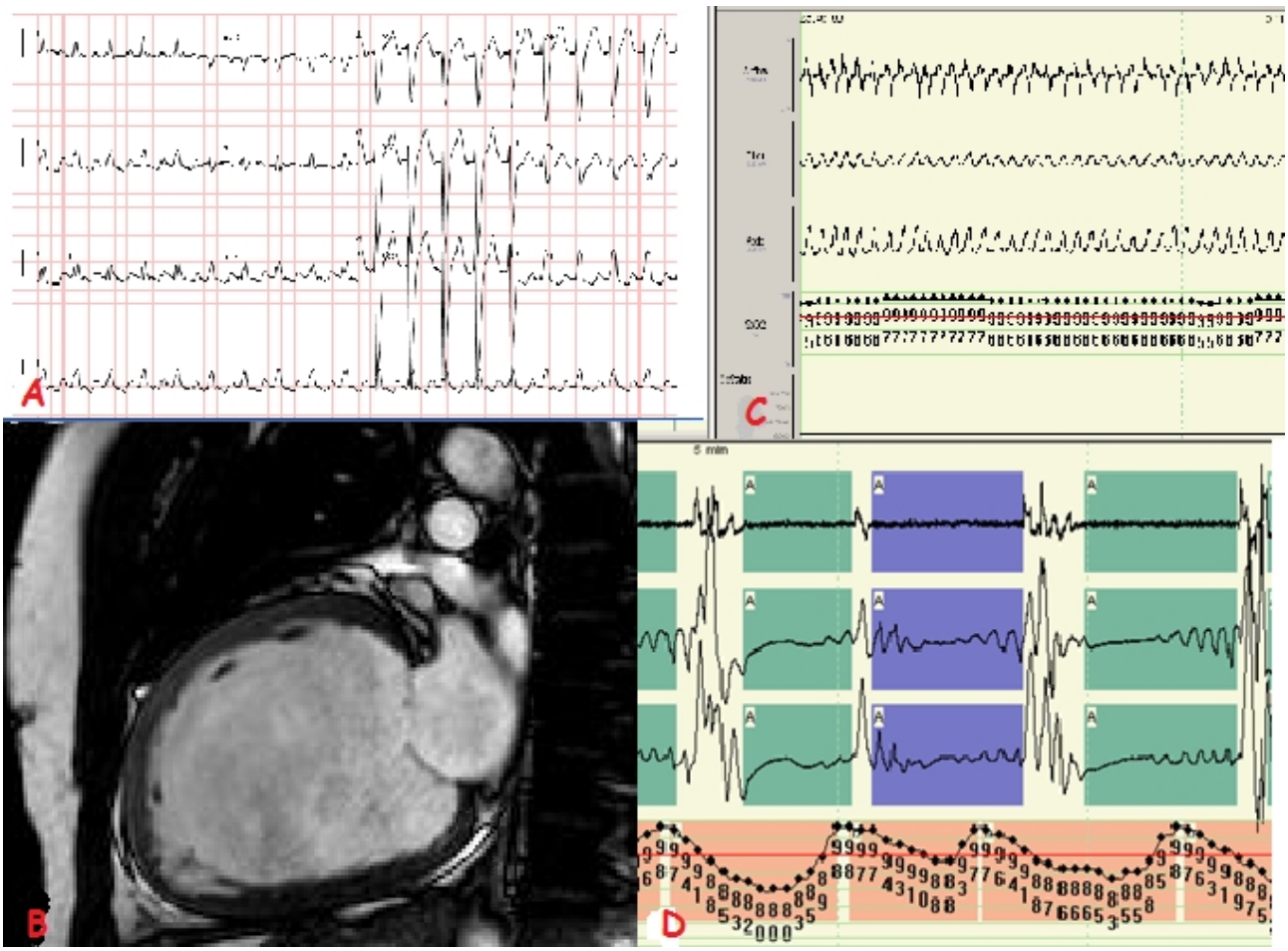

Figure 3: Patients with HF show increased fluid retention with a nocturnal rostral fluid shift from the legs and increased neck circumference and loss of dilator pharyngeal muscles tone and pharyngeal obstruction, thus explaining the occurrence of obstructive apnea events. On the other hand, in patients experiencing central apnea events part of these fluids may be responsible of augmented pulmonary congestion directly related to the pathogenesis of central apnea events through an imbalance of pulmonary gas exchange and stimulation of pulmonary J receptors. The combination of these alterations triggers hyperventilation, subsequently leading to PaCO2 reduction below the so-called apnea threshold, thus suppressing stimulation of the respiratory muscles and causing phases of apnea. This imbalance of PO2 and PCO2 concentration stimulates the central nervous system, thus increasing the ventilation rate and provoking arousals with sleep fragmentation and respiratory fatigue that further worsen the underlying cardiac condition (Figure 3).