Obstructive sleep apnea: one more target in cardiac rehabilitation

Apnea ostruttiva nel sonno: un altro obiettivo per la riabilitazione cardiologica

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ABSTRACT: *Obstructive sleep apnea: one more target in cardiac rehabilitation. M.T. La Rovere, F. Fanfulla, O. Febo.*

Obstructive sleep apnea (OSA) is a highly prevalent sleep-related breathing disorder, often unrecognized and undiagnosed, in patients with established cardiovascular diseases. Considerable evidence is now available in support of a significant association between OSA and increased risk for cardiovascular disease morbidity. OSA has also been recognised as a potential public health issue associated with societal consequences including accidents and work economics. Treatment of OSA would reduce cardiovascular risk and the overall usage of health care resources. OSA might be a modifiable risk factor and screening for OSA should be implemented in cardiac rehabilitation settings.

Keywords: cardiac rehabilitation, obstructive sleep apnea, cardiovascular risk.

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Introduction

There is compelling evidence that sleep-related breathing disorders are very common in cardiac disease patients and are associated with increased morbidity and mortality [1,2]. According to the current classification, there are five major types of sleep-related breathing disorders [3], among which the obstructive sleep apnea (OSA) and the central sleep apnea (CSA) syndromes are the most frequently occurring. OSA is caused by repetitive collapse of a narrow upper airway during sleep and has been reported affecting up to 24% of the US population [4-6]. CSA occurs in the background of a decreased ventilator drive that originates from an instability in the chemical control of ventilation [7] and is a common comorbidity in patients with heart failure, despite optimal pharmacological therapy [8]. It is now well acknowledged that OSA may contribute to the pathogenesis of major public health issues including accidents as well as cardiovascular and metabolic diseases and its treatment may improve the function of several target organs. However, the awareness of this disorder among both physicians and the general population is relatively low leaving a significant proportion of subjects affected not to benefit from effective interventions.

The aim of this review is to discuss the relationship between OSA and increased cardiovascular risk, its public heath burden and to highlight the potential of a cardiac rehabilitation setting to fill the present gap in evaluation and treatment.

Definitions and Epidemiology

OSA is defined as repeated episodes of obstructive apneas (a complete cessation of airflow lasting 10 seconds or more) and hypopneas (a reduction in airflow to < 50% of normal lasting 10 seconds or more) triggering hypoxia and hypercapnia and unconscious (EEG) arousals. Snoring, episodes of dyspnea, asphyxia or suffocation and body movements are common between apneic events and can cause sleep fragmentation. Feeling of unrefreshing sleep, exhaustion and daytime sleepiness (which is the most common symptom) can severely impair quality of life of the patients.

Daytime sleepiness is usually defined on the basis of answers to a cluster of related questions about sleepiness or clinical observations. The Epworth sleepiness scale is a simple, well validated questionnaire that evaluates the likelihood of falling asleep in eight different situations [9], that is used in both research and epidemiological studies.

The severity of OSA is classified with an overnight polysomnography or cardiorespiratory polygraphy which define an apnea/hypopnea index (AHI), i.e. the total number of apneic and hypopneic events per hour. The 1999 Task Force of the American Academy of Sleep Medicine [10] agreed the AHI cut-points for mild, moderate and severe OSA into 5-15, 15-30, >30, respectively.

There are been methodological difficulties in characterizing the epidemiology of OSA as prevalence estimates are extremely vulnerable to a number

of issues including the methods used to measure OSA, the methodology used to quantify airflow, the use of more restrictive definitions of hypopnea, etc. In the Wisconsin study, the first detailed assessment of the prevalence of sleep-related breathing disorders in the general US population, AHI ≥ 5 and ≥ 15 events/h were found respectively in 24% and 9% of men and 9% and 4% of women between the age of 30 to 60 years [4]. Daytime symptoms were present in 4% and 1.4% of men and in 2% and 0.9% of women with mild and moderate OSA, respectively. The average estimates from two other cohort studies using similar methods and definitions led to the conclusion that in predominantly white men and women with mean body mass index BMI of 25 to 28, roughly 1 of every 5 adults has at least mild OSA and 1 of every 15 has at least moderate OSA [11]. In Europe, the latest epidemiological survey reported a prevalence of OSA among the general population of 21% in males and 13% in females using a AHI/≥5 cut-off, and a prevalence of 11% in males and 6% in females using a AHI/≥15 cut-off [6].

Predisposing factors are obesity, congenital or acquired craniofacial and neck defects, menopause, endocrine abnormalities, whereas smoking and alcohol use can precipitate the disorder.

Continuous positive airway pressure (CPAP) represents the standard treatment of OSA [12]. The value of non-positive-pressure therapies, including conservative and surgical approaches, have been recently reviewed in a European Respiratory Society Task Force Report [13].

OSA and Cardiovascular Disease

OSA is a frequent comorbidity in several cardiovascular conditions (Table 1).

Epidemiological data provide strong evidence indicating OSA as an independent risk factor for cardiovascular disease and mortality.

OSA commonly coexists with systemic hypertension. Prevalence data indicate that about half of patients with OSA are hypertensive, and an estimated 30-40% of hypertensive patients (up to 83% in the context of resistant hypertension) are diagnosed with OSA [14,15]. Data largely support a causal link between OSA and hypertension. The strong dose-response relationship between OSA severity and incidence of new hypertension reported

in the Wisconsin Sleep Cohort Study after adjustment for confounding factors [16], has been confirmed in a recent observational study with a median 12.2 years of follow-up [17]. This study also found a strong association between adherent CPAP therapy and incidence of hypertension, after adjustment for important known confounders [17].

A large population-based study, the Sleep Heart Health Study (SHHS) was specifically designed to investigate the role of sleep-related breathing disorders in incident coronary heart disease, stroke, increased blood pressure, and all-cause mortality [18]. Home polysomnography studies were performed on a sample of 6600 men and women, 40 years of age, who were followed-up for 8.2 years. In a longitudinal analysis of more than 4000 participants who were initially free of coronary heart disease and heart failure, men with an AHI ≥ 30 were 68% more likely to develop coronary heart disease and 58% more likely to develop heart failure than those with an AHI < 5 [19]. With a follow-up time extended up to 24 years, the Wisconsin sleep study showed that untreated subjects with severe OSA (AHI >30) were 2.6 time more likely to have an incident coronary heart disease or heart failure compared to those without sleep disordered breathing [20].

Recent data also reported that OSA prevalence is up to 69% in patients presenting with acute coronary syndromes [21]. Furthermore, OSA has been associated with increased risk of adverse events after an acute coronary syndrome and in patients with established ischemic heart disease [21, 22]. In a case-control study including 192 patients with acute myocardial infarction (63 patients without OSA, 52 untreated patients with OSA and 71 OSA patients treated with CPAP), over a 6-year follow-up, the risk of recurrent myocardial infarction and revascularization procedures was lower in treated than untreated OSA and similar to non-OSA patients [23]. Similarly, in 390 patients who had undergone percutaneous coronary intervention, over a median follow-up of 4.8 years, untreated moderate-severe OSA was independently associated with a significant increased risk of repeat revascularization that was reduced by CPAP treatment [24].

Although the prevalence of OSA in patients with heart failure is higher than the general population, ranging from 15% to 26% using an AHI ≥15/h as a diagnostic threshold for sleep disordered breathing [25], CSA is the predominant form in this patient population.

Patients with untreated OSA have an elevated risk of developing stroke, and the data are more consistently positive than for cardiac disease. Estimates of prevalence showed approximately 50%-70% of patients with stroke having an AHI > 10/h, mainly represented by OSA events [26].

There is an important, still under recognized, association between OSA and atrial fibrillation. In a cross-sectional analysis of the Sleep Heart Health Study in 566 subjects undergoing continuous electrographic monitoring, atrial fibrillation occurred in 5% of those with severe sleep apnea and only in 1% of those without sleep apnea [27]. Other studies reported that OSA was present in 49% of patients referred for electrical cardioversion, while untreated

Table 1. - Average prevalence of obstructive sleep apnea in cardiovascular conditions

30%-40% of patients with hypertension (14)

Up to 80% of patients with resistant hypertension (15)

30% of patients with coronary artery disease (21)

Up to 70% in patients presenting with acute coronary syndrome (21)

Up to 33% of patients with heart failure (25)

Up to 70% of patients with acute stroke/TIA (26)

50% of patients with atrial fibrillation requiring cardioversion (28)

33% of patients with lone atrial fibrillation (28)

OSA was associated with a significantly higher recurrence rate following cardioversion [28].

In a recent meta-analysis of 17 prospective studies moderate-to-severe OSA carried an almost 2.5-fold risk of developing cardiovascular events and had a 2.0-fold risk of developing stroke [29].

By increasing the risk for the development of cardiovascular diseases, OSA also impact on cardiovascular mortality. In a 10-year observational study on a large group of subjects with and without OSA, those with untreated severe OSA (defined as AHI ≥ 30 events/h) had a higher incidence of fatal and nonfatal cardiovascular events than simple snores and untreated mild OSA. By contrast, severe OSA patients treated with CPAP had fewer fatal and nonfatal cardiovascular events than untreated patients [30]. The longitudinal analyses of the two population-based cohorts of the Wisconsin Sleep Cohort [31] and the Sleep Heart Health Study [32] confirmed the independent association of severe OSA with all-cause and cardiovascular mortality. Finally, in a retrospective analysis on death certificate of patients known to have OSA, the AHI was correlated with risk of sudden cardiac death from cardiac causes from midnight to 6 am [33]. In a more recent study on 10,701 consecutive adults undergoing a diagnostic polysomnogram who were followed-up up to 15 years, OSA predicted incident sudden cardiac death, and the magnitude of risk was predicted by multiple parameters characterizing OSA severity [34].

On the basis of the data discussed above, the American Society of Sleep Medicine established that subjects with BMI > 35, heart failure, atrial fibrillation, treatment refractory arterial hypertension, type 2 diabetes, nocturnal dysrhythmias, stroke should be regarded as patients at high risk for OSA who should be evaluated for OSA symptoms [35].

A detailed analysis of the several plausible biological mechanisms that have been advocated to explain the association between OSA and cardiovascular disease is beyond the scope of the present review. These include sympathetic activation, endothelial dysfunction, oxidative stress, metabolic dysregulation, inflammation and have been largely reviewed elsewhere [36, 37].

Non cardiovascular risks of OSA

OSA is the most common medical disorder that causes excessive daytime sleepiness; a majority of research supports the finding that OSA is a significant risk factor for motor vehicle crashes. In 2009, a review of 18 published studies in the field found that the mean crash-risk was more than doubled (Relative Risk = 2.43, 95% CI 1.21-4.89, p=0.013) in drivers with OSA when compared to comparable individuals without OSA [38]. Several factors were also identified as predictors of crash in drivers with OSA. These factors – all of which serve as surrogate indicators of disease severity – include the AHI, the severity of hypoxemia, the BMI and possibly daytime sleepiness. Total costs attributable to sleep apnea related crashed are estimated to be very high. In the United States, in 2000, there were 800,000 collisions that could be attributed to sleep apnea with 1400 lives lost and $15,9 billion cost [39].

As a consequence of excessive daytime sleepiness, subjects with OSA are similarly at increased risk of occupational injuries [40].

OSA is also associated with significant work disability including complete or partial missed work days, fall asleep on job, decreased job effectiveness also resulting in long-term work-duty modification. In a study comparing work performance of 331 sleep apnea and 100 non-apneic workers, workers with OSA reported more difficulties in memory, vigilance, concentration, performing monotonous tasks, responsiveness, and manual ability than non-apneic [41]. Interestingly, some job functions which might be thought of as more cognitive in nature have been found to be associated with an increased risk of work disability when compared with activities which may be thought of as more physically active in nature [42]. Finally, shift-workers may be at increased risk of falling asleep at work or having a car accident in the presence of OSA [43].

Economic Impact OSA

Because of the previously discussed role of OSA in the pathogenesis of major public health issues, OSA results in significant costs in the community. The associated costs include the direct care-related health costs of the sleep disorders itself and the costs of medical conditions occurring as a result of them.

Untreated patients with OSA consume a disproportionate amount of health care resources. When comparing the direct medical costs of patients with and without sleep apnea during the 10 years prior to the diagnosis of OSA, OSA patients used approximately twice as many health care services (defined by physician claims and overnight hospital stays) as their randomly selected age, gender, and geographically matched controls from the general population [44]. Therapy of OSA appears to reduce healthcare utilization. In a study including 344 OSA patients and a group of matched controls, two years after diagnosis and treatment the yearly difference in physician claims between OSA patients and their matched controls was significantly less than the difference in the year before diagnosis. Examining the subgroups of patients adhering or not adhering to treatment revealed that it was adherence to OSA treatment that resulted in a significant reduction in physician claims and hospital stays [45].

Other financial costs include the non-health costs of work-related injuries, motor vehicle accidents and productivity losses while non-financial costs derive from loss of quality of life and premature death.

Given its high prevalence, the economic costs of OSA have substantial relevance and are comparable to other chronic diseases. An Australian study estimated that the total cost of sleep apnea (including both direct and indirect costs) represents the 0.8% of the Australian gross domestic product assuming that 2.1% of hypertension, 0.5% of ischemic heart disease, 0.7% of stroke, 0.9% of renal disease, and 0.2% of peripheral vascular disease are attributable to OSA [46].

OSA in Cardiac Rehabilitation

So far, there are very few data are available concerning OSA in the context of cardiac rehabilitation.

Sharma *et al* [47] assessed the prevalence of OSA in a series of 118 patients who had been referred to cardiac rehabilitation following CABG, myocardial infarction or angina. The Berlin Questionnaire was used to predict OSA presence. A pre-existing formal diagnosis of OSA was present in 20 patients. Out of the remaining 98, 43 (44%) were found to have a high probability of OSA as predicted by the Berlin Questionnaire. No difference were observed in the male to female ratio, mean age or BMI between OSA and non-OSA patients while a lower frequency of CABG was present in non-OSA patients. The predictive value of a positive Berlin Questionnaire in this population was estimated from the 15 patients who underwent a polysomnography by their treating physicians, of which 13 had a positive study with an AHI > 5 (range from 15 to 73 per hour).

The Berlin Questionnaire has been proposed as a suitable means for the screening of OSA in cardiac rehabilitation settings. Out of 382 patients with coronary disease enrolled in an early outpatient cardiac rehabilitation program, Sert-Kuniyoshi *et al* [48] found that 52% had a high risk for OSA based on the questionnaire. Out of the 74 patients who subsequently completed their evaluation at the sleep clinic, 39 (53%) were found to have OSA with an AHI ≥ 5 events/h.

Hargens *et al* [49] determined whether resting hemodynamic variables were altered in OSA subjects entering an early cardiac rehabilitation program compared to those without OSA. Patients were screened for OSA using an at-home screening device and verified by a sleep physician. Out of 73 subjects participating into the study, 48 (66%) were found to be positive for OSA. Subjects with and without OSA did not differ by age, BMI, heart rate, diastolic blood pressure, or the distance walked at the 6-minute walking test, while cardiac hemodynamics – as determined by impedance cardiography – were significantly decreased in the OSA group compared with the control group. The Authors suggest that the decreased cardiac function in OSA patients entering cardiac rehabilitation, likely because of pressure and volume changes associated with apneic events, may place those individuals at a disadvantage in recovering from their cardiac event, and place them at increased risk for secondary complications.

Further studies are necessary to better define the epidemiology of OSA in the setting of cardiac rehabilitation and to identify the more appropriate identification criteria.

Conclusions

A number of reasons support the need for cardiac rehabilitation to include sleep apnea as an integral component to the comprehensive care of patients with cardiovascular disease.

First sleep apnea is a common comorbidity of cardiovascular disease. Thus, cardiac rehabilitation seems to offer a suitable setting for identification of OSA patients.

Second, sleep apnea increases cardiovascular risk. OSA treatment reduces cardiovascular risk. Optimization of cardiovascular risk reduction is among the goals of secondary prevention programs in the context of cardiac rehabilitation.

Third, a recent meta-analysis suggests that physical training might be effective in reducing sleep apnea severity independently of weight loss [50]. Thus, specific programs might be identified for OSA patients.

Riassunto

L'apnea ostruttiva nel sonno è disturbo del pattern respiratorio (sebbene spesso non riconosciuto né diagnosticato) che si verifica con una elevata prevalenza nel contesto delle patologie cardiovascolari. Molteplici evidenze cliniche dimostrano una associazione significativa fra apnea ostruttiva nel sonno ed aumentato rischio di morbilità cardiovascolare. L'apnea ostruttiva nel sonno determina, inoltre, un maggior rischio di incidenti alla guida di veicoli e di infortuni domestici e lavorativi e pertanto rappresenta un problema di salute pubblica con elevati costi sanitari. Il trattamento dell'apnea ostruttiva migliora la qualità di vita e riduce il rischio cardiovascolare e l'uso di risorse sanitarie. L'apnea ostruttiva nel sonno, configurandosi come un fattore di rischio modificabile, può rappresentare un nuovo ambito di interesse per la cardiologia riabilitativa.

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