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Review

Obstructive sleep apnea and cardiovascular risks in the elderly population

M. Mollica[1], A. Nicolai[1], R. Maffucci[1], M.R. Gioia[1], G. Paoli[1], E. Grella[1], C. Calabrese[1], S. Lavoretano[1], I. Forzano[1], F. Perrotta[2]

[1] Department of Translational Medicine, University of Campania "L. Vanvitelli", Naples, Italy; [2] Department of Medicine and Health Sciences "V. Tiberio", University of Molise, Campobasso, Italy

Sleep disorder breathing (SDB) is a group of diseases common in the elderly population which are strongly associated with development of cardiovascular comorbidities including stroke, heart failure, hypertension and atrial fibrillation. Age-related anatomical and functional changes in upper airways are partially responsible for increasing prevalence of SBD in the elderly. Full-night polysomnogram remains the gold standard in diagnostic workup; symptoms assessment using validated scoring system such as Epworth Sleepiness Scale may underestimate the severity of disease in the elderly population. Therapeutic approach for SDB depends on symptoms and disease severity in addition to the presence of cardiovascular or metabolic disorders. CPAP and NIV treatment in the elderly with associated OSA and cardiovascular disease improves quality of life and may reduce incidence of future cardiovascular events.

Key words: Obstructive Sleep Apnea, Sleep Disorder Breathing, Cardiovascular Risk, CPAP

INTRODUCTION

Sleep disturbances (insomnia, sleep disordered breathing, restless leg syndrome and periodic movement of sleep, REM sleep behavior disorder) are common in older adults [1]. Obstructive Sleep Apnea (OSA) is characterized by frequent episodes of total and/or partial collapse of upper airways (respectively causing apnea and hypopnea) during sleep, for a time longer than ten seconds, in presence of thoracic and abdominal movements. The prevalence of OSA in general population is estimated from 9 to 38% [2 3] and is higher in men than in women. However, the gender gap decreases with age; prevalence of OSA among women shows a sharp increase after the age of 50, catching up with the males [4]. In a large population-based sample, age has been reported to be a central epidemiological factor associated with sleep-disordered breathing [5]. The authors found that moderate-to-severe sleep-disordered breathing increased significantly in participants aged 60 or older compared with younger age group. However, elderly patients are often under-represented in clinical sleep studies and specific knowledge in frail patients is still lacking, even in other respiratory diseases [6-9]. The increased OSA prevalence among older subjects could be primarily related to aging. In murine model, age-related upper airway muscle function impairment has been proved to be a major risk factor for sleep apnea [10]. Likewise, similar results have been reported in humans [11]. Furthermore, in the elderly patients the instable ventilatory control is associated to obstructive and central respiratory events [12]. OSA causes systemic adverse consequences and is associated to different comorbidities arising from different biological pathways including those involved in metabolic dysregulation [13-28].

Several researches have highlighted that OSA is an independent risk factor for cardiovascular and metabolic diseases, involving an increased risk to develop systemic and/or pulmonary hypertension, arrhythmias, heart failure,

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Correspondence: Fabio Perrotta, Department of Medicine and Health Sciences "V. Tiberio", via F. De Sanctis, 86100 Campobasso, Italy - E-mail: fabio.perrotta@unimol.it

coronary heart disease, stroke and diabetes though different molecular pathways not fully elucidated [29–32].
Sunnetciouglu et al. [33] showed that increased oxidative stress and failure in antioxidant mechanisms have been observed in obstructive sleep apnea.
An integrated approach in older patients harbouring these co-morbid respiratory disorders may results in better outcomes when compared to standard therapies [34-39].
This review investigates the principal features of OSA pathogenesis and cardiovascular consequences among older subjects. Thus, we debate the management and therapeutic strategies in this subgroup of patients.

SLEEP DISORDERED BREATHING EPIDEMIOLOGY

A growing body of research have documented that SDB prevalence increases with age. According to the World Health Organization, the number of people aged 65 years or older is projected to grow to nearly 1.5 billion in 2050 and the amount of older people affected by SDB is expected to increase similarly. In view of these considerations, it should not be surprising that untreated SDB in older adults is associated with significant medical costs [40].
SDB is an umbrella term including obstructive sleep apnoea (OSA), primary or secondary Central sleep apnoea (CSA), high-altitude periodic breathing, Cheyne-Stokes respiration and hypoxemia disorders secondary to various pulmonary and chest pathologies. OSA is the most common SDB and it is characterized by a distinctive snoring pattern caused by intermittent airway collapse, resulting in drowsiness, as the most common symptom. The count of apnoea and hypopnea episodes per hour of sleep is known as apnea hypopnea index (AHI).
The prevalence of SDB in people aged 65 years or older has been reported above 20% in various epidemiological studies [40]. In frail elderly patients, prevalence rates reach as high as 60% [41].
In large sleep cohort clinical study [42 43], the prevalence of SDB in older adults has been assessed stratifing the study population into two age categories, younger than 60 years and 60 years or older patients. Moderate-to-severe sleep-disordered breathing increased significantly in older participants compared with those in the younger age group [44].
The known risk factors for SDB in older adults, include male gender, positive family history, smoking, several craniofacial abnormalities, central obesity [45]. Data from Miner et al. [1] reported that the difference in prevalence of SDB between men and women seemed to diminish in participants aged 60 years or older, probably because of the increased proportion of postmenopausal women in this age category. Although women and men with an AHI of 15 or more had a similar BMI, women had a lower neck circumference and waist-to-hip ratio compared with men. This finding confirms that not only central obesity but also hormonal status affects the prevalence of sleep-disordered breathing in women. Many studies aim to determine whether sleep apnea in the elderly constitutes a specific entity. Many studies investigate several mechanisms proposed to account for the higher prevalence of sleep apnea in elderly. They include the increased upper airway resistance during sleep with advancing age and upper airway diameter narrow in older people due to increased pharyngeal wall fat deposit and bony structure changes.
Edwards et al. [46] showed that collapsibility of the pharyngeal airway worsens with aging, whereas the sensitivity of the ventilatory control system. In younger adults, dominant traits likely to contribute to the pathogenesis of OSA may be the reduced upper airway collapse and a higher ventilatory response to the disturbance of ventilation together with greater ventilatory demand. By the contrast OSA in older adult could be considered as a unique phenotype due to a worsening of the upper airway anatomy/collapsibility, mitigated by a reduced ventilatory demand and feedback control sensitivity. Although the age related reduction in ventilatory drive should protect against OSA, any reduction in the predisposition toward OSA is balanced by worsening anatomy with age [46].
SDB, in older populations as in younger ones, is associated with serious outcomes including stroke, occult nocturnal hypertension, open angle glaucoma, falls with fractures, impaired quality of life decreased, pain tolerance frailty and mortality [40].
The combination of sleep and ventilatory instability is likely to account for the high occurrence of central events in the elderly, a situation that is not observed in younger subjects with sleep instability. Untreated SDB in the elderly appears to have a lesser impact on mortality than in middle-aged adults. The milder clinical impact of OSA in older adults could be based on the underlying mechanism of worsening upper airway anatomy and reduction in ventilatory drive, supporting the concept of redefining OSA as a different phenotype in young versus old individuals, not based purely on AHI [46].

SLEEP-DISORDERED BREATHING PATHOPHYSIOLOGY

Several mechanisms have been proposed to clarify the increased prevalence of sleep breathing SDB in older subjects. Firstly, the parapharyngeal fat pads deposition increases significantly in the elderly population rea and regardless the BMI. Thus, the ratio of antero-posterior to lateral length of the bony shape become progressive lower with aging and can be associated

to soft palate length increase. Finally, the genioglossus nerve has been showed to be less responsive to negative pressure [47]. Central events in the elderly are more frequent than middle age population because of increasing sleep fragmentation and ventilatory instability [48]. Several studies have investigated the correlation between sleep breathing disorders and cardiovascular risk, with contrasting results. While in the young middle age population severe untreated OSA is related to higher risk due to cardiovascular mortality, in the elderly this association is not so clear. Punjabi and colleagues [49] in a multicentric prospective community based cohort study – The Sleep Heart Health Study – investigated the cardiovascular effects of SDB in subjects aged 70 or older. They did not observe a significant increase of all cause mortality related to sleep breathing disorders. Conversely, Martinez Garcia and colleagues [50] in their prospective, observational study have found that untreated severe OSA is associated with an higher risk of mortality from stroke and from heart failure, but not from ischemic heart disease compared with patients that did not suffer from OSA. CPAP treatment compliant patients reduced risk of cardiovascular mortality to levels similar to mild-moderate OSA untreated group or non OSA subgroup [51]. The ischemic preconditioning hypothesis suppose that intermittent hypoxia in SDB could trigger collateral neovascularization genesis, giving a sort of protection versus cardiovascular ischemic accidents [52]. SDB are also associated with heart rhythm disorders onset and particularly with Atrial Fibrillation (AF). Tung et al. [53] performed a subgroup analysis in the cohort of patients affected by AF in the population of The Sleep heart Health study in order to assess the linkage between obstructive sleep apnea, central sleep apnea and AF. Mean age of this of this group was 62.8 years at baseline. Results of the study showed that atrial fibrillation was more common in severe obstructive sleep apnea than in mild OSA but no statistical significant association between OSA and incident atrial fibrillation has been demonstrated. Conversely, Central sleep apnea, defined by CAI ≥ 5/h by Cheyne stokes respiration or by a combination of them, was associated with a significant increase in the odds of developing AF. Periodic arousals and intermittent variation in PaCo2 as occurs with CSA, may predispose to arrhythmia by enhancing sympathetic activation, changing the sensitivity of central chemoreceptors to PaCo2 and causing structural and electrical remodeling of the heart [53]. The Wisconsin Sleep cohort study was designed to evaluate the relationship between obstructive sleep apnea during REM sleep and prevalent and incident hypertension, comparing apnea-hypopnea events during non rem sleep and rem sleep and their correlation with blood pressure. Conclusions of the study underlined that only REM-OSA group was associated with a significantly higher prevalence of hypertension [54]. Further prospective studies are needed to evaluate the correlation between REM OSA and hypertension in the elderly population.

DIAGNOSIS AND TREATMENT

Results in the elderly population

OSA is characterized by a distinctive snoring pattern caused by intermittent airway collapse; there are periods of snoring or brief gasping followed by cessation of respiration lasting at least 10 seconds. Patients are not aware of snoring and nighttime arousals, but often they complain excessive daytime sleepiness. These patients present apneas (complete cessation of respiration) and/or hypopneas (30% reduction in airflow associated with 4% oxygen desaturation) both lasting more than 10 seconds and occur several times during the night, leading to frequent arousals and fall in oxygen saturation. Physical examination findings that supports OSA include: neck circumference > 40 cm in males and 37 cm in females, body mass index (BMI) > 25 kg/m^2, low-lying soft palate, elongated uvula, large tongue, or large tonsils or narrow distance between the tonsillar pillars. In elderly, an additional risk factor is an edentulous state, as this leads to a reduction in the vertical dimension that increases the occurrence of upper airway obstructive events [45]. The impact of OSA may be more severe in older people, including increases in the risk of falls and fractures and in overall fragility and mortality. OSA can also affect cognitive function and quality of life [55]. Epworth Sleepiness Scale may be used to document day-time sleepiness and it is significant if the total score of the evaluation items is 11 or higher, but in elderly patients it could underestimate the disorder because of other causes of insomnia (i.e. depression or medications) or nocturia (i.e. prostate adenoma in men or urinary incontinence in women), the under-report of nocturnal symptoms (snoring, choking etc.) in who do not have a bed partner, and the fact they may not drive. Periodic leg movements (PLM) have high prevalence in elderly subjects and may co-exist with SDB contributing to sleep fragmentation and daytime symptoms [51].

The “gold standard” for the diagnosis of SDB is full-night polysomnogram (PSG). The total number of apnea and hypopnea episodes per hour of sleep is known as apnea/hypopnea index (AHI) and is considered significant in presence of 5 or more events per hour of sleep in patients with symptoms or comorbidities, and ≥ 15 events per hour in patients without symptoms or comorbidities. Staging of OSA is the following: mild AHI 6-15, moderate AHI 16-30, and severe AHI > 30.

Management of sleep disorders includes a careful respiratory functional assessment coupled with comorbidities diagnostic evaluation [56-64].

Treatments for SDB depend on the symptoms and disease severity, and the presence of cardiovascular or metabolic disease. In mild-to-moderate SDB, positional measures and oral mandibular advancement splints are used. Oral appliances, prescribed by a qualified dentist, are helpful in improving respiration and sleep quality in patients with mild-to-moderate OSA. The mouthpiece is prepared so that the lower jaw and tongue are pushed forward during sleep. The effectiveness of the use of oral appliances is not specifically studied in older adults mainly because of incidence of their edentulous state. Although there is no full remedy for OSA, in moderate-to-severe OSA (associated with other comorbidities) continuous positive airway pressure devices (CPAP) are considered the most cost-effective treatment and the gold standard treatment. During sleep, these devices remove apnoeas by continuously running air from a mask and applying pressure so the airway obstruction is prevented. Manual CPAP device is usually preferred. Bilevel PAP device is advisable when the patient is not able to tolerate CPAP pressure or when PAP pressure requirement is > 20 cmH_2O. Several meta-analysis showed that CPAP is the most effective treatment for OSA. In patients with severe OSA who cannot tolerate CPAP therapy, behavioral modification and oral appliances may be used.

In elderly patients with severe OSA, CPAP treatment results in an improvement in quality of life, including daytime and night-time symptoms, as choking, nocturia and daytime sleepiness, depression, anxiety and memory [55]. Some reports have shown that severe OSA was a high-risk factor for cardiovascular mortality in elderly patients [65]. Some authors showed good results on improvement in hypertension and heart failure that are considered severe complications related to OSA.

Evidence for the effectiveness of CPAP treatment for the secondary prevention of cardiovascular events (CVEs) in elderly patients are scarce [40 66]. Martinez-Garcia et al. [51] reported that not treated severe OSA in elderly patients was associated with a twofold increase in cardiovascular mortality compared with elderly patients without OSA. Other evidence shows that in elderly patients, severe OSA not treated with CPAP was associated with an increase in cardiovascular mortality due to stroke and heart failure, whereas treatment with CPAP reduced CVEs, including re-hospitalization due to heart failure, acute coronary syndrome, arrhythmia, stroke, and aortic dissection [67]. CPAP treatment seems to inhibit the development of CVD, directly reducing intrathoracic negative pressure and venous return. Moreover, it reduces the intramural pressure, lowers pulmonary capillary wedge pressure, and increases cardiac output in patients with heart failure. Furthermore, CPAP indirectly reduces sympathetic nervous activity, oxidative stress, and inflammation. These effects may contribute to the prevention of coronary plaque rupture, thrombotic formation, arrhythmias, and cardiac dysfunction [67].

SLEEP-DISORDERED BREATHING AND FRAILTY

Current knowledge and perspective

Frailty impacts negatively on long-term outcomes and intrinsically increases mortality risk. Frailty is generally considered as “primary” when it is independent from specific clinical disorders or “secondary” when underlying chronic comorbid conditions are present. In a cross-sectional study including subjects aged 74.2 ± 6.3 years, Galizia et al. showed that both COPD (HR = 1.34; 95% CI = 1.02-1.81; p = 0.042) and frailty score (HR = 1.69 for each unit of increase of frailty; 95% CI = 1.42-2.00; p < 0.001) were predictive of long-term mortality in a 12-years follow-up. Interestingly, influence of frailty on mortality was higher in presence of COPD [68].

Similar results have been reported in chronic cardiovascular and metabolic diseases [62 69 70].

Sleep breathing disorders may influence both prevalence and severity of age-related chronic comorbidities as well frailty of older subjects. Ensrud et al. [71] reported a strong correlation between frailty status and prevalence of sleep disturbances, including poor sleep quality, excessive daytime sleepiness, short sleep duration, nocturnal hypoxemia and sleep fragmentation; however there are several multiparametric indexes to measure frailty and there is not general consensus on standard definition [72]. Future researches in sleep disordered breathing should include the two principal tools to evaluate the frailty, “Fried’s frailty” and “frailty index” to best define phenotype of elderly subject [73].

CONCLUSIONS

Identification of causes of sleep disordered breathing in the elderly is crucial to provide, for clinicians, appropriate treatments.

Management of sleep disordered breathing includes a multidimensional evaluation of cardiovascular and metabolic associated disorders. CPAP and NIV treatment in this age group with OSA and cardiovascular diseases improves quality of life and could be associated with prevention of future cardiovascular events, though further studies in this subgroup are required. Finally, the implementation of adherence to CPAP is an

urgent need and specific strategies should be carefully evaluated in the clinical setting.

Conflict of Interest

The authors declare no conflict of interest.

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