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SLEEP APNEA IN THE GOLDEN AGE (D GOZAL, SECTION EDITOR)

OSA and Ischemic Heart Disease in the Elderly

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Abstract

Purpose of Review Obstructive sleep apnea (OSA) is associated with increased incidence of both cerebrovascular and coronary events and of overall cardiovascular risk. However, it seems that these relationships are less clear in the elderly population. On the other hand, continuous positive airway pressure (CPAP), the treatment of choice for severe and symptomatic OSA patients, seems to be more effective in preventing cerebrovascular than coronary events, also in the elderly. This review describes the existing literature in the field and exposes the different hypotheses that try to explain these phenomena.

Recent Findings There is a growing body of evidence showing that low-grade intermittent hypoxia (a feature that characterized OSA) is associated with increased levels of hypoxia-inducible factor 1 (HIF-1) and vascular endothelial growth factor (VEGF) which in turn lead to neovascularization in the coronary tree (preconditioning hypoxia hypothesis). However, little is known about the effect of intermittent hypoxia in the formation of new vessels in the cerebral vasculature. Moreover, the effect of intermittent hypoxia in both coronary and cerebral vessels could change with age. On the other hand, recent randomized clinical trials have shown that CPAP may not be effective in preventing cardiovascular events in the context of secondary prevention. However, a more detailed analysis of the results and subsequent meta-analyses show that this treatment exerts a protective effect in cerebrovascular disease but not in cardiovascular diseases, especially in elderly patients.

Summary Although OSA is clearly related to an increased cardiovascular risk, this seems less obvious in the elderly and in the coronary vessels. As a consequence, the effect of CPAP in the elderly with coronary disease remains controversial.

Keywords Obstructive sleep apnea · Elderly · Coronary disease · Cardiovascular disease · Cerebrovascular disease · Stroke · Myocardial infarction

Introduction

The population pyramid is changing all over the world. It has been estimated that by 2050, over 25% of the world's population will be aged over 65 years and that life expectancy should reach in excess of 90 years [1]. This situation will require a change in health strategy to ensure that care is provided to a mass of elderly people, especially those with chronic diseases and their associated complications [2].

Obstructive sleep apnea (OSA) is no exception to this rule. Its prevalence increases with age, rising to over 20% in people older than 65 years [3]. However, this age group has been scarcely studied, partly because of the greater difficulties entailed exploring elderly population and also for the following reasons: (a) The cut-off point in the normal number of sleep-related respiratory disorders is not known in the elderly; (b) there are various physiological and age-dependent factors in the elderly that predispose them to increased airway collapsibility; (c) the potential influence of OSA and, more particularly, its two foremost physiological perturbations — i.e., intermittent hypoxemia (IH) and sleep fragmentation (SF) — on the cognitive, cardiovascular, and metabolic spheres is still not completely delineated; (d) the common phenotypic clinical pattern of OSA in the elderly is not known; (e) no clinical scales or diagnostic instruments have been specifically designed and validated for the elderly; and (f) the effect of continuous positive airway pressure (CPAP) treatment on the impact of OSA on the elderly is not known, and even today, its

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use is justified by studies obtained among younger patients, even though the validity of this strategy has not been demonstrated. Generally speaking, these gaps in our knowledge about the role of OSA in relation to the elderly are due to a lack of observational studies and of clinical trials focused exclusively on the elderly population [4, 5•, 6, 7].

Furthermore, the term "elderly" has evolved over time, and whereas a few decades ago it was applied to people aged over 60 years, current studies tend to use it to denote people aged over 70 years, in light of the overall increase in life expectancy. This review examines the findings of those few studies that exclusively focused on elderly patients (defined according to various cut-off points) and particularly focused on the effects of OSA and CPAP on the cardiovascular system and, more specifically, on ischemic heart disease.

Impact of OSA on the Cardiovascular Sphere

One of the aspects of OSA that has been most comprehensively studied in recent years is the impact of OSA (mostly in the context of IH and sleep fragmentation) on the intermediate mechanisms causing cardiovascular diseases, such as sympathetic activity, hypercoagulability, systemic inflammation, endothelial dysfunction, and various metabolic factors [8–14]. As a result, OSA has been associated with the presence of increased atherosclerosis, even in milder forms of the disease [15, 16]. The association between OSA and the cardiovascular system that has probably been the most extensively investigated to date is the direct relationship between a greater number of sleep-related respiratory events and a higher prevalence and lack of control of idiopathic hypertension [17–21]. In fact, it has now been established that the most frequent cause of hypertension, be it resistant or refractory to treatment, is OSA and appears to be readily responsive to CPAP [22]. This finding undoubtedly suggests that the incidence of cardiovascular events as a result of OSA (especially in its untreated severe forms) should rise, as apparently confirmed by various studies (both population based and clinical) [23–26]

Impact of CPAP Treatment on the Cardiovascular Sphere

It is logical to assume that this excess of cardiovascular risk induced by OSA should be reduced (or normalized) by CPAP treatment, especially when it is well tolerated and used for an appropriate number of hours of sleep, as it has been shown to eliminate both IH and SF in these patients. There have been discrepancies, however, between large long-term observational studies that have mainly confirmed this protection afforded by CPAP [23–26] and large clinical trials that have failed to find conclusive evidence of this protection, at least in this type of patient [26–31].

At this time, it will be of importance to point out the various methodological explanations related to the discrepancies in findings between these two types of studies [32, 33]: (a) Obviously, observational studies inevitably suffer from substantial biases. (b) Although the clinical trials to date have been large scale, they have a number of drawbacks, namely, the diagnostic test used was inadequate in most cases, the adherence to CPAP treatment was low and highly heterogeneous, and cardiovascular events that are markedly different (coronary and cerebral) and of radically different severities (a transitory ischemic accident and an established stroke; angina pectoris and fatal acute myocardial infarction) were all lumped together as the primary umbrella outcome. Such an approach presupposes that it is possible and mechanistically justifiable to compare the effects of IH and SF, as well as the effect of CPAP, on the cerebral and coronary circulations as if these were similar and that pooling is therefore a legitimate way of achieving such goal. However, it is highly probable that this is not the case, because, among many other reasons, the two vasculatures are regulated by different physiological mechanisms, and these mechanisms can be affected by a diverse wide range of factors, including age [34]. In fact, upon a closer examination of the results obtained from these cohort studies, it becomes apparent that IH/SF and CPAP could have a more robust effect on cerebral circulation than on the coronary circulation, and therefore, CPAP would provide protection against cerebrovascular events but less likely to manifest such impact in the coronary circulation [30]. Indeed, some authors have even advanced the hypothesis that IH induced by OSA could protect against ischemic heart disease mortality and acute coronary events, as explained in the next section [35, 36•].

Hypoxic Preconditioning: Does OSA Protect Against Acute Coronary Events?

One of the most encouraging findings with respect to the relationship between OSA and cardiovascular disease was provided by Lavie et al. [35, 36•], who suggested that the excess cardiovascular mortality induced by OSA — particularly mortality in the context of coronary heart disease — decreased with age. These authors explained this putative phenomenon by the presence of a pathophysiological mechanism known as "hypoxic preconditioning," whereby the presence of low frequency and milder forms of intermittent hypoxemia triggers a series of pathophysiological pathways governed by two key molecules — hypoxia-inducible factor 1 (HIF-1) and VEGF — that induce coronary neo-vascularization and therefore provide protection against a future coronary event in those elderly patients who have survived long-standing OSA

[37–40]. This hypothesis was subsequently corroborated by various pathophysiological studies and imaging techniques. For example, in an excellent review by Semenza and colleagues, the authors described how exposure of the coronary vascular bed to short periods of ischemia/reperfusion provided protection against the death of myocardial cells during severe ischemic episodes and how this phenomenon seems to be mediated by HIF-1 [41]

This topic is still an area of intense debate; however, due to the scarcity of studies analyzing whether this neovascularization also occurs in cerebral vasculature and whether the presence of OSA can therefore protect the elderly from a stroke, at this stage, this seems not to be the case. In this respect, Wegener et al. [34] concluded that the protection against stroke produced by periods of intermittent hypoxemia depends not on the putative neovascularization but rather is contingent on neuroprotective mechanisms that differ from those occurring in coronary arteries, which could explain the different responses to intermittent hypoxia in coronary and cerebral vascular beds. Moreover, the protective effect of neovascularization could diminish with age [37, 38], but it is not known whether this loss of efficacy occurs in the same way in the coronary and cerebral circulation. All this could explain, at least in part, the different responses with respect to the higher incidence of cerebral and coronary events due to OSA and the different protective effects of CPAP treatment. Initial work in a murine model of sleep apnea in recent years has begun to unravel the "aging paradox" and should ultimately shed light on whether the protection of older age is real for all or only selected vascular beds and target organs [39, 40, 42, 43].

Effect of OSA on the Cardiovascular Sphere in Elderly Versus Young People

Some studies that have exclusively addressed elderly patient populations have observed a relationship between the presence of OSA and a rise in some intermediate cardiovascular risk factors, such as increased inflammation, hypercoagulability, arterial stiffness, and endothelial dysfunction, although it generally seems that this relationship is less intense than that found in younger people [44]. This finding could explain the more limited impact on quality of life [45•] and the reduced incidence of cardiovascular events observed in some studies of elderly people compared to younger ones [46, 47].

This finding therefore raises doubts yet again as to whether the impact of OSA is the same, in cardiovascular terms, at different chronological ages. Li et al. [48] observed that OSA has less impact on cerebrovascular reactivity in elderly individuals than in younger ones, suggesting the existence of age-related cerebrovascular susceptibility to OSA. Similarly, Castro-Grattoni [40] concluded that cardiovascular remodeling induced by severe chronic intermittent hypoxia is affected by the age at which the onset of that hypoxia occurs, suggesting that deleterious cardiovascular effects may be more pronounced in younger populations and that such changes reflect age-related chronological declines in cardiovascular structural integrity.

Observational Studies on the Roles of OSA and CPAP in the Cardiovascular Sphere in the Elderly

Most of the observational studies that have examined the impact of OSA and the effect of CPAP on cardiovascular parameters have not found sufficient statistical power (number of cardiovascular events) to undertake a separate analysis of those parameters related to coronary events. There was one exception however as discussed subsequently.

The largest observational study to date has undoubtedly been the one undertaken by Martinez-Garcia et al. [46] which included 939 individuals aged at least 65 years who referred to a sleep unit due to clinical suspicion of OSA. A very striking finding was that general and adjusted cardiovascular mortality were greater in individuals with severe untreated OSA than in those with treated OSA, mild-to-moderate forms, or no OSA at all; this excess of mortality was the result of an excess of stroke and heart failure rather than of coronary events (the risk was no greater). Similarly, CPAP treatment reduced the risk of stroke and heart failure but not of coronary events (Fig. 1). Using the same cohort, Catalan-Serra et al. [45•] observed that this phenomenon was reproduced in nonfatal cardiovascular events and that the incidence of stroke, but not coronary heart disease, increased in elderly patients with untreated severe OSA compared with those with treated OSA, mild-to-moderate OSA, or no OSA. Furthermore, CPAP treatment normalized the excess risk of stroke without having any effect on the risk of ischemic coronary events.

Other observational studies that were exclusively focused on the elderly found a harmful effect of OSA and a protective effect of CPAP in the elderly, even in those studies that included only very elderly participants (aged more than 80 years) [49, 50]. However, the low number of individuals included in these studies — and, therefore, the low number of cardiovascular events found — precludes any separate analysis of the different types of cardiovascular events (coronary vs cerebrovascular). No study to date has analyzed the impact of OSA or the effect of CPAP on coronary events solely in the elderly. Regarding cerebrovascular events, Muñoz et al. [50] analyzed a series of 394 elderly patients aged between 71 and 100 years, with a mean age of 77.3 years, and found that the presence of severe OSA (AHI > 30 events/h of sleep) was associated with a risk of incident stroke of 2.52 (95% CI: 1.04–6.10) times greater than that of those individuals with no severe OSA (after adjustment for age; gender; smoking and

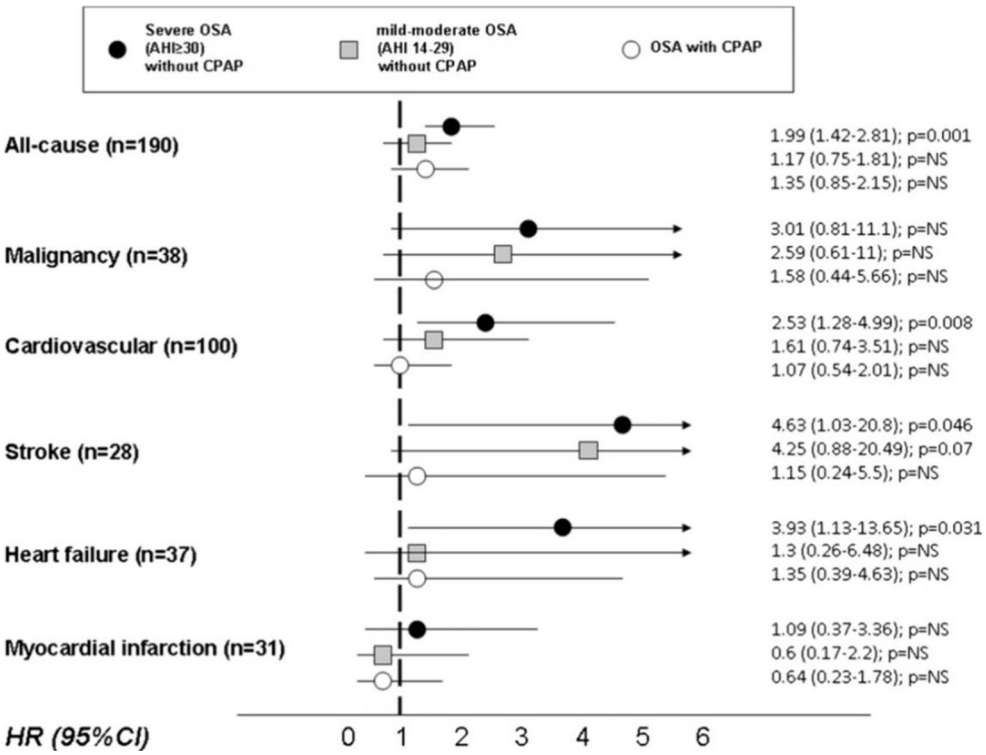

Fig. 1 All-cause and cardiovascular death in a series of 969 elderly with different severities of obstructive sleep apnea with or without CPAP treatment

alcohol consumption status; body mass index; systolic and diastolic blood pressure; total serum cholesterol levels; and the presence or absence of diabetes mellitus, atrial fibrillation, and hypertension).

Clinical Studies on the Role of OSA and CPAP in the Cardiovascular System Among the Elderly

When examining the effect of CPAP treatment exclusively among elderly patients (>65 or >70 years of age), only four clinical studies have been reported in the literature, and none of these used cardiovascular outcomes as the main variable [51–54]. There are no data available on the effects of CPAP on coronary circulation or coronary ischemic events in aged populations. The effect of CPAP on blood pressure at 3 months was evaluated in only two of the clinical trials performed by the Spanish Sleep Group, and no significant changes were found in patients aged over 70 years with moderate or severe OSA. Martinez-Garcia et al. [51••] observed a change in office-based blood pressure levels among 224 patients with severe OSA (AHI > 30) randomized to receive CPAP (n = 115) or no CPAP (n = 109) for 3 months: systolic (−1 vs −0.1 mmHg, p = 0.9) and diastolic (−1.5 vs −12 mmHg, p = 0.2) blood pressure. In another study with a very similar methodological approach, this time confined to patients with moderate OSA (AHI between 15 and 30 events/h), Ponce et al. [50] also failed to find any significant differences in blood pressure readings (0.9 vs −0.2 mmHg, p = 0.9, and −1.3 vs −1.2 mmHg, p = 0.8) for systolic and diastolic blood pressure, respectively) in 145 patients randomized to receive CPAP (n = 73) or no CPAP (n = 72).

The only RCT that has evaluated the effect of CPAP treatment (albeit not as the main variable) on various cardiovascular events or risk factors was undertaken by McMillan et al. [53••], who randomized 278 patients aged over 65 years to receive CPAP (n = 140) or no CPAP (n = 138) and followed them up for 12 months. At 3 months follow-up, CPAP reduced total cholesterol (treatment effect −0·2 mmol/L, 95% CI: −0.3–0.0; p = 0.048) and LDL cholesterol (−0.15 mmol/L, −0.29 to −0.01; p = 0.042), but the effect had not been sustained at 12 months. Systolic blood pressure improved (treatment effect −3.7 mm Hg, 95% CI: 0.2–7.3; p = 0.040) at 12 months, because of a drop in systolic blood pressure in the control group. The incidence of new cardiovascular events did not significantly differ between groups at 3 months (p = 0.48) or at 12 months (p = 0.72).

The Problem of CPAP Adherence in the Elderly

It seems that one of the key factors to assess whether there is a positive effect of CPAP on the cardiovascular system is the a priori documentation of good to excellent adherence to the treatment [55]. Although there is some debate about whether adherence differs in young and elderly people, it is apparent

that the elderly exhibit specific characteristics that are liable to reduce adherence: living on their own and forgetfulness, joint problems, cognitive problems, dental problems (i.e., edentulous or dentures), and so on [56].

A study undertaken exclusively on OSA patients aged over 65 showed that the mean adherence to CPAP treatment fell below acceptable limits, i.e., less than 3 h per day (2.9 +/- 1.7 h), particularly in patients aged 80 years and above. In fact, only 23% of the patients used CPAP for at least a mean of 4 h a night, making it difficult to evaluate any potentially favorable effect of CPAP. Nevertheless, no study to date has examined the influence of poor adherence to CPAP, particularly with respect to coronary circulation in the elderly [57] (Fig. 2).

Conclusions

From the evidence that has been presented, it becomes apparent that very little is known about the impact of OSA and CPAP treatment on the cardiovascular system in elderly patients. Some findings suggest that the impact could be more limited than that found in younger individuals, but there are many confounding variables that still need to be entertained. Moreover, some authors have speculated that intermittent hypoxemia, a key aspect of OSA, could have different effects on the coronary and cerebral circulation directly, and also as a function of age. This discrepancy could explain the variable impact of OSA on the incidence of cerebrovascular and coronary events that have been documented in both young and elderly individuals.

Very few studies have been conducted on this topic (particularly in cohorts that exclusively recruited elderly patients), and none of the studies conducted to date has identified a restricted cardiovascular outcome as its main variable instead of pooling all cardiovascular-related outcomes. In parallel with such scarcity of data, more elderly people are being referred to sleep units with a clinical suspicion of OSA, and the global trends of increased life expectancy mean that this number of referral will undoubtedly rise in the future — thereby only adding to the urgency and the need to undertake the studies that will answer the most pertinent questions raised herein.

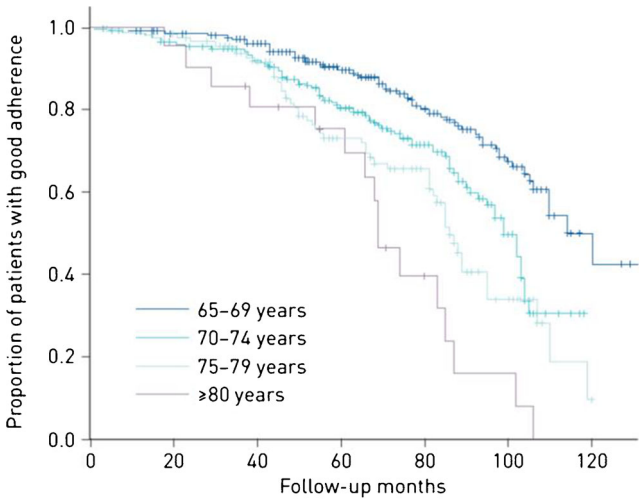

Fig. 2 Kaplan–Meier curves according to the age group for the proportion of patients with a good CPAP adherence (at least 4 h/day)

Declarations

Conflict of Interest None of the authors declare a conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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