ABSTRACT

Evidências crescentes têm demonstrado os importantes efeitos da falta de sono sobre a saúde. A restrição de sono tem se tornado comum na sociedade 24/7 atual. Evidências de estudos epidemiológicos sugerem que a duração de sono reduzida é associada com importantes efeitos sobre a saúde, tais como obesidade, diabetes, infarto do miocárdio e mortalidade. Pesquisas de abordagem mecânica têm sido conduzidas buscando avaliar as vias causais para essas relações. A apnéia obstrutiva do sono é uma doença comum que implica na importantes sequelas cardiovasculares. O colapso repetitivo das vias aéreas superiores, acompanhado por hipoxemia e hipercalemia e somado a disparos catecolaminérgicos e variações na pressão intratorácica contribuem para os efeitos deletérios sobre a função cardíaca. Até o presente momento, os dados não são completamente convincentes sobre a possibilidade de o tratamento da apnéia obstrutiva prevenir eventos cardiovasculares, contudo, estudos de larga escala estão em andamento. Pacientes com insuficiência cardíaca comumente apresentam distúrbios respiratórios do sono, tanto na forma de apnéias obstrutivas quanto centrais. Ensaios randomizados têm sido conduzidos buscando definir a melhor abordagem terapêutica. Por meio das pesquisas atuais, novos alvos e estratégias terapêuticas podem emergir, as quais serão úteis para a maximização da terapêutica. Por meio das pesquisas atuais, novos alvos e estratégias terapêuticas podem emergir, as quais serão úteis para a maximização da terapêutica.

Keywords: apnéia, CPAP, coração, hipoxemia, pulmão, sono.

INTRODUCTION

Sleep disturbances have been recently linked to cardiovascular consequences, with evidence supporting the notion that cardiac disease can disrupt sleep and that sleep disorders can impact the cardiovascular system(1). Data in this area are rapidly evolving since, until recently, many investigators believed that obstructive sleep apnea (OSA) was not really a disease but simply a marker of an unfit lifestyle(2). For example, some attributed the cardiac risk of OSA not to the sleep disorder per se, but to the lifestyle of the older obese sedentary male who was at risk for this condition. Rigorous research has been performed over the past decade which has definitely established a causal link between OSA and certain cardiovascular outcomes (e.g. hypertension(3)) although the data regarding a protective effect of OSA therapy on hard cardiovascular outcomes is still evolving.

SLEEP RESTRICTION

A growing percentage of the population achieves less than the recommended 8 hours of sleep in a 24 hour period(4). Such individuals are at risk of impaired neurocognitive performance(5), but newer data also show important cardiometabolic effects of sleep curtailment. From the Nurses’ Health Study(NHS), women who reported only 5 hours of sleep per night had a 70% increase in relative risk of incident myocardial infarction as compared to women who slept adequately(6). Although the mechanism for this association is unclear, the data are potentially concerning. Spiegel et al. have shown impairments in glucose metabolism by inducing sleep deprivation in normal individuals, suggesting that adequate sleep duration may be needed to optimize metabolic function(7). Similarly, appetite related hormones such as leptin and ghrelin are impacted by inadequate sleep, such that sleep deprived individuals have major hormonal changes which would be predicted to stimulate hunger and appetite(8). From the NHS, individuals with inadequate sleep weighed more at baseline than women reporting adequate sleep(9). In addition, short sleepers gained more weight over time as compared to
women reporting the recommended 7-8 hours of sleep. Thus, evolving data suggest important cardiometabolic effects of sleep restriction\textsuperscript{106}; these data are concerning in our modern 24/7 society\textsuperscript{111,112}.

SLEEP APNEA

Sleep apnea is defined by cessations or reductions in airflow during sleep\textsuperscript{101}. Obstructive sleep apnea describes airflow attenuation with ongoing respiratory effort whereas central sleep apnea defines reduced airflow without respiratory effort. OSA is by far the more common disease, although central sleep apnea (CSA) is quite common in patients with congestive heart failure\textsuperscript{14}. Both diseases are associated with intermittent hypoxemia followed by reoxygenation leading to oxidative stress and recurrent arousals from sleep leading to catecholamine surges.

OSA

OSA is common, particularly among people with obesity, male gender, post-menopausal women, and daytime sleepiness. People with OSA are at risk of hypertension, above and beyond the common risk factors shared by the two diseases. The causal level of proof between OSA and hypertension has been established based on rigorous animal models, cross sectional epidemiological studies, longitudinal cohort studies and human interventional trials. First, Brooks et al.\textsuperscript{16} induced sleep apnea in normal dogs to assess its impact on systemic blood pressure as assessed by a femoral arterial line. The dogs did experience a rise in both nocturnal and daytime blood pressure with OSA which resolved upon elimination of the breathing abnormality. These data provide fairly conclusive proof that OSA causes systemic hypertension in the dog and is not simply a marker of some epidemiological risk factor. Secondly, OSA has been linked to hypertension in both cross sectional and longitudinal epidemiological studies. For example, Peppard et al.\textsuperscript{13} reported a three fold increased incidence of hypertension in moderate OSA as compared to matched controls without OSA over the course of 4 years. These data, as well as other reports, suggest a link between OSA and hypertension in humans. Third, interventional studies have been performed which show an improvement in blood pressure with sleep apnea therapy\textsuperscript{16,17}. Both oral appliances and nasal CPAP therapy lead to reductions in blood pressure\textsuperscript{17}, although the magnitude of this benefit is quite variable across different studies. Comparative effectiveness studies have shown more marked improvement in blood pressure with pharmacological interventions as compared to nasal CPAP\textsuperscript{18}, emphasizing the need for benefits to CPAP above and beyond blood pressure improvement. Patients with refractory hypertension\textsuperscript{19,20}, may have a greater benefit from standpoint of blood pressure reduction as compared to other hypertension populations, although the data in this area are still evolving. In aggregate, the data support some effect of OSA therapy on systemic blood pressure, although the magnitude of the effect is relatively modest.

STROKE, MYOCARDIAL INFARCTION, DEATH

The benefits of treating OSA from standpoint of hard cardiovascular outcomes remain to be defined. Using a prospective observational cohort study, Marin et al.\textsuperscript{23} observed an improvement in risk of fatal and non-fatal cardiovascular events in patients treated for OSA as compared to patients with severe untreated sleep apnea. However, given that this was not a randomized trial, the possibility exists that CPAP may be a marker a ‘healthy user’ rather than working through pressuring the airway alone\textsuperscript{22}. For example, patients adherent with CPAP may also be more adherent with diet, exercise and medications, making any definitely conclusions from the Marin study difficult to draw.

Other epidemiological studies have been performed which have shown some association between OSA and hard cardiovascular outcomes, although again definitive data are lacking. For example, the Sleep Heart Health Study showed some risk of stroke and death in patients with OSA as compared to controls without OSA\textsuperscript{24-26}. However, multiple comparisons were performed in this study based on numerous different outcome measures, interim analyses and non-pre-specified subgroup analyses\textsuperscript{27}. As such, corroborative data are needed to draw rigorous conclusions regarding the magnitude of OSA effects and the attributable risk of OSA in various subgroups.

Regarding interventional studies, randomized trials have been difficult to achieve for both logistical as well as ethical reasons\textsuperscript{28}. Such studies would require a relatively large sample size with patients followed for a prolonged period of time in order to observe any impact of OSA therapy on hard cardiovascular outcomes. Such studies are expensive given the costs of polysomnography, CPAP equipment and intensive follow-up. In addition, both patients and clinicians are reluctant to randomize patients to the possibility of now active therapy given that symptomatic improvements (including improvement in motor vehicle accident risk) is likely to occur with active treatment\textsuperscript{29}. Thus, the design of a study which requires symptomatic patients to remain untreated for prolonged periods has been questioned. On the other hand, the enrollment of asymptomatic patients may be problematic since such patients may have modest adherence to therapy\textsuperscript{30}. In addition, some data suggest that asymptomatic patients may be relatively protected from sleep apnea effects, emphasizing the need for assessment of clinical cohorts\textsuperscript{30}.

Potential solutions to this problem exist including further research into novel therapies for OSA such that adherence is no longer a major impediment to the completion of these trials. Comparative effectiveness studies are also possible in which two active treatments are compared e.g. nasal CPAP therapy vs. oral appliance therapy. In such studies no patient group is left untreated, improving any ethical dilemma with placebo or sham-controlled studies. Such studies also have an advantage over sham-controlled studies, since accumulating data suggest that sham devices are poorly tolerated and that adherence with such devices
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is relatively poor. As such, sham devices are ineffective at maintaining blinding since both clinicians and patients may be aware of their treatment assignment. Another strategy is to define robust surrogate outcome measures, such that shorter term studies can be performed which allow the assessment of the impact of apnea therapy without the need for prolonged follow-up to demonstrate improvements in hard cardiovascular outcomes(39). Although the ideal biomarker for OSA studies has yet to be defined, several candidates exist which are currently being evaluated by various investigators.

OSA AND DIABETES MELLITUS

Obstructive sleep apnea and type 2 DM often co-exist for a number of possible reasons(32,33). First, both diseases are associated with obesity and as such the association between OSA and DM may be via common risk factors. Second, OSA may lead to hyperglycemia by a counter-regulatory hormonal response to apnea, such that glycemic control may be made worse by concomitant OSA. Third, DM may increase the risk of OSA via mechanisms such as neuromyopathy(34). That is diabetes is known to affect neuromuscular function, thus the possibility exists that DM could impair upper airway reflexes which protect pharyngeal patency. Fourth, OSA may worsen vascular complications in DM(35-38). Considerable data have shown that macrovascular risk in DM is not reduced by further improvements in glycemic control, blood pressure management and lipid control. Thus, new therapeutic targets in DM are clearly required. Given that a recent report suggested that clinically important OSA was present in 86% of obese type II DM patients(32,33), OSA may represent a major opportunity in the management of type II DM. Indeed, some data suggest that OSA yields abnormalities in endothelial function whereas DM affects the vascular smooth muscle and the microcirculation. Thus, there is reason to believe that OSA and DM may work synergistically to raise vascular risk in afflicted individuals. As a point of emphasis, one recent study showed that one year after both the patient and their physicians were given the OSA diagnosis, fewer than 5% of these patients were actually receiving therapy(32,33). These data emphasize the need for raised awareness and appreciation for OSA and its treatment.

CENTRAL SLEEP APNEA

Central sleep apnea is a relatively uncommon problem, apart from in the setting of congestive heart failure(39). In most clinical sleep laboratories, central sleep apnea represents less than 10% of the disease burden. However, in the setting of congestive heart failure, roughly one third of afflicted individuals have OSA, one third have CSA, and one third are normal(14). Cheyne Stokes Respiration (CSR) is the form of central sleep apnea typically observed in patients with congestive heart failure and left ventricular systolic dysfunction(40). CSR is defined by a waxing and waning pattern of breathing classically referred to as crescendo-decrescendo with periods of airflow cessation with an absence of respiratory effort. Arousals typically occur during the hyperpnic phase leading to paroxysmal nocturnal dyspnea in some patients. Intermittent desaturations frequently occur but are delayed in time due to circulatory delays in heart failure patients. Catecholamine surges also occur such that a burst of tachycardia is frequently observed in the electrocardiogram. This breathing pattern in CHF has been controversial since some studies suggest important risk to this breathing pattern per se whereas other studies suggest no major risk(41). As such, interventional studies will likely be required to draw definitive conclusions.

The CANPAP study was published in NEJM 2005 showing no benefit to treatment of CSR with nasal CPAP therapy(42). The study had reasonably compelling preliminary data based on multiple publications showing improvements in cardiac function, catecholamine levels and possibly transplant free survival(43-45). However, the CANPAP trial showed no change in transplant free survival with nasal CPAP therapy as compared to standard medical therapy. The reasons for these observations are unclear, but may reflect heterogeneity among the treatment responses to PAP therapy as well as residual disease which persisted despite CPAP therapy. The hemodynamic response to positive airway pressure therapy is complex(46), given that reductions in preload and afterload can have varying effects depending on the underlying cardiac function and volume status(47). In patients who are hypovolemic, positive airway pressure can reduce cardiac output through reductions in preload. In contrast, patients with impaired ventricular function can experience improvements in cardiac output with positive airway pressure through reductions in cardiac afterload. Based on Laplace’s law, ventricular wall tension (or wall stress, afterload) is a function of the transmural pressure (inside minus outside) and the radius of curvature of the ventricle. Positive airway pressure reduces the transmural pressure (by raising extra-cardiac pressure) and reduces the radius of curvature, by lowering preload, both of which can effectively reduce ventricular afterload. In essence positive airway pressure can ‘squeeze’ the ventricle allowing greater cardiac output in patients who are afterload dependent. Thus, in theory, hypovolemic patients may have had deleterious effects of PAP in the CANPAP studies, whereas hypervolemic patients may well have benefited(48). In addition, patients in the CANPAP study showed considerable residual disease, such that the treatment group still had an apnea hypopnea index of about 20/hr. In post-hoc analyses, Arzt et al.(49) showed that some patients had resolution of apnea whereas other patients had persistence of disease. Of interest, patients with resolution of apnea had an excellent outcome whereas patients with persistent disease had a relatively poor outcome. This observation has two potential interpretations based on the post-hoc design. On one hand, strategies which eliminate apnea may provide an excellent outcome. Such hypotheses are now being tested via industry funding to assess whether newer devices which can eliminate apnea would lead to outcome benefit.
as compared to standard medical therapy. On the other hand, the resolution of apnea may be a good prognostic sign perhaps due to patient adherence to medications, diet, exercise etc. As such, randomized trials will be required to draw definitive conclusions about whether apnea elimination is beneficial to CHF patients.

REFERENCES


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