Cardiovascular outcomes of CPAP therapy in obstructive sleep apnea syndrome

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CONSIDERABLE EVIDENCE IS NOW available of an independent association between obstructive sleep apnea syndrome (OSAS) and cardiovascular disease. However, this population of patients also has a high incidence of other coexisting cardiovascular risk factors such as obesity, hyperlipidemia, increased age, male sex, smoking history, and excessive alcohol intake, which makes the identification of a clear independent association of OSAS with cardiovascular disease more difficult (30). The independent association of OSAS with cardiovascular disease is particularly strong for systemic hypertension, and large population-based studies such as the Sleep Heart Health Study and the Wisconsin Sleep Cohort study have provided clear evidence of an association, independent of possible confounding factors such as age, sex, or obesity (43, 49, 59, 66). The prevalence of OSAS is particularly high in patients with drug-resistant hypertension, and one report found occult OSAS in up to 83% of patients who had uncontrolled hypertension despite taking three or more antihypertensive agents at optimal doses (34). Because effective treatment of patients with OSAS with continuous positive airway pressure (CPAP) can decrease blood pressure, this may be especially efficacious in patients with drug-resistant hypertension.

Data linking OSAS to other cardiovascular diseases are not as clear cut but are nonetheless persuasive. Indeed, in the Sleep Heart Health Study cohort, OSAS emerged as an independent risk factor for coronary artery disease (CAD), congestive cardiac failure, and cerebrovascular disease (59), and a recent report concerning this cohort has also demonstrated an independent association with cardiac arrhythmias, including atrial fibrillation and complex ventricular arrhythmias (39). Furthermore, long-term outcome studies of patients with CAD have demonstrated higher death rates from cardiovascular disease in patients with coexisting OSAS compared with those without, even after controlling for important confounding risk factors such as age, weight, and smoking (47).

The independent association of OSAS with cardiovascular morbidity and mortality has naturally led to the evaluation of specific therapy for OSAS in these cardiovascular outcomes. Although there are a number of therapeutic interventions that can benefit OSAS, including weight reduction, mandibular advancement devices, and occasionally surgery (32, 54), the most effective therapy is CPAP, which is usually delivered via a tight-fitting nasal mask (21, 61). The great majority of reports that have evaluated cardiovascular outcomes of therapy in OSAS have particularly addressed CPAP therapy, which thus will be the specific focus of this review.

CPAP FOR OSAS

Obstructive sleep apnea is fundamentally based on recurring obstruction of the upper airway during sleep and reflects an imbalance of the negative intrapharyngeal pressure associated with inspiration and the counteracting forces of the upper airway dilating muscles (9). During sleep, the physiological reduction in tonic and phasic contraction of these muscles is diminished, which predisposes to closure. In OSAS, the upper
airway is narrowed, which increases the collapsing forces and predisposes to obstruction. Indeed, the contracting forces of the upper airway dilating muscles while awake are increased in an effort to counteract these collapsing forces, but the reduction during sleep in OSAS is magnified (40).

The current management of moderate-to-severe OSAS is largely dependent on nasal CPAP, which acts to splint the upper airway open during sleep and thus counteracts the negative suction pressure during inspiration (9). Nasal CPAP completely controls the condition and has a dramatic effect on the patient’s awake performance because of the normalized sleep pattern (29). Because OSAS patients may experience several hundred episodes of apnea or hypopnea during one night’s sleep, each of which is typically associated with a microarousal at termination (9), the normalized breathing patterns and consequent greatly improved sleep quality results in major improvements in a broad array of daytime measures of quality of life and neurocognitive function (14, 19, 29), in addition to driving performance (17). The latter aspect has important medicolegal and public safety implications, because CPAP therapy has been associated with a significant reduction in the rate of road traffic accidents (18, 31). Although nasal CPAP is highly effective in controlling OSAS, the device is cumbersome and compliance data show only moderately satisfactory results (35, 37, 60, 62). Compliance relates positively to the severity of OSAS, the level of daytime sleepiness, and duration of use.

CPAP therapy has significant benefits in reducing cardiovascular morbidity and mortality, both in short-term studies addressing specific aspects of morbidity such as hypertension and long-term studies that have evaluated major outcomes of cardiovascular morbidity and mortality. The purpose of this review is to evaluate the effects of CPAP on cardiovascular morbidity and mortality associated with OSAS and the basic mechanisms involved in the pathophysiology of cardiovascular disease in these patients. We will not address the potential role of CPAP in the management of congestive heart failure, which is a separate topic and is still under considerable debate.

IMPACT OF CPAP ON SPECIFIC CARDIOVASCULAR DISORDERS

Hypertension. Several reports have demonstrated a clinically significant reduction in blood pressure with CPAP therapy in OSAS patients. In particular, several studies have utilized a placebo-controlled design that have compared sham (ineffective) CPAP therapy with therapeutic CPAP. An early report by Dimsdale and co-workers (10) demonstrated a significant fall in blood pressure levels during sleep in a group of OSAS patients compared with sham CPAP. Blood pressure levels also fell with sham therapy, which demonstrates the importance of a placebo-controlled design in studies of CPAP efficacy. Faccenda and co-authors (15) reported a significant fall in blood pressure levels among normotensive OSAS patients when therapeutic CPAP was compared with a tablet placebo, and the reduction was most pronounced in patients with severe OSAS. Pepperell and co-authors (50) also found a greater fall in blood pressure levels among severe OSAS patients in a study where therapeutic CPAP was compared with sham CPAP. The study of Becker and co-workers (4) focused particularly on severe OSAS patients and found a reduction in mean arterial pressure in the region of 10 mmHg with therapeutic CPAP, whereas there was no change with sham CPAP. On the other hand, the recent report of Robinson and co-authors (53) found no significant reduction in blood pressure levels with CPAP therapy in a group of patients with moderately severe OSAS who were not sleepy. A recent meta-analysis of the impact of CPAP therapy on blood pressure levels in OSAS has confirmed an overall significant clinical benefit (3).

CAD. The association of OSAS with ischemic heart disease has been suggested for many years, initially from a case series of patients with OSAS who demonstrated nocturnal myocardial ischemia. The early report of Liston and co-authors (33) implicated sleep-related hypoxemia as an important mediator. The subsequent report of Franklin and co-authors (16) demonstrated the simultaneous association of nocturnal ST-segment changes with obstructive apnea among OSAS patients with co-existing ischemic heart disease. Furthermore, Peled and co-workers (48) demonstrated a reduction in sleep-related myocardial ischemia with CPAP therapy in a group of OSAS patients who had coexisting ischemic heart disease. However, the most convincing evidence of beneficial effects of CPAP therapy on the progression and outcomes of CAD in OSAS comes from long-term outcome studies (see LONG-TERM OUTCOME STUDIES OF CARdiovascular Morbidity and MORTALITY).

Cardiac arrhythmias. Early studies of a possible association of OSAS with cardiac arrhythmias produced differing results, but the recent report from the Sleep Heart Health Study (39) provides convincing evidence of an independent association between OSAS and nocturnal cardiac arrhythmias, including atrial fibrillation and complex ventricular arrhythmias. CPAP therapy has been reported to result in resolution of pathological cardiac dysrhythmias (22), and another report found a higher rate of recurrence of atrial fibrillation in OSAS patients who did not accept CPAP therapy compared with OSAS patients who were effectively treated (27).

Stroke. Although there is considerable evidence of a higher-than-expected incidence of OSAS in patients suffering a cerebrovascular event, the evidence for an independent causative effect of OSAS in the pathogenesis of stroke is less persuasive. In particular, there is uncertainty about the potential cause-or-effect relationship between the two disorders, because it is recognized that stroke can be complicated by either central or obstructive sleep apnea (38). However, recent reports have added support to OSAS as an independent risk factor for the future development of stroke. OSAS patients have been reported to be twice as likely to suffer a stroke compared with non-OSAS subjects over a 3.5-yr follow up after adjustment for confounders (64). Further supportive evidence is provided by large population-based studies such as the Sleep Heart Health Study (59) and most recently the Wisconsin cohort study (1). The report of Minoguchi and co-workers (41) demonstrating evidence of silent brain infarction and platelet activation in patients with OSAS provides further support of a causative association.

CPAP therapy is generally poorly tolerated in the setting of stroke, and various reports have indicated low but variable levels of compliance (6, 25). Broadley and co-workers (6) found that CPAP was generally tolerated among patients with an acute stroke who had evidence of OSAS on objective testing. However, Hsu and co-workers (25) found a poor tolerance of CPAP in patients with acute stroke and coexisting
obstructive sleep apnea in a randomized controlled study. Overall, tolerance of CPAP appears to be best in subjects where there is evidence of OSAS preceding the stroke. Nonetheless, the finding that measures of platelet activation are diminished by effective CPAP therapy supports a potential benefit of CPAP to cerebrovascular disease in OSAS (41). Thus the association of stroke and OSAS remains a topical subject, and the potential benefit of CPAP therapy, particularly in the acute setting, requires further investigation.

### Basic mechanisms of CPAP benefit to cardiovascular pathophysiology in obstructive sleep apneas

There has been considerable research interest in recent years concerning the basic cell and molecular mechanisms of cardiovascular disease in OSAS. In conjunction with this basic research, several groups have evaluated the impact of CPAP therapy on these basic mechanisms. Although a detailed review of this research is beyond the scope of the present work, a broad outline is appropriate. The basic mechanisms of cardiovascular disease in OSAS are likely to involve a multifactorial process including sympathetic nervous system overactivity, selective activation of inflammatory pathways, endothelial dysfunction, and metabolic dysregulation, the latter particularly involving insulin resistance and disordered lipid metabolism (38). Although many studies have reported specific aspects of these basic mechanisms, there is a dearth of studies that integrate basic mechanisms in the overall cardiovascular morbidity of OSAS. However, the recent report of Drager and co-authors (12) demonstrating beneficial effects of CPAP on early signs of atherosclerosis in OSAS emphasizes the clinical importance of this topic.

### Sympathetic nervous system overactivity

The repetitive episodes of upper airway obstruction that are characteristic of OSAS result in intermittent hypoxia and large swings in intrathoracic pressure that trigger autonomic responses, and sympathetic overactivity has been reported in patients with OSAS, which is diminished by effective therapy (24, 67). Furthermore, treatment with nasal CPAP results in significant lowering of muscle sympathetic nerve activity (30). OSAS patients are characterized by a reduced baroreflex sensitivity during both wakefulness and sleep, which can be reversed by CPAP (4). Further support for the role of sympathetic overactivity in the pathogenesis of hypertension in OSAS comes from animal models. An increase in blood pressure was found in a dog model of OSAS and declined once the airway occlusion was abolished (7).

### Inflammation

Inflammation is known to play an important role in the development of atherosclerosis. Various markers of inflammation are recognized cardiovascular risk factors such as the proinflammatory cytokines TNF-α and IL-6, chemokines such as IL-8, adhesion molecules such as soluble ICAM-1, and the acute-phase factor C-reactive protein (20, 56, 63). A number of previous reports have selectively examined the expression of inflammatory factors in OSAS patients, including IL-6, IL-8, and ICAM-1 (45, 65). We and others (13, 55, 56) have demonstrated elevated circulating TNF-α in OSAS patients compared with controls, independent of obesity, and a significant fall with effective CPAP therapy.

### Endothelial dysfunction

A role for endothelial dysfunction in the pathogenesis of cardiovascular complications in OSAS has been supported by studies demonstrating impairment in endothelium-dependent vasodilatation (26, 28, 44), and treatment with nasal CPAP has been reported to reverse endothelial dysfunction (44). A major vasodilator substance released by the endothelium is nitric oxide (NO), and decreased production or activity of NO may be an early sign of atherosclerosis. Decreased levels of NO have been found in OSAS patients, and levels increase with CPAP therapy (58).

### Metabolic dysregulation

There have been many studies that have reported an independent association of OSAS with several components of the metabolic syndrome, particularly insulin resistance and abnormal lipid metabolism (8). Both the Sleep Heart Health Study and the Wisconsin Cohort Study have recently identified OSAS as an independent risk factor for insulin resistance, after adjustment for potential confounding variables such as age, sex, and body mass index (51, 52). Furthermore, effective CPAP therapy has been associated with improved insulin sensitivity in OSAS (23). There is evidence of an independent association between OSAS and abnormalities in lipid metabolism. Leptin is an adipocyte-derived hormone that regulates body weight through control of appetite and energy expenditure and has been implicated as an independent cardiovascular risk factor. OSAS has been associated with hyperleptinemia (2), and effective treatment with CPAP has been reported to be associated with a decrease in leptin levels (57). However, obesity and visceral fat distribution represent important confounding variables.

### Long-term outcome studies of cardiovascular morbidity and mortality

There have been several long-term outcome studies in OSAS during recent years that have specifically focused on the impact of CPAP on cardiovascular morbidity and mortality. Peker et al. (46) reported an increased incidence of cardiovascular disease among incompletely treated OSAS patients compared with those efficiently treated over a 7-yr follow-up period in a group of patients that were free of cardiovascular disease at baseline. Two recent studies have assessed cardiovascular prognosis in OSAS over 10 yr after diagnosis. In both studies, patients were free to accept or refuse CPAP treatment. The study by Marin and co-workers (36) showed that long-term cardiovascular morbidity and mortality increased only in patients with untreated severe OSAS, whereas simple snorers, OSAS patients with mild disease, or patients with severe OSAS who accepted CPAP treatment showed morbidity and mortality figures very similar to those obtained in the general population. The study by Doherty and co-workers (11), instead, suggested that untreated OSAS may increase the severity rather than the prevalence of cardiovascular disease. Indeed, incidence of hypertension, ischemic heart disease, and other cardiovascular disorders during follow up was not significantly different between treated and untreated patients irrespective of acceptance or refusal of CPAP treatment. However, only untreated patients showed excess cardiovascular mortality during follow up.

### Summary

There is now convincing evidence of a high incidence of morbidity and mortality from cardiovascular diseases in patients with OSAS, and recent long-term outcome studies have demonstrated that this high incidence can be alleviated by...
CPAP therapy. The prevalence of cardiovascular disease is sufficiently high in OSAS and the disorder is so common that the possibility of OSAS should be considered in any patient presenting with cardiovascular disorders such as hypertension, particularly because therapy is likely to be influenced by the coexistence of OSAS.

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REFERENCES
Invited Review

OUTCOMES OF CPAP THERAPY


