

# Obstructive Sleep Apnea

## Implications for Cardiac and Vascular Disease

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**A** LONG WITH THE EPIDEMIC OF obesity, there is a growing awareness of sleep-disordered breathing as a potential and treatable risk factor for cardiovascular disease.<sup>1-4</sup> The repetitive nocturnal hypoxemia experienced by patients with obstructive sleep apnea (OSA) is associated with activation of a number of neural, humoral, thrombotic, metabolic, and inflammatory disease mechanisms, all of which have also been implicated in the pathophysiology of cardiac and vascular disease. Activation of these mechanisms is often evident even in patients with OSA who are free of overt cardiovascular disease, suggesting that OSA may conceivably contribute to the initiation and progression of cardiovascular disease (FIGURE 1).

Sleep apnea can be categorized as OSA, in which there is preserved and increased respiratory effort despite partial or complete occlusion of the upper airway; or as central sleep apnea (CSA), in which there is absence of both respiratory efforts and airflow. The apnea-hypopnea index (ie, the number of apneic and hypopneic events per hour) is used as one index of the presence and severity of sleep apnea.<sup>5</sup> For OSA, an apnea-hypopnea index of 5 to 15 indicates mild apnea; of 15 to 30, moderate apnea; and of greater than 30, severe apnea. Approximately 1 in 5 adults has at

**Context** Obstructive sleep apnea (OSA) has been increasingly implicated in the initiation and progression of cardiovascular diseases.

**Objective** To systematically review the interactions of OSA with cardiovascular pathophysiology and diseases.

**Data Sources and Study Selection** The MEDLINE database from January 1966 to March 2003 was searched using the Medical Subject Headings *sleep, sleep apnea, obesity, hypertension, heart failure, cardiac arrhythmia, coronary artery disease, stroke, sympathetic activity, endothelium, inflammation, and continuous positive airway pressure (CPAP)* to identify peer-reviewed studies of OSA. Priority was given to large prospective cohort studies and to randomized controlled trials.

**Data Extraction** We identified 154 original investigations and reviews of sleep-related breathing disorders. Data from these studies were examined for relevance and extracted by one of the authors.

**Data Synthesis** Approximately 1 in 5 adults has at least mild OSA (apnea-hypopnea index [ie, the number of apneic and hypopneic events per hour], 5-15), and 1 in 15 adults has at least moderate OSA (apnea-hypopnea index, 15-30). Repetitive apneic events disrupt the normal physiologic interactions between sleep and the cardiovascular system. Such sleep fragmentation, as well as abnormalities evident in patients with OSA (eg, increased sympathetic activation, vascular endothelial dysfunction, increased oxidative stress, inflammation, increased platelet aggregability, metabolic dysregulation), may be implicated in the initiation and progression of cardiac and vascular disease. Persuasive data implicate OSA in the development of hypertension, and OSA also may contribute to cardiac ischemia, congestive heart failure, cardiac arrhythmias, and perhaps also to cerebrovascular disease and stroke.

**Conclusions** Obstructive sleep apnea is common, readily diagnosed, and usually treatable. It frequently coexists undiagnosed in patients with cardiovascular disease, activates disease mechanisms known to elicit cardiac and vascular damage, and may be implicated in progression of cardiovascular disease and resistance to conventional therapeutic strategies. In the absence of definitive evidence from large-scale trials and a better understanding of potential cost-effectiveness, the likely benefits of diagnosis and treatment of OSA are presently best appraised on an individualized patient basis.

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least mild OSA (apnea-hypopnea index, 5-15), and 1 in 15 adults has at least moderate OSA (apnea-hypopnea index, 15-30).<sup>6</sup> Other measures of the severity of sleep apnea include the sever-

ity of oxygen desaturation and the level of daytime sleepiness.

Obstructive sleep apnea is commonly associated with obesity and also is often present in patients with

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established cardiac and vascular disease,<sup>2</sup> including hypertension,<sup>4</sup> heart failure,<sup>2</sup> arrhythmia,<sup>7</sup> and stroke.<sup>3</sup> By contrast, CSA is most evident in patients with heart failure.<sup>8,9</sup> This overview will focus predominantly on OSA and its interactions with cardiovascular disease conditions. However, brief reference will be made to CSA in the context of heart failure, since CSA may have an impact on prognosis and treatment.

**METHODS**

The MEDLINE database from January 1966 to March 2003 was searched using the index terms *sleep, sleep apnea, obesity, hypertension, heart failure, cardiac arrhythmia, coronary artery disease, stroke, sympathetic activity, endothelium, inflammation, and continuous positive airway pressure (CPAP)*. Additional data were assimilated from bibliographies of identified articles. We selected 154 original investigations and reviews of the epidemiology, pathophysiology, and clinical investigations of sleep-related breathing disorders. Data published in peer-reviewed literature were included and priority was given to large prospective cohort studies and to randomized controlled trials. The evidence was considered strongest when results from different types of studies were consistent. Data were examined for relevance and extracted by one of the authors (A.S.M.S.).

**ACUTE CARDIOVASCULAR EFFECTS OF OSA**

**Normal Sleep**

In healthy persons, physiologic sleep is associated with distinct sleep stage-related changes in cardiovascular regulation. Sympathetic nervous traffic to muscle, as well as heart rate, blood pressure, stroke volume, cardiac output, and systemic vascular resistance, all decrease progressively during deeper stages of non-rapid eye movement sleep.<sup>10</sup> However, rapid eye movement sleep (when dreams are most likely to occur) is accompanied by striking increases in sympathetic drive. Blood pressure and heart rate are very

labile during rapid eye movement sleep, and on average are similar to levels recorded during relaxed wakefulness.<sup>10</sup>

**Hypoxia, Hypercapnia, and Apnea**

Repetitive apneic events disrupt the normal physiologic interactions between sleep and the cardiovascular system.<sup>11,12</sup> The acute hemodynamic consequences of obstructive apnea include sympathetic-mediated vasoconstriction and consequent increases in systemic and pulmonary pressure, increased left ventricular (LV) afterload, and breathing-related changes in cardiac output. Several factors contribute to the neural and circulatory responses to OSA. These include hypoxemia and retention of CO<sub>2</sub> (both of which activate the chemoreflexes), as well as abrupt changes in intrathoracic pressure and arousal from sleep (Figure 1).

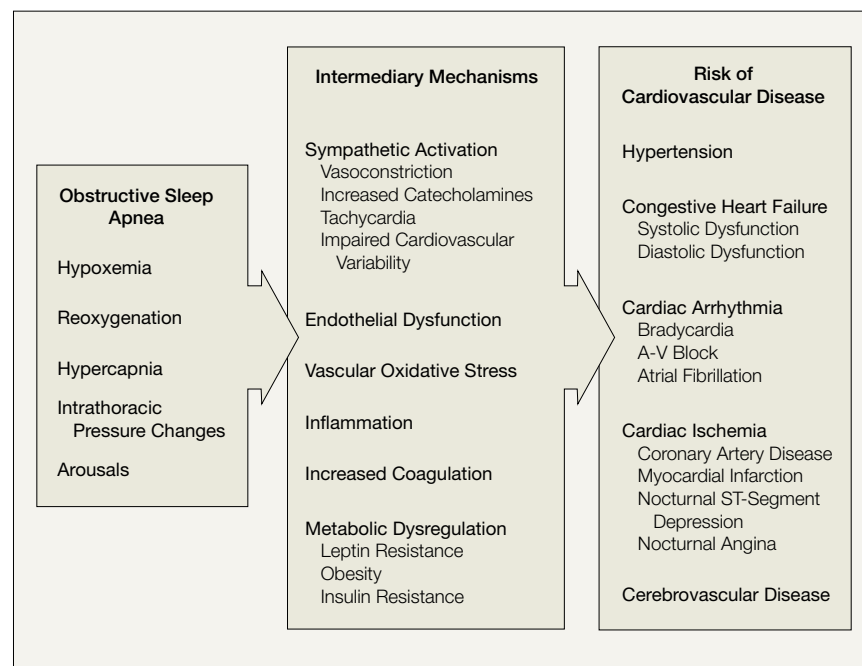
During apnea, there is a progressive chemoreflex-mediated increase in sympathetic activity with consequent vasoconstriction (FIGURE 2).<sup>12</sup> During re-

sumption of breathing, the restoration of venous return and consequent increased cardiac output, together with severely constricted peripheral circulation, results in acute increases in blood pressure. At termination of apnea, sympathetic vasoconstriction is inhibited through several mechanisms, including the resumption of breathing and the surge in blood pressure.<sup>12</sup> Repeated episodes of hypoxemia in patients with OSA also cause acute increases in pulmonary artery pressure.<sup>13</sup>

**Negative Intrathoracic Pressure**

Inspiratory effort against a closed upper airway (ie, the Mueller maneuver) is a cardinal feature of OSA, resulting in negative intrathoracic pressures reaching as low as -80 cm H<sub>2</sub>O,<sup>14</sup> consequently affecting intrathoracic hemodynamics. Changes in the configuration of intrathoracic structures also can substantially alter cardiac filling and cardiac function.<sup>15,16</sup> Left ventricular transmural pressure may increase, with

**Figure 1.** Intermediary Mechanisms Associated With Obstructive Sleep Apnea That Potentially Contribute to Risk of Cardiovascular Disease



Abnormalities associated with obstructive sleep apnea may be intermediary mechanisms that contribute to the initiation and progression of cardiac and vascular pathology. These mechanisms may interact with each other, thus potentiating their pathophysiological implications.

increases in afterload,<sup>17</sup> and negative intrathoracic pressure may impair LV relaxation, further impeding LV filling.<sup>16</sup> The combination of increased LV afterload and reduced LV preload leads to a reduction in stroke volume and cardiac output.<sup>18</sup> Negative intrathoracic pressure also alters aortic pressure, inducing stretch of the aortic wall and activating aortic baroreceptors, and thus intermittently inhibiting sympathetic outflow due to repetitive Mueller maneuvers.<sup>19,20</sup> On resumption of breathing, increased venous return may distend the right ventricle, producing an interventricular septal shift toward the left, thereby reducing both LV compliance and LV diastolic filling.<sup>14</sup>

### Arousal

Electroencephalographic arousal is common during and after apneic or hypopneic episodes during sleep. Arousal activates upper airway dilator muscles and prevents prolonged apnea in OSA. Arousal also may contribute to the acute increases in blood pressure at termination of OSA events.<sup>21</sup> Frequent arousal causes sleep fragmentation and may relate to excessive daytime sleepiness, the cardinal symptom of sleep apnea.

The sleep deprivation that occurs as a result of repetitive nocturnal arousals may be associated with neurocognitive impairment and predisposition to occupational injuries and motor vehicle crashes.<sup>22,23</sup> Sleep deprivation

also has been associated with metabolic<sup>24,26</sup> and inflammatory dysregulation,<sup>27-29</sup> and may induce increased levels of cytokine production, impaired glucose tolerance, and higher blood pressures. How the sleep fragmentation accompanying sleep apnea contributes to any eventual cardiac and vascular pathology remains unclear.

### POTENTIAL MECHANISMS LINKING OSA TO CHRONIC CARDIOVASCULAR DISEASE

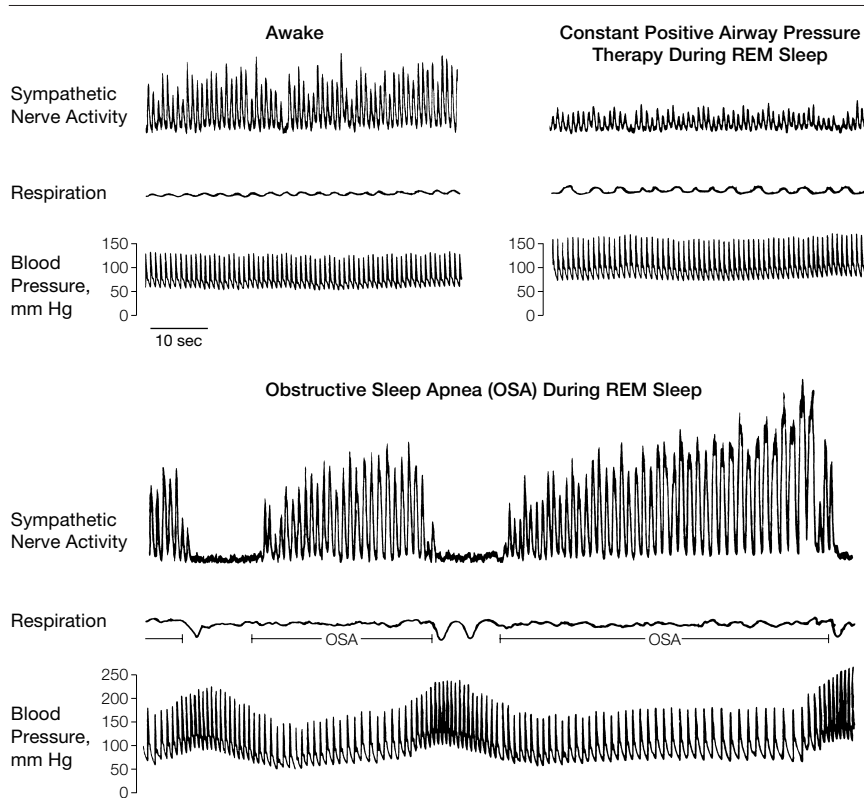
A number of neural, humoral, vascular, and inflammatory abnormalities that are evident in patients with OSA may be implicated in the initiation and progression of cardiac and vascular disease conditions and are outlined below. What remains to be determined is the relative importance of each mechanism in the development of specific cardiac conditions.

#### Sympathetic Activation

Patients with OSA have high levels of sympathetic nerve traffic to peripheral blood vessels, even during daytime normoxic wakefulness.<sup>12,30</sup> The reasons for this high level of tonic sympathetic excitation are unclear but may be linked to increased chemoreflex drive.<sup>31,32</sup> When patients with OSA breathe 100% oxygen, with consequent chemoreflex deactivation, their blood pressure, heart rate, and sympathetic activity all decrease significantly.<sup>31</sup>

Compared with control patients without sleep apnea but closely matched for age, sex, and body mass index, patients with OSA also have faster heart rates, decreased heart rate variability, and increased blood pressure variability.<sup>33</sup> These abnormalities in cardiovascular variability have been linked to increased cardiovascular risk.<sup>34-37</sup> Specifically, normotensive individuals with diminished heart rate variability have an increased risk of future hypertension.<sup>34</sup> Decreased heart rate variability in patients with heart failure has been linked to an increased mortality.<sup>35</sup> An increase in blood pressure variability has been associated with an increased risk for damage to target organs.<sup>36,37</sup>

**Figure 2.** Neural and Circulatory Changes in Obstructive Sleep Apnea



Recordings of sympathetic nerve activity, respiratory rate, and intra-arterial blood pressure in the same individual when awake, with OSA during rapid eye movement (REM) sleep, and with elimination of OSA episodes by continuous positive airway pressure (CPAP) therapy during REM sleep. Sympathetic nerve activity is very high during wakefulness, but increases even further secondary to obstructive apnea during REM sleep. Blood pressure increases from 130/65 mm Hg when the individual is awake to 256/110 mm Hg at the end of the apneic episode. Elimination of apneic episodes by CPAP therapy results in decreased sympathetic activity and prevents blood pressure surges during REM sleep. Reproduced with permission from Somers et al.<sup>12</sup>

### Vascular Endothelial Dysfunction

The hypoxia, hypercapnia, and pressor surges accompanying obstructive apneic events may serve as potent stimuli for the release of vasoactive substances and for impairment of endothelial function. Increased levels of endothelin,<sup>38</sup> presumably in response to the hypoxemia of sleep apnea, may contribute to sustained vasoconstriction and other cardiac and vascular changes. Patients with OSA who are free of any other overt cardiac or vascular disease also have impaired endothelial function.<sup>39,40</sup> Endothelial dysfunction is often seen in patients with hypertension,<sup>41</sup> hyperlipidemia,<sup>42</sup> diabetes,<sup>43-46</sup> or smoking,<sup>47-49</sup> and has been linked to increased risk of cardiovascular events.<sup>50,51</sup> While the comorbidities associated with sleep apnea may result in endothelial dysfunction, OSA itself may be an independent risk factor for the development of impaired endothelial function.

### Oxidative Stress

Intermittent hypoxia and reperfusion during repetitive episodes of nocturnal apnea may be involved in the generation of highly reactive free oxygen radicals, as well as in ischemia-reperfusion injury to the vascular wall, resulting in increased risk for atherosclerosis.<sup>52,53</sup> Low oxygen tension is a trigger for activation of polymorphonuclear neutrophils, which adhere to the endothelium and release free oxygen radicals. In OSA, repeated and cyclical arterial oxygen desaturation and reoxygenation occur in response to apneas followed by hyperventilation. This phenomenon of hypoxia/reoxygenation, which occurs frequently during each hour of sleep, every night, and over several decades in untreated patients with OSA, may elicit increased vascular oxidative stress.<sup>54,55</sup> Prevention of OSA by CPAP reduces production of superoxide.<sup>54</sup>

### Inflammation

Inflammation has been shown to be an important component in the progression of cardiovascular disease conditions,<sup>56</sup> particularly ischemic heart disease<sup>57</sup> and heart failure.<sup>58,59</sup> Hypoxia at

altitude may evoke the production of inflammatory cytokines<sup>60</sup> and increased levels of C-reactive protein.<sup>60</sup> Sleep deprivation also may be involved in production of cytokines.<sup>61,62</sup> The combination of hypoxemia and sleep deprivation characterizes patients with OSA and may lead to increased levels of inflammatory markers in these patients. Indeed, patients with sleep apnea have increased levels of interleukin 6, tumor necrosis factor  $\alpha$ ,<sup>62</sup> and C-reactive protein.<sup>63</sup> C-reactive protein itself may contribute to vascular disease and dysfunction by inhibiting nitric oxide synthase<sup>64</sup> and increasing expression of cell adhesion molecules.<sup>65</sup>

Adhesion of circulating leukocytes to the endothelial cells is considered one of the initial steps in the pathogenesis of atherosclerosis.<sup>66</sup> Hypoxic stress induced by OSA may directly modulate the expression of adhesion molecules.<sup>67</sup> Levels of adhesion molecules in the circulation may be elevated in patients with moderate to severe OSA and may be reduced by CPAP therapy.<sup>67-70</sup>

### Coagulation

Platelet aggregability increases in patients with OSA,<sup>71</sup> and in part may be secondary to elevated nocturnal levels of catecholamines.<sup>72</sup> Abolition of OSA by CPAP therapy reduces platelet aggregability in association with reductions in nocturnal levels of catecholamines.<sup>71-73</sup> Increases in hematocrit,<sup>74</sup> nocturnal and daytime levels of fibrinogen,<sup>75,76</sup> and blood viscosity<sup>77</sup> likely also contribute to a predisposition to clot formation and atherosclerosis in patients with OSA. The observations that CPAP therapy can alleviate some of these abnormalities and can reduce factor VII clotting activity<sup>78</sup> suggest that OSA may be causally related to increased coagulability.

### Metabolic Dysregulation

Obstructive sleep apnea may be associated with abnormalities in metabolism that could predispose to both weight gain and cardiovascular risk. Leptin is an adipocyte-derived hormone that suppresses appetite and promotes satiety.<sup>79</sup> Leptin levels are elevated in obese

individuals,<sup>80</sup> suggesting resistance to the metabolic effects of leptin. Leptin may predispose to platelet aggregation<sup>81</sup> and has been implicated as an independent marker of increased cardiovascular risk.<sup>82</sup> Men with OSA have higher leptin levels than similarly obese individuals without sleep apnea,<sup>83</sup> suggesting even greater resistance to leptin than is observed in obese individuals. Patients with sleep apnea are predisposed to significant weight gain in the year prior to diagnosis of the sleep apnea.<sup>83</sup> Thus, resistance to leptin in patients with sleep apnea may be implicated in susceptibility to weight gain. Treatment with CPAP reduces leptin levels and also may be associated with decreased visceral fat accumulation.<sup>84</sup>

Obstructive sleep apnea also may impair glucose tolerance. Patients with OSA have higher levels of fasting blood glucose, insulin, and glycosylated hemoglobin, independent of body weight.<sup>85,86</sup> The severity of sleep apnea appears to correlate with the degree of insulin resistance.<sup>87,88</sup> Severe OSA is accompanied by a 5-fold increase in the risk of overt diabetes mellitus.<sup>86</sup> Impaired glucose tolerance in patients with OSA, independent of the effects of obesity per se, may be linked to sleep deprivation,<sup>25</sup> sympathetic activation, and leptin resistance. However, treatment with CPAP does not show any consistent improvement in glucose tolerance.<sup>89</sup>

## OSA-RELATED CARDIAC AND VASCULAR DISEASES

There is, for the most part, only indirect evidence implicating OSA in the etiology and progression of cardiovascular disease. Reasons include the omission of measures of OSA in many epidemiologic studies. To some extent this has been a consequence of the considerable expense involved in establishing the diagnosis of OSA in large population samples. In addition, patients with OSA often have coexisting disease conditions such as obesity, hypertension, and impaired glucose tolerance, and any independent effect of OSA on cardiovascular risk may be obscured by these comorbidities. Nevertheless, smaller



longitudinal studies of incident cardiovascular disease, as well as studies evaluating the effects of intervention with CPAP therapy, have provided evidence that strongly suggests a causal interaction between OSA and several cardiovascular disease conditions.

### Hypertension

The most persuasive data implicating OSA in the development of hypertension have been the findings from the Wisconsin Sleep Cohort. In this study population, an apnea-hypopnea index of 15 or greater was independently associated with a 3-fold increased risk of developing new hypertension when participants were evaluated 4 years after the initial sleep study.<sup>90</sup> These data would imply that a substantial proportion of what is generally considered to be essential hypertension may in fact be hypertension secondary to undiagnosed and untreated OSA. The consensus guidelines for the management of hypertension reflect the increasing evidence implicating OSA in the development of hypertension. In 1997, the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure first acknowledged the importance of sleep apnea by recommending that OSA be ruled out as a contributor to resistant hypertension.<sup>91</sup> The most recent recommendations published in 2003 have included OSA as first on the list of identifiable causes of hypertension.<sup>92</sup>

Treatment of sleep apnea may have significant effects on lowering daytime blood pressure, not only in patients with resistant hypertension,<sup>93</sup> but also in patients with relatively mild hypertension.<sup>94</sup> While there is no clear blood pressure-lowering effect when normotensive patients with OSA are treated with CPAP in the long term,<sup>95</sup> 2 randomized placebo-controlled studies, in which the placebo consisted of subtherapeutic levels of CPAP, demonstrated that several months of CPAP therapy resulted in a small but significant reduction of daytime blood pressure of between 1.3 and 5.3 mm Hg.<sup>96,97</sup> Thus there appear to be consistent data implicating untreated

OSA in the development of new hypertension, and demonstrating that nocturnal treatment of OSA is accompanied by lower daytime blood pressures.

### Cardiac Ischemia

Obstructive sleep apnea induces acute and chronic stresses that could predispose to myocardial ischemia during sleep. Acutely, the profound hypoxemia, CO<sub>2</sub> retention, sympathetic activation, and surges in blood pressure may invoke myocardial ischemia. In the longer term, the development of daytime hypertension, the production of vasoactive and trophic substances such as endothelin, and the activation of inflammatory and procoagulant mechanisms also may contribute to the development and progression of ischemic heart disease. Indeed, in the Sleep Heart Health Study cohort, OSA emerged as an independent risk factor for coronary artery disease (CAD).<sup>2</sup>

Nocturnal ST-segment changes consistent with myocardial ischemia are evident in patients with OSA who are free of clinically significant CAD.<sup>98</sup> ST-segment depression is more frequent in those with more severe OSA or with prior complaints of nocturnal angina, and is related to oxygen desaturation.<sup>99,100</sup> Treatment with CPAP significantly reduces the total duration of ST-segment depression in persons with sleep apnea.<sup>101</sup>

Epidemiologic studies further support an association between OSA or snoring and myocardial infarction (MI).<sup>102-105</sup> Obstructive sleep apnea is common in patients with prior MI.<sup>105</sup> The post-MI changes of cardiac function may predispose to the development of OSA, or may affect OSA severity. Obstructive sleep apnea in patients with CAD also may be a prognostic indicator. Five-year follow-up of 62 patients with established CAD suggested a significantly higher mortality (38%) in those with OSA compared with those without OSA (9%), after adjusting for other confounding factors.<sup>106</sup>

### Cerebrovascular Disease

A history of snoring is associated with an increased risk of stroke, indepen-

dent of other cardiovascular risk factors.<sup>2,3,107-109</sup> Stroke has been linked to OSA in both cross-sectional and case-control studies,<sup>2</sup> and sleep apnea is highly prevalent in patients with stroke.<sup>110,111</sup> However, it remains unclear whether sleep apnea is an independent risk factor for cerebrovascular disease.

The hemodynamic, vascular, inflammatory, and thrombotic disease mechanisms activated by OSA may contribute to any enhanced risk for cerebrovascular disease. Acute apneic events are accompanied by dramatic reductions in cerebral blood flow.<sup>112</sup> Ischemic effects of repetitive episodes of nocturnal apnea would be potentiated by the associated hypoxemia and any preexisting impairment of cerebrovascular autoregulation and impaired vasodilator reserve.

However, the relationship between thrombotic stroke and OSA remains circumstantial. The population of patients at risk for stroke is demographically similar to the population of patients who are at risk for sleep apnea. Any causal association between OSA and stroke is further affected by the constraints that stroke may induce sleep apnea, and that only survivors of stroke are tested. Further longitudinal studies are needed to determine whether OSA is indeed a significant cause of cerebrovascular disease, independent of other factors.

### Congestive Heart Failure

Observations from epidemiologic studies suggest an association between both OSA and CSA and congestive heart failure.<sup>8,113,114</sup> Patients with congestive heart failure and with diastolic dysfunction may have an especially high likelihood of OSA<sup>115-117</sup>—about half of a small sample of patients with diastolic dysfunction had an apnea-hypopnea index greater than 10.<sup>116</sup>

An important caveat in interpreting prevalence data for sleep apnea from studies in patients with heart failure relates to the patient selection criteria that were used. Very often, prevalence data may reflect findings from patients referred to the sleep laboratory rather than from a random sample of the population of patients with heart failure. De-

spite these concerns, there is substantial evidence that sleep-related breathing disorders are indeed common in heart failure, especially CSA,<sup>9,114,118-120</sup> which is associated with a poorer outcome.<sup>121</sup> Central sleep apnea also may be highly prevalent in patients with LV dysfunction, even in the absence of overt heart failure.<sup>122</sup>

Obstructive sleep apnea may contribute directly to the development of both systolic and diastolic dysfunction. The hypoxemia, catecholamine surges, and increases in blood pressure during sleep, together with daytime hypertension, may predispose to hypertensive heart failure. This may manifest either as systolic or diastolic dysfunction. Systolic dysfunction also may be induced by inflammatory cytokines that affect myocardial contractility,<sup>123-127</sup> as well as by increases in both afterload and myocardial-wall stress during rapid changes in cardiac transmural pressure associated with generation of extreme negative intrathoracic pressure during episodes of obstructive apnea.<sup>14,18</sup> Hypertension, together with the trophic effects of substances such as endothelin and catecholamines, may induce structural cardiac changes that may be implicated in diastolic dysfunction.

Congestive heart failure itself may contribute to the development of OSA. Patients with congestive heart failure are predisposed to periodic breathing. During periodic breathing, respiratory drive and drive to pharyngeal dilator muscles decline,<sup>128,129</sup> leading to collapse of the upper airway. Edema in patients with congestive heart failure may involve the soft tissues of the neck and pharynx, particularly in the supine position, and could further narrow the upper airway, increase airway resistance, and make the airway more likely to collapse.<sup>130</sup>

The activation of the adrenergic, inflammatory, and other mechanisms in sleep apnea would reasonably be expected to worsen prognosis in heart failure. Indeed, preliminary data suggest that treatment of both OSA and CSA in patients with heart failure may have important beneficial effects. In small groups

of patients with heart failure and OSA, there was modest improvement in both ejection fraction and functional class after treatment with CPAP.<sup>113,131,132</sup> Withdrawal of treatment in some of these patients resulted in a deterioration in both of these measurements. Preliminary studies of the effects of CPAP therapy for CSA in patients with heart failure suggested that treatment of CSA tended to improve transplant-free survival.<sup>131</sup>

### Cardiac Arrhythmias

Nocturnal disturbances of cardiac rhythm have been reported in patients with OSA.<sup>7,133-136</sup> Heart block,<sup>135-137</sup> atrial fibrillation,<sup>138-140</sup> and ventricular ectopy<sup>141-143</sup> have been described, but the most common arrhythmias are severe sinus bradycardia and atrioventricular block, representing in part the diving reflex response to apnea and hypoxia.<sup>144</sup> These bradyarrhythmias occur even in the absence of any disease of the cardiac conduction system and often are eliminated by effective treatment of the OSA. It is important that OSA be excluded as a cause for bradyarrhythmia in the high-risk patient before treatment with a permanent pacemaker is instituted.

A recent study has, however, added a new perspective to pacemaker placement in patients with OSA.<sup>145</sup> Interactions between cardiac arrhythmias and OSA may extend beyond the traditional concepts of OSA as a cause of abnormalities in cardiac rhythm. Provocative evidence suggests that modulation of cardiac rhythm characteristics by atrial overdrive pacing may attenuate the severity of both OSA and CSA.<sup>145</sup> The mechanisms of any pacing-induced amelioration of sleep apnea and the implications for future therapeutic strategies are presently uncertain, but intriguing.

However, any therapeutic strategy that would incorporate long-term atrial pacing would need to recognize the potential interactions between OSA and atrial fibrillation. The hypoxemia, adrenergic activation, pressure surges, and cardiac distortion occurring during episodes of obstructive apnea may conceivably predispose to the development of atrial fi-

brillation. In patients cardioverted for atrial fibrillation, the presence of untreated sleep apnea doubles the likelihood of recurrence of atrial fibrillation within 12 months, compared with patients with OSA receiving CPAP therapy.<sup>146</sup>

Definitive evidence implicating OSA in the genesis of other serious arrhythmias is lacking. Methodological limitations, small sample sizes, comorbid conditions, medication use, and lack of control groups have allowed only a limited interpretation of the existing data addressing the prevalence and types of arrhythmias associated with OSA.

### THERAPEUTIC STRATEGIES

In addition to CPAP and surgery, several novel approaches to treating OSA have emerged over the last few years. These include dialysis for attenuating the severity of OSA in patients with chronic renal failure.<sup>147</sup> Cardiac pacing also may provide a potential but poorly understood intervention for reducing the severity of OSA.<sup>145</sup> If inflammatory mediators are indeed important contributors to cardiovascular pathology in patients with OSA, it is conceivable that drugs that lower these measures of inflammation, such as aspirin<sup>148,149</sup> and statins,<sup>150-153</sup> may be of benefit in patients with OSA, particularly in those who do not tolerate more conventional therapeutic strategies.

### CONCLUSIONS

It is primarily over the past 2 to 3 decades that the implications of OSA for cardiovascular disease have become recognized. Nevertheless, the general cardiovascular community has been slow in assimilating OSA into the cardiovascular diagnostic and therapeutic paradigms. This lag between information and intervention can be attributed to a number of factors, including the considerable expense and wait time required for sleep studies, and the variable and sometimes unsuccessful responses to initiation of CPAP therapy. Furthermore, the cardiovascular community is accustomed to management strategies driven by evidence from large-scale random-

ized trials and has come to regard smaller studies with appropriate caution, even those that show substantial benefit. While the evidence for activation of a broad spectrum of cardiovascular disease mechanisms in patients with OSA is compelling, there are very few longitudinal studies of the effects of OSA on cardiovascular outcomes, and no large-scale, randomized, double-blind trials of the cardiovascular effects of therapeutic intervention.

Such studies are constrained by the numerous comorbid conditions that accompany OSA, as well as by the technical problems associated with double-blind studies of CPAP treatment. Furthermore, there is reasonable evidence that CPAP will reduce daytime sleepiness, favorably affecting the likelihood of motor vehicle crashes.<sup>154</sup> Thus, any long-term outcome study focused on the effects of CPAP therapy on cardiovascular end points would be limited by the proven benefit of CPAP on daytime somnolence. Possible solutions to this limitation would be to ensure that participants in any such study understand the known benefits they could derive from CPAP, or alternatively limiting such an outcomes study to patients without significant daytime sleepiness.

Even should OSA be conclusively implicated in adverse cardiovascular outcomes, it is important that cost-effectiveness issues be addressed, given the expense of current diagnostic and therapeutic strategies. For example, should all obese patients with hypertension, heart failure, or atrial fibrillation be evaluated for OSA? Even if significant OSA is identified and effectively treated in these patients, what is the likelihood that this approach would improve cardiovascular outcomes? Mechanistic and technical advances that would enable more economical and effective diagnostic and therapeutic approaches would greatly enhance resolution of these questions.

What is known is that OSA is common, readily diagnosed, usually treatable, frequently coexists undiagnosed in patients with cardiovascular disease, activates disease mechanisms known to

elicit cardiac and vascular damage, and may be implicated in progression of cardiovascular disease and resistance to conventional therapeutic strategies. The epidemic of obesity speaks to the likelihood of a dramatic increase in the prevalence of OSA. Further investigation of the implications of OSA and its treatment is an important priority in the study of cardiovascular disease. In the absence of definitive evidence from large-scale trials and a better understanding of potential cost-effectiveness, the likely benefits of diagnosis and treatment of OSA are presently best appraised on an individual patient basis.

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