Obstructive Sleep Apnea and Cardiovascular Disease and Mortality: The Argument for Causality

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There is solid evidence linking obstructive sleep apnea (OSA) to cardiovascular mortality. Although it has yet to be scientifically proven that OSA causes cardiovascular disease, many investigators consider it an independent cardiovascular risk factor. Its impact on the cardiovascular mortality risk of a given applicant varies depending upon the severity of the condition, compliance with treatment, and the applicant’s specific cardiovascular milieu. This review is aimed at making mortality risk assessment more accurate by describing what is known of the physiologic mechanisms by which OSA may influence cardiovascular mortality and providing an appreciation for the magnitude of this risk. In doing so, an argument supporting OSA as a cause for cardiovascular disease and mortality emerges.

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An understanding of the relationship between obstructive sleep apnea (OSA) and cardiovascular disease has evolved exponentially in recent years despite challenges to scientific inquiry. For example, there are ethical prohibitions to randomizing patients with known OSA into untreated control groups. Also, it is difficult to isolate the cardiovascular influence of OSA from that of common confounders such as hypertension and obesity. Some confounding conditions may be in the causal pathway from OSA to cardiovascular disease frustrating attempts to adjust for them. Notwithstanding these challenges, investigators have created a compelling body of data implicating repetitive nocturnal hypoxia and airway obstruction as causes of cardiovascular morbidity and mortality.

Obstructive sleep apnea causes acute and chronic cardiovascular changes. Acutely, there are repetitive fluctuations of heart rate, blood pressure (BP) and stroke volume. These result from apnea-induced hypoxia and oscillations of intrathoracic pressure due to inspiratory efforts against an obstructed airway. In addition to hemodynamic swings, these influences can acutely disrupt normal autonomic balance stimulating cardiac dysrhythmias. Chronically, repetitive nocturnal airway obstructions lead to persistent hemodynamic and autonomic changes that may result in hypertensive cardiovascular disease. Likewise, these obstructions result in proinflammatory, prothrombotic, and metabolic changes that may lead to atherosclerotic cardiovascular disease.
Due to a paucity of mortality data pertaining to OSA, as well as the complexity of the cardiovascular milieu in which OSA occurs, when assessing mortality risk, we must rely more on informed intuition than science. This review summarizes current knowledge pertaining to the relationship between OSA and cardiovascular disease and should serve to inform the intuition of those who estimate mortality risk for life insurance applicants with OSA.

**PATHOPHYSIOLOGY OF OBSTRUCTIVE SLEEP APNEA**

Obstructive sleep apnea is characterized by multiple nocturnal airway obstructions brought about by relaxation of the pharyngeal musculature coupled with a narrow upper airway. Inspiratory efforts eventually “suck” a relaxed and encroaching upper airway structure, frequently the base of the tongue or soft palate, into the airway preventing further inhalation. Inspiratory efforts of the chest muscles and diaphragm continue against this obstruction, creating cyclic negative intrathoracic pressure that can reach $-90$ cm H$_2$O. As the apnea progresses, arterial oxygen saturation falls and the carbon dioxide level rises stimulating peripheral and central chemoreceptors, which causes a release of catecholamines and arousal. Sympathetic neuromuscular activity increases as well, reestablishing patency of the airway.

In addition to arousing the endangered sleeper, the adrenergic surge increases heart rate, stroke volume, and peripheral vascular resistance, elevating systolic blood pressure to levels commonly exceeding 200 mm Hg, thereby increasing left ventricular afterload and cardiac work. Negative intrathoracic pressure, generated by inspiratory efforts against an obstructed airway, also serves to increase left ventricular afterload by increasing the transmural pressure gradient across the myocardium. The negative intrathoracic pressure draws the myocardium into the chest cavity, thereby increasing the force against which it must work to contract. Negative intrathoracic pressure also increases right ventricular filling causing a leftward shift of the interventricular septum, which encroaches into the left ventricular cavity lowering left ventricular end-diastolic volume, or preload. Finally, left ventricular diastolic relaxation is inhibited in OSA. In sum, hypoxia-induced adrenergic surges along with hemodynamic changes resulting from the effort to inspire against an obstructed airway serve to increase cardiac workload.

Meanwhile, due to the delay between termination of apnea and reoxygenation at the tissue level, the increased cardiac workload coincides with post-apnea hypoxia. This mismatch between myocardial oxygen demand and oxygen delivery can occur as often as once or twice each minute allowing little time for recovery and potentially compromising myocardial oxygenation. This may help to explain the disproportionate number of cardiovascular deaths that occur between midnight and 6 am.

In dogs, Brooks et al showed that over time, repeated nocturnal airway obstruction results in diurnal blood pressure elevations as well as the aforementioned nocturnal surges. Humans with OSA have high sympathetic nerve activity during wakefulness and elevated diurnal urinary catecholamine levels, suggesting that repetitive nocturnal airway obstruction may increase the resting drive of peripheral chemoreceptors during wakefulness. Indeed, when Narkiewicz et al gave OSA patients 100% O$_2$, the dismal up-regulation of their chemoreceptors was overridden, and their sympathetic nerve activity and blood pressure returned to normal. No such change was seen in controls without OSA. In rats exposed to repetitive hypoxia, Lesske et al demonstrated the development of hypertension, whereas in rats with denervation of peripheral chemoreceptors, or adrenal demedullation, repetitive hypoxia produced no hypertension. Thus,
there is evidence to suggest that the mechanism for diurnal hypertension in patients with OSA is up-regulation of the resting drive of chemoreceptors resulting from repetitive episodes of nocturnal hypoxia.

There is evidence that cyclic hypoxia with reoxygenation, a characteristic of OSA, increases the production of reactive oxygen species (ROS) in a dose-response fashion, as well as evidence that these elevated ROS levels are fully reversed by effective continuous positive airway pressure (CPAP).26–29 Radical oxygen species are among those influences known to cause endothelial dysfunction, which is thought to be central to the genesis of atherosclerotic cardiovascular disease.30 OSA is associated with many of the defining features of endothelial dysfunction, for example, decreased production of the vasodilator, nitric oxide (NO)31 and increased production of the vasoconstrictor endothelin-1.32 OSA and endothelial dysfunction are both associated with a proinflammatory milieu characterized by increased expression of endothelial adhesion molecules such as intercellular adhesion molecule 1, (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and L-selectin.8 Other inflammatory molecules overexpressed in this milieu include C-reactive protein and interleukin-6.7,33 Prothrombotic factors, too, are overexpressed in both OSA and endothelial dysfunction including fibrinogen,34,35 plasminogen activator inhibitor,36 and platelet aggregability.37 Repetitive hypoxia has also been shown to increase lipid loading in human macrophages,38 another process central to the new paradigm of atherogenesis is an inflammatory phenomenon. There is good evidence that CPAP reverses endothelial dysfunction39,40 in those with OSA.

OSA is independently related to increased insulin resistance.41 It is also associated with increased levels of leptin, a hormone secreted by adipose tissue that signals satiety.32,43 A high leptin level in the presence of obesity implies leptin resistance, just as a high insulin level in the presence of diabetes implies insulin resistance. Leptin resistance may explain the accelerating weight gain frequently experienced in the months before a person is diagnosed with OSA.44 Leptin resistance with obesity, insulin resistance with diabetes, hypertension, and dyslipidemia define the metabolic syndrome, which has recently been shown to be independently associated with OSA.13 The full nature of this relationship is not yet fully understood.

Obstructive sleep apnea is associated with a variety of nocturnal cardiac rhythm disturbances,45 due to apnea-induced hypoxia, blood pressure surges, and other hemodynamic changes. Zwillich et al46 showed that hypoxia in the absence of air movement induces bradycardia, whereas hypoxia with ventilation causes tachycardia. Periods of pronounced vagal dominance in the apnea cycle may lead to bradycardia, sinus arrest and atrioventricular blocks, while sympathetic surges may result in atrial and ventricular ectopy. Hypoxemia, increased adrenergic activity, blood pressure surges, and cardiac distortion may help to explain a strong independent association between atrial fibrillation and OSA.47 CPAP and tracheostomy have been shown to normalize most, if not all, of the physiologic changes listed above45,48,49 lending further support to the thesis that airway obstruction and hypoxia are the driving physiologic abnormalities responsible for cardiovascular disease associated with OSA.

**OSA AND CARDIOVASCULAR MORTALITY**

There have been relatively few all-cause mortality studies on OSA and even fewer focusing on cardiovascular mortality. In a pre-CPAP study, Partinen et al50 compared 5-year mortality in a group of 198 OSA patients treated either with tracheostomy or weight loss. All of the 14 deaths in this study were in the weight loss group, despite a substantially lower mean apnea hypopnea index (AHI) and mean body mass index
(BMI) in the weight loss group. These investigators also noted a modest elevation of the crude cardiovascular mortality rate. That same year, He et al.\textsuperscript{51} reported on the mortality of 706 men with OSA over a 9-year period demonstrating a positive linear correlation between apnea index (AI) and mortality. They also found a negative correlation between age and mortality, and they observed that none of the patients treated with tracheostomy or CPAP died. In 1995 Lavie et al.\textsuperscript{52} reporting on 1620 patients with OSA found a substantially higher death rate for those under age 50 compared with those over age 50. They reported a 22% incidence of death from myocardial infarction (MI), significantly higher than that found in the general population. Unfortunately, they did not adjust for confounding conditions. More recently Marti et al.\textsuperscript{53} studied mortality in a group of 444 patients with OSA. They reported a 20.92 relative cardiovascular mortality risk, and a 16.06 relative all-cause mortality risk, for males aged 17–50. With treatment for OSA, these rates fell to 2.11 and 1.29, respectively. This study also compared the mortality rates for those treated with diet, surgery, or CPAP to those without treatment, and of 19 cardiovascular deaths only 2 were in the group treated with CPAP. CPAP also appeared protective against non-cardiovascular causes of death, suggesting OSA may have played a role in these deaths as well.

A 2005 cohort observational study by Marin and colleagues\textsuperscript{54} compared fatal and non-fatal cardiovascular events in 1411 people divided into groups of healthy people, snorers, OSA patients treated with CPAP, untreated patients with mild OSA, and untreated patients with severe OSA. (Figure 1) Monitors were used to verify CPAP compliance. Adjusting for confounding variables, they showed that untreated severe OSA (AHI >30) was associated with odds ratios of 2.87 and 3.17 for fatal and non-fatal cardiovascular events respectively over a 10-year period. Use of CPAP lowered the risk of fatal cardiac events to near that of healthy subjects.

Gami et al.\textsuperscript{55} investigated the time of day people were most likely to experience sudden death from cardiovascular causes. Those with OSA were most likely to die suddenly of cardiovascular causes between midnight and 6 am. Whereas those without OSA, and the general population, were more likely to die suddenly between 6 am and noon. Apnea duration and oxygen desaturation nadir are generally greater during REM sleep when muscles are atonic. REM sleep is most frequent in the second half of the sleep period, usually between midnight and 6 am.

These studies implicate OSA in cardiovascular mortality due to myocardial infarction, stroke, congestive heart failure (CHF), and fatal arrhythmia. The pathways by which OSA might result in cardiovascular mortality are primary atherogenesis, aggravation of pre-existing atherosclerosis, hypertensive cardiovascular disease, or rhythm disturbances induced by autonomic dysfunction or hypoxia. While much remains to be uncovered, much has been learned, and knowledge is growing rapidly in this dynamic area of study.

**OSA AND HYPERTENSION**

The evidence supporting an independent association between OSA and hypertension is strong. Hla et al.\textsuperscript{56} identified subjects with
and without OSA in the Wisconsin Sleep Study cohort. Using ambulatory blood pressure monitoring and adjusting for potentially confounding obesity, age, and sex, they demonstrated a linear correlation between OSA and hypertension. The odds ratios for hypertension ranged from 2.0 for an apnea hypopnea index (AHI) of 5, up to 5.0 for an AHI of 25.

Further support for an independent association between OSA and hypertension came from the Sleep Heart Health Study. Nieto et al. found a dose-response relationship between OSA severity as measured by AHI, and hypertension, after adjusting for body mass index (BMI), neck circumference, waist-to-hip ratio, alcohol intake, and smoking. The best evidence for a causal relationship between OSA and hypertension was reported by Peppard et al. They followed subjects with similar blood pressures at the outset for 4 years and found that those with OSA had an adjusted odds ratio for the development of hypertension of 1.42 for AHIs from 0.1-4.9 that rose to 2.89 for AHIs above 15.0. This finding was independent of body mass index, neck and waist circumference, age, sex, and use of alcohol and cigarettes.

Using a dog model in which OSA was simulated by repetitive nocturnal airway occlusion during sleep, Brooks et al. measured blood pressure during wakefulness and sleep before, during, and after a 1-3 month period. Initially there were transient rises only in nocturnal BP, but eventually sustained daytime hypertension appeared. One month after the repetitive nocturnal airway obstructions were discontinued, the daytime blood pressure returned to normal. In a similar experiment, rats exposed to 12 seconds of hypoxia twice each minute, 7 hours per day for 35 days showed significant increases in blood pressure and were found to have increased left ventricle-to-body weight ratio compared with controls. A later rat study showed that surgical denervation of the peripheral chemoreceptors, or demedullation of the adrenals, prevented the blood pressure increase implicating these organs as mediators of the hypertensive response.

While proof that OSA causes hypertension is lacking, there is a growing body of knowledge demonstrating a strong independent dose-response relationship between OSA and hypertension with at least one study providing strong evidence for a causal relationship. This knowledge coupled with what is known of the pathophysiology of OSA, and evidence that CPAP normalizes blood pressure in those with OSA, makes a compelling argument for causality.

**OSA AND CONGESTIVE HEART FAILURE (CHF)**

It is intuitive to hypothesize that the repetitive episodes of nocturnal hypoxia, acute and chronic elevations of catecholamines, and acute and chronic elevations of systolic blood pressure, characteristics of OSA, could cause or aggravate CHF, but proof has been elusive. While there is strong evidence for an independent association between OSA and CHF, determining to what extent each influences the other has proven challenging.

Using CPAP to increase intrathoracic pressure in patients with CHF has been shown to improve left ventricular performance. In men with OSA and dilated cardiomyopathy, CPAP has been shown to increase left ventricular ejection fraction from an average of 37% to 59% after 4 weeks.

Epidemiologic studies have shown an independent association between OSA and CHF. In the Sleep Heart Health Study, for those with OSA, the odds ratio for CHF, comparing the upper and lower quartile for AHI values, was 2.38. While the prevalence of OSA in the general population is 2%–4%, Javaheri et al. found that 11% of males with stable heart failure had OSA. Sin et al. found that 37% of 450 patients with CHF had OSA. Withdrawal of CPAP for 1 week in
a subset of the latter group caused the average ejection fraction to fall from 53% to 45%.

Obstructive sleep apnea has also been shown to affect diastolic dysfunction independent of other possible factors. At the outset of a prospective, randomized, placebo-controlled, double-blinded crossover study, Arias et al. found that 15 of 27 patients with OSA had an abnormal left ventricular filling pattern, whereas only 3 of 15 controls did. Those with OSA also had thicker septal and posterior myocardial walls, although these values were still within the normal range. These investigators also showed that CPAP could stop the progression of diastolic dysfunction and might reverse it if used before severe structural changes were established. An earlier study by Fung et al. demonstrated a linear relationship between OSA severity and left ventricular diastolic dysfunction.

Knowing the pathophysiology of OSA, there is reason to believe that it could compromise left ventricular function and in doing so aggravate or cause congestive heart failure. Evidence for an independent relationship between OSA severity and left ventricular diastolic dysfunction.

OSA AND ISCHEMIC HEART DISEASE

As with congestive heart failure, proof that OSA causes coronary artery disease is lacking. However, given the aforementioned evidence that OSA causes oxidative stress and endothelial dysfunction, and that CPAP resolves these changes, one could reasonably hypothesize such a relationship. Notwithstanding proof of causality, there is evidence that OSA causes myocardial ischemia in patients with previously established atherosclerotic cardiovascular disease. ST-segment depression has been shown in patients with coronary artery disease (CAD) and OSA. Peled et al. showed that nocturnal ischemic events in patients with CAD and OSA occurred following apnea periods when increased cardiac workload coincides with arterial oxygen desaturation. In the same study, CPAP significantly improved nocturnal ST-depression. Similarly, Marin et al. found that CPAP essentially extinguished the increased risk for fatal myocardial infarction (MI) and stroke associated with OSA, which suggests that OSA is an independent cardiovascular risk factor.

After adjusting for confounders, Peker et al. found a 38% mortality rate over 5 years for patients with CAD and OSA, whereas the rate for those with CAD but no OSA was only 9%. In a 5-year prospective cohort study of 408 patients with verified CAD, Mooe et al. found that those with sleep-disordered breathing had a significantly higher risk for death, stroke, and myocardial infarction. After adjustment for age, BMI, hypertension, smoking, and cholesterol level, Hung et al. found OSA to be an independent risk factor for myocardial infarction for those with an apnea index greater than 5.3/hr. These investigators judged the risk imposed by OSA to be roughly equivalent to that of hypertension, obesity, or smoking. They also noted a linear relationship between OSA and MI with those in the highest quartile for AHI being 23.3 times more likely to have an MI than those in the lowest quartile.

In summary, there is good evidence for an independent correlation between OSA and CAD. The evidence that OSA aggravates pre-existing CAD is strong. Although a causal relationship between OSA and CAD remains to be proven, the association between OSA and pathogenic factors for atherosclerosis, along with evidence correlating OSA with very early physical measurements of atherosclerosis, suggests such is the case.

OSA AND STROKE

Under normal circumstances cerebral blood flow is controlled locally by fluctuations of cerebrovascular resistance such that
relatively constant flows exist over a wide range of perfusion pressures. In normal non-REM sleep, flow is decreased 5%–28%. In REM sleep, it is increased by 4%–41%. Normal nocturnal reductions of cerebral blood flow converge with the abnormal cerebral hemodynamics of OSA making sleeping hours a time of vulnerability for ischemic cerebral events.

Cerebral blood flow falls during apneas proportional to the duration of apnea and the degree of oxygen desaturation. Obstructive apneas and hypopneas are associated with a 50% reduction of cerebral blood flow compared with central apneas. Balfors and Franklin demonstrated that 5 seconds after apnea termination, mean arterial pressure and cerebral blood flow velocity (CBFV) increased (11% and 15%, respectively) compared with baseline, and that this was followed by a decrease of CBFV (−8% and −23%, respectively) approximately 20 seconds after apnea termination. Because CBFV parallels the mean arterial pressure, it indicates that autoregulation of cerebral blood flow is insufficient to protect the brain from the systemic pressure fluxes surrounding apnea events. Other features of OSA may also serve to increase the risk of cerebral ischemic events. Along with apnea-induced hypoxia and hypertension, the prothrombotic and proinflammatory changes described above may contribute to the development of an ischemic event.

Palomaki and Partinen found the odds ratio was 8.0 for stroke in people with a history of OSA and obesity, when compared with age-matched controls after adjusting for hypertension, coronary artery disease, and alcohol consumption. Others have found odds ratios for stroke in people with snoring or OSA ranging between 3.2 and 10.3. In the Sleep Heart Health Study, obstructive sleep apnea was associated with an increased prevalence of stroke that grew as the AHI increased.

As with hypertension, ischemic heart disease, and congestive heart failure, it has proven difficult to firmly establish a causal relationship between OSA and stroke, but the association between the two is strong, and causality is at least suggested by what is known of the pathophysiology.

### OSA AND CARDIAC RHYTHM DISTURBANCES

Normal sleep is a parasympathetic state, although sympathetic surges occur during phasic REM sleep. Obstructive sleep apnea imposes further autonomic influences as described above, and the expression of these influences in a given individual is difficult to predict. The largest study to date exploring the range of cardiac rhythm disturbances associated with OSA was published by Guilleminault et al in a 1983 study of 400 patients with sleep apnea syndrome. (Table) These investigators found nocturnal rhythm disturbances in 48% of OSA patients without relationship to apneic events, age, weight, or oxygen desaturation nadir. The most significant rhythm disturbances were unsustained ventricular tachycardia, sinus arrest, and second-degree heart blocks. Other dysrhythmias included sinus bradycardia, atrial tachycardia, paroxysmal atrial fibrillation, and premature ventricular contractions. Of interest, 50 of the patients with rhythm disturbances underwent tracheostomy, and with the exception of four who continued to have premature ventricular contractions, all rhythm disturbances in this group resolved. Other studies have shown that those with OSA are more likely to develop atrial

| Cardiac Arrhythmia and Conduction Disturbance During Sleep in 400 Patients with Sleep Apnea Syndrome |
|---------------------------------------------------|-------------------|
| Ventricular tachycardia                          | 12                |
| Sinus arrest                                     | 43                |
| Second degree A-V block                         | 31                |
| Atrial tachycardia                              | 28                |
| Sinus bradycardia                               | 29                |
| Atrial fibrillation/flutter                      | 13                |
| PVCs over 2 per minute                          | 75                |
fibrillation after coronary artery bypass surgery and more likely to develop recurrence after cardioversion for atrial fibrillation.

Which of the cardiac rhythm disturbances associated with OSA is likely to be expressed cannot be predicted. It depends on how the individual physiologic context is affected by the summed hemodynamic and autonomic influences arising from repetitive obstructive apneas. It can be said with confidence, however, that OSA is associated with potentially fatal rhythm disturbances and that those with OSA are more likely to die suddenly between midnight and 6 am. Further study is needed in this area.

**CONCLUSION**

This review provides substantial support for the thesis that OSA aggravates, and may cause, atherosclerotic cardiovascular disease, hypertensive cardiovascular disease, and a variety of cardiac rhythm disturbances, all potentially fatal conditions. Multiple studies have demonstrated not only independent associations between OSA and these conditions, but also that these relationships are linear in nature and that treatment with CPAP or tracheostomy reverses these effects. Other studies have shown positive correlations between OSA and the pathophysiologic underpinnings of cardiovascular disease, and again, treatment of OSA reverses these influences. Notwithstanding the absence of scientific proof, these studies taken as a whole provide provocative, if not compelling, evidence that OSA causes cardiovascular mortality.

The greater challenge for those estimating the mortality risk of life insurance applicants with OSA is to establish the magnitude of cardiovascular risk imposed by OSA. As data quantifying this risk is lacking, this calls for reliance on informed intuition. Risk assignment requires an appreciation for the severity of OSA, estimation of compliance with treatment, and qualitative and quantitative awareness of the applicant’s cardiovascular risk factor profile. At this juncture in the understanding of this condition, this is the best that can be done.

**REFERENCES**


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