

Pro: Sleep Apnea Causes Cardiovascular Disease

The association between sleep apnea syndrome and cardiovascular morbidity has been evident since the first apneic patients were investigated in the laboratory: these anecdotal observations were dramatic. In one of the first documentations of tracheostomy in sleep apnea, Coccagna and coworkers (1) observed the complete disappearance of a severe “atrial flutter” the day after the tracheostomy, and a rapid postoperative decrease in systemic blood pressure. Likewise, Guilleminault, Eldridge, and Dement (2) reported that blood pressure in two hypertensive children with severe sleep apnea was normalized within 24 hours after a tracheostomy! These are no longer exotic anecdotes. Since then, it has been repeatedly demonstrated that sleep apnea syndrome is causally linked with cardiovascular morbidity, and impressive progress has been made in delineating how sleep apnea causes cardiovascular diseases.

The first line of evidence came from cross-sectional and case-control studies, revealing high rates of sleep apnea in unselected cardiovascular patients on the one hand, and high rates of cardiovascular morbidity in sleep apnea patients on the other (3). A fundamental problem confronting such studies is the notorious contribution of confounders. Both sleep apnea and cardiovascular diseases share similar risk factors such as male gender, obesity and middle age; therefore, skeptics have raised doubts as to how much can be attributed to these confounders. The fitting response to this valid criticism appeared in the form of larger studies that allowed a better control over confounding variables. The year 2000 was particularly prolific, with eight studies, all relying on very large cohorts, providing supporting evidence for an independent association between sleep apnea and cardiovascular morbidity (4). This association was evident in both sleep laboratory cohorts as well as in general population cohorts. Further support came from studies demonstrating that effective treatment of sleep apnea with nasal continuous positive airway pressure (CPAP) reduced daytime and night time blood pressure (5). Animal models contributed when Brooks and coworkers (6) induced sleep apnea in dogs by intermittent airway occlusion, which resulted in sustained daytime hypertension. Here, obviously, there were no “confounding variables” that could account for these results.

Still, skeptics would demand mechanisms by which sleep apnea could give rise to cardiovascular diseases and insist on knowing the natural history of this association. Several mechanisms were proposed to mediate the effects of sleep apnea on the cardiovascular system, including sustained sympathetic activation (7), swings in intrathoracic pressure (8) and, more recently, oxidative stress and consequently vascular inflammation resulting from the nocturnal hypoxia/reoxygenation cycles (9). This latter mechanism that has been the focus of intense research in our laboratory in recent years allows to chart the natural history of this association. What is the evidence that oxidative stress is a major contributor to cardiovascular morbidity in sleep apnea? Increased production of oxygen reactive species was found in

granulocytes and monocytes obtained from sleep apnea patients (10–11). This was associated with increased expression of adhesion molecules and proinflammatory cytokines, which resulted in increased avidity of monocytes and lymphocytes and increased cytotoxicity of lymphocytes against endothelial cells in culture (11–12). Moreover, the increased adhesion and cytotoxicity of sleep apnea patients' monocytes and lymphocytes to endothelial cells in culture could be blocked by employing antibodies against selectins and tumor necrosis factor- α , suggesting the active involvement of adhesion molecules and inflammatory cytokines in endothelial cell injury and dysfunction (11–12). Importantly, exposing cultured monocytes of normal subjects to hypoxia *in vitro* simulated the above findings, while nasal CPAP treatment of sleep apnea patients prevented them (11). Reports on increased plasma lipid peroxidation, C-reactive protein and serum amyloid-A, and decreased levels of plasma nitric oxide (13–16) in sleep apnea, confirmed the existence of increased oxidative stress, vascular inflammation, and endothelial cell injury, all implicated in atherogenic sequelae. These observations are complemented by the demonstration that cardiovascular disease-free sleep apnea patients display endothelial dysfunction as determined by assessment of endothelium-dependent vasodilation (17). Endothelial dysfunction is considered to be the earliest manifestation of atherosclerosis and to predict cardiovascular events (18). Finally, sleep apnea was shown to be associated with classical markers of atherosclerosis such as increased carotid wall thickness (19) and the prevalence of calcified carotid artery atheromas (20).

Collectively, the above evidence implicates exaggerated oxidative stress in initiating a cascade of events which culminates in atherogenesis and diverse cardiovascular morbidities in sleep apnea. This has far reaching clinical implications for diagnosis and treatment of the syndrome. From the above chain of events, it appears likely that atherogenesis starts at a very early stage after sleep apnea onset, perhaps even during the very first night in which patients experience apneic events. By the time they are diagnosed with the syndrome, usually at the age of 47–50 years when symptoms become apparent, they have already accumulated substantial atherosclerotic insults which may be irreversible. Diagnosis at this age may be too late. This can explain why so many sleep apnea patients exhibit cardiovascular morbidity at the time of diagnosis. Furthermore, starting treatment years after atherogenesis has been initiated may slow it down or abort its progress but not necessarily reverse it. Thus, to prevent cardiovascular morbidity, sleep apnea diagnosis and treatment should be made as early as possible.

To conclude, there is no real debate if sleep apnea causes cardiovascular morbidity: not only do we know for sure that it does, we even have convincing evidence regarding the underlying mechanisms and the natural history of these relationships. The challenge, however, is entirely different. With the help of PubMed, I retrieved 250 editorial papers that include in their title the key term “sleep apnea.” None appeared in a leading cardiovascular journal, and only 14 were published in major general medical journals! Thus, the medical community, and cardiologists in particular, are yet to embrace the idea that sleep apnea syndrome causes cardiovascular morbidity, which is crucial to any change in

the diagnosis and treatment of the syndrome. This is the real challenge facing the medical sleep community today, and not to prove what is so clearly evident.

Conflict of Interest Statement: P.L. is a consultant and board member of Itamar Medical Ltd. and SLP Ltd. that produce medical devices for diagnosis of sleep apnea and is a board member of Sleep Medicine Center, Israel, and Sleep Health-Centers, U.S., that provide diagnostic and treatment services to patients with sleep disorders. In 2001, he received \$40,000, in 2002 \$40,000, and \$20,000 in 2003 as consultant fees and owns options in these companies and has five patents relevant to the subject matter of this article and some of his research was supported by grants from Itamar Medical and SLP for a total of approximately \$50,000 and in the last three years he participated as a speaker in scientific meetings and courses organized and financed by industrial companies (Itamar Medical, Respironics, ResMed).

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Con: Sleep Apnea Does Not Cause Cardiovascular Disease

Obstructive sleep apnea has been linked to cardiovascular disease since the first case series published by Guilleminault in 1976 reported the high prevalence of hypertension (1). Indeed, it was the Stanford group that provided the first long-term data suggesting that treating obstructive sleep apnea reduced cardiovascular deaths (2). Partinen and Guilleminault compared patients with obstructive sleep apnea who accepted advice to have a tracheotomy with those who rejected this surgical approach (and opted for conservative treatment). Over 10 years there was a significant 10% difference in mortality favoring tracheotomy. This was not a randomized trial, however, and patients who accept medical advice tend to do better than those who do not. For example, in a study comparing clofibrate with placebo, the 5-year mortality was 15% in good compliers, but 24.6% in poor compliers, regardless of the treatment they received (3).

Over the 1980s and 1990s many studies were published looking at the relationship between hypertension (occasionally stroke) and obstructive sleep apnea (4), usually finding correlations, but rarely controlling adequately for potential confounding variables. Upper-body obesity, smoking, alcohol, exercise levels, and caffeine consumption (patients with obstructive sleep apnea drink

nearly three times more coffee) (5) could all be postulated to correlate with obstructive sleep apnea severity (6) and influence blood pressure. Using the "Framingham" predictors of cardiovascular risk on their own shows that patients with obstructive sleep apnea, on average, are rather unhealthy (10-year risk of coronary heart disease and stroke being ~ 30%, rising to 36% in those with the most severe obstructive sleep apnea) (7).

The most quoted epidemiological study exploring the relationship between obstructive sleep apnea and hypertension comes from the Wisconsin cohort of Young and coworkers (8). The degree of obstructive sleep apnea on an initial sleep study predicted the development of new hypertension during the subsequent four years, with an odds ratio of between two and three, even after controlling for most confounders, such as age, sex, upper-body obesity, and alcohol and cigarette usage. The measured blood pressures, however, were actually lower four years later in the subjects with more severe obstructive sleep apnea, and the incident hypertension had been defined on the basis of new drug treatment for hypertension, not the actual blood pressures. It is conceivable that a positive result on the initial study influenced subsequent screening for hypertension and thus its more frequent diagnosis and treatment in the subgroup with the