Obesity, Obstructive Sleep Apnea, and Cardiovascular Risk

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Obesity is a major risk factor for cardiovascular disease, the number one killer of Americans. It is also a major risk factor for obstructive sleep apnea, which is rising in the US population as the obesity epidemic continues. Obstructive sleep apnea, in turn, has been implicated as a risk factor for hypertension, glucose dysregulation, and cardiovascular disease. Understanding the pathophysiologic links and the common-soil hypothesis for these rapidly growing disorders is of paramount importance for developing strategic therapeutic and preventive plans. This article discusses the associations of obesity, obstructive sleep apnea, and cardiovascular disease, highlighting the pathophysiologic mechanisms, including increased oxidative stress, endothelial dysfunction, and inflammation.

Introduction

Cardiovascular disease (CVD), the major cause of death worldwide, causes more deaths than cancer, influenza, and trauma combined [1•]. It is projected to become the leading cause of disability globally by the year 2020 [2]. Although the incidence of CVD has reached a plateau in developed countries, it has been the leading cause of death in the United States since 1919 and continues to be a crisis of epidemic proportions [1•].

According to American Heart Association estimates, CVD affected 79.4 million Americans and was responsible for 36.3% of all deaths in 2004. The economic burden of CVD in the United States was estimated to be $431.8 billion in 2007. Established risk factors for CVD include hypertension, physical inactivity, smoking, high blood cholesterol, diabetes mellitus, and obesity [3,4]. Obesity is an independent modifiable risk factor for CVD that directly affects cardiac function and increases the risk of coronary heart disease. Moreover, a modest amount of weight loss has been shown to significantly improve diastolic function and positively affect the coronary heart disease risk ratio [5].

The enormity of this problem has led to numerous public health efforts to curb the burden of CVD by identifying risk factors and formulating primary prevention guidelines. Data from the Nurses' Health Study demonstrated that recognition and control of modifiable risk factors such as body weight, diet, inactivity, smoking, and alcohol can reduce the risk of CVD in women by 84% [6]. Moreover, a separate analysis of these data concluded that obesity appears to prevent further decline of the incidence of CVD, reinforcing the role of obesity as a major risk factor [7].

As a global epidemic, obesity has replaced malnutrition and infectious disease as the major contributor to sickness in the world [8]. The National Health and Nutrition Examination Survey demonstrated that the prevalence of overweight or obesity is 65% among US adults [9]. The association between obesity and sleep apnea has been well known for the past three decades, and numerous studies have established the fact that obese patients have compromised respiratory function, leading to well-recognized symptoms of sleep apnea syndrome [10–12]. An independent association also exists between sleep-disordered breathing and hypertension as well as coronary artery disease [13,14].

This article reviews obesity, sleep apnea, and their relation to CVD.

Obesity and Cardiovascular Disease

Obesity is considered to be a group of disorders resulting from a constellation of genetic, psychosocial, and lifestyle factors [15]. Although the adverse effects of obesity have been discussed since Victorian times [16],

it was not until 1933 that Smith and Willius [17] provided the first scientific evidence of obesity as a risk factor for cardiac dysfunction, via postmortem examination of 135 obese subjects

Historically, attempts to define obesity date to 1959, when Metropolitan Life Insurance Company produced tables indicating the range of weights by height and frame size. Since then, the definition of obesity has evolved from using 20% above median body weight to body mass index (BMI) [18,19]. The World Health Organization and National Heart, Lung, and Blood Institute define overweight as a BMI of 25 to 29.9 and obesity as a BMI of 30 or greater [20,21].

The prevalence of obesity in adults (20–74 years of age) in the United States has steadily increased from 11% in men and 16% in women in the 1960s to 32% in men and 34% in women in 2003–2004 [22]. A similar trend has been observed in teenagers, with a rise in prevalence from 9.7% to 17% over four decades (1966–2004) [22]. Data from other countries, including England, Portugal, and China, suggest similar, if not larger, increases in the prevalence of obesity in adults and teenagers, making it a global issue of enormous clinical significance [21,23•,24].

The detrimental effects of obesity arise from its association with many diseases that contribute to CVD, especially dyslipidemia, hypertension, left ventricular hypertrophy, obstructive sleep apnea (OSA), atherosclerosis, and diabetes [25]. The strong clinical association between obesity and atherogenic dyslipidemia is characterized by increased production of very-low-density lipoprotein, high triglycerides, low levels of high-density lipoprotein cholesterol, and enhanced cholesterol synthesis, all leading to increased risk of coronary heart disease [26].

Obesity is a well-known risk factor for hypertension in adults and children. Lurbe et al. [27] demonstrated a positive correlation between systolic blood pressure and BMI among children and adolescents. The Muscatine Study demonstrated a similar relationship between blood pressure and BMI in adults [28]. There is a direct relationship between weight loss and blood pressure: the greater the weight loss, the greater the improvement in blood pressure [29].

Several mechanisms are postulated in the pathogenesis of obesity-related hypertension, including alterations in renal function and structure; adrenergic overactivity due to biochemical, neurochemical, and hormonal mediators; activation of the renin-angiotensin-aldosterone system; and genetic mechanisms. El-Atat et al. [30] provide an in-depth review of these mechanisms.

In obesity, the increased cardiac output and decreased peripheral vascular resistance result in the development of elevated ventricular filling pressures, thereby causing diastolic dysfunction and left ventricular hypertrophy [31]. Strong clinical evidence has established left ventricular hypertrophy as an independent predictor of CVD and sudden death in adults [26]. Moreover, increasing BMI is a risk factor for right ventricular dysfunction, independent of sleep apnea and underlying heart disease [32].

Childhood obesity is a strong predictor of adult obesity as well as CVD morbidity and mortality. Furthermore, CVD mortality in adults is directly related to BMI. Long-term studies have demonstrated that obesity enhances the progression and severity of atherosclerosis [33]. The precise pathophysiologic mechanisms leading to enhanced atherosclerosis in obesity are incompletely understood; however, mechanisms such as inflammation and oxidative stress have been extensively studied and found to be contributory.

The atherosclerotic effects of obesity come from adipose tissue, which is a dynamic organ producing a variety of mediators, including tumor necrosis factor-α, interleukin-6, interleukin-1β, adiponectin, plasminogen activator inhibitor-1, tissue factor, and others [18,34]. Production of interleukin-6 by adipose tissue is increased in obese individuals, resulting in elevated free fatty acid and hepatic C-reactive protein levels. Recent data suggest a direct atherogenic role of C-reactive protein at the endothelial level. Additionally, these mediators target the liver, resulting in increased lipoprotein production, enhancing the well-established cascade of lipoprotein-mediated atherogenesis. Adipose tissue–derived mediators have been shown to disrupt vessel wall homeostasis by altering gene expression in endothelial cells, arterial smooth muscle cells, and monocytes/macrophages [34]. Collectively, these mediators secreted by adipose tissue result in progression of atherosclerosis to plaque rupture, leading to acute coronary syndrome.

Another mechanism by which obesity leads to atherosclerosis is oxidative stress. Strong clinical evidence demonstrates increased levels of oxidative stress in obesity. Obesity is known to be associated with increased asymmetric dimethylarginine concentrations, resulting in endothelial nitric oxide synthase dysfunction and decreased endothelial nitric oxide, thus leading to endothelial dysfunction, which is not only an early marker but a trigger of atherosclerosis [35].

The relationship between obesity and atherosclerosis is further strengthened by several clinical studies establishing a positive linear correlation between the two. The Bogalusa Study reported a direct relationship between BMI and fatty streaks in the coronary arteries in 15- to 24-year-old men, independent of other CVD risk factors [26]. Mahoney et al. [36] reported increasing coronary artery calcification in young adults in direct association with weight in childhood, BMI in young adulthood, and BMI at the time of the study. Furthermore, there is growing evidence linking premature endothelial dysfunction to obesity in children. Studies have shown a significant clinical relationship between development of early fatty streaks, carotid intimal thickening, and fibrous plaques in severely obese children [37•].

Table 1. Cardiovascular diseases associated with obstructive sleep apnea

Hypertension
Atrial fibrillation
Bradyarrhythmia
Stroke
Heart failure
Ischemic heart disease

In addition to being an independent risk factor, obesity is a major contributor to other pathological states, such as metabolic syndrome, insulin resistance, diabetes, and OSA, all of which are independent cardiovascular risk factors.

New mediators such as resistin and leptin recently have surfaced as contributors to obesity-associated atherosclerosis. Further research on these and previously known mechanisms is required to help us understand the pathophysiology of obesity-associated endothelial dysfunction.

Obstructive Sleep Apnea and Cardiovascular Disease

The word "apnea" is defined as cessation of breathing. In the field of medicine, it has been arbitrarily defined as a cessation lasting more than 10 seconds. In 1966, Gastaut et al. [38] identified the first case of OSA—based on polygraphic study—that led to the differentiation of apnea into three types: obstructive, central, and mixed. Obstructive apnea is the result of cessation of airflow in the presence of persistent chest wall movement [38].

In a widely cited study, Young et al. [39] reported in 1993 that about 12 million men and 6 million women are affected by OSA in North America. However, the accuracy and applicability of these statistics is debatable. Primarily, the prevalence of obesity, a principal risk factor for OSA, has increased markedly since the study was published. Moreover, the authors applied the Epworth Sleepiness Score (ESS) as an assessment tool, but the Sleep Heart Health Study showed that the apnea-hypopnea index (AHI), which is used to diagnose and stratify OSA, does not correlate well with the ESS [40]. It is now established that limitation based on the ESS is inappropriate, because patients with an ESS below 10 may have other important symptoms, such as nonrestorative sleep and fatigue, that warrant further investigation by polysomnography. Furthermore, greater AHI values would be expected if Young et al. [39] repeated their study today using nasal pressure technology, which has largely replaced and is more sensitive than a thermistor.

It is difficult to estimate the current prevalence of OSA because differences in reference standards, dissimilarities in equipment, and other factors bring into question the validity of epidemiologic data. This results in many undiagnosed cases of OSA [41,42].

Considerable evidence has emerged over the past two decades implicating OSA as a comorbid condition in a number of CVDs (Table 1). Several mechanisms are implicated in the pathogenesis of OSA-mediated CVD progression, including oxidative stress, endothelial dysfunction, inflammatory response, adrenergic activity, metabolic derangements, production of vasoactive substances, and changes in intrathoracic pressure (Fig. 1).

Although early data were inconsistent, recent studies have documented a strong association between OSA and increased markers of oxidative stress [43]. In patients with OSA, the increased frequency of nocturnal hypoxemia and reperfusion leads to increased production of free radicals, with consequent injury to cardiovascular tissue [44]. Endothelial dysfunction, a direct consequence of free radical–mediated injury [34], is also enhanced in OSA. Although several studies [45–47] demonstrate that this dysfunction is reversed by use of nasal continuous positive airway pressure (CPAP), the overall data remain inconclusive [48]. Similarly, inflammatory and vasoactive mediators are implicated in the pathophysiology of OSA-mediated CVD progression, as evidenced by increased C-reactive protein, adhesion molecules, cytokines, and endothelin levels in patients with OSA [49–51].

In patients with OSA, episodes of sleep apnea result in hypoxemia and hypercapnia, which synergistically lead to increased sympathetic nerve flow, resulting in development of heart and blood vessel injury [52]. Additionally, patients with OSA have consistently shown metabolic dysregulations characterized by increased leptin levels and insulin resistance, leading to CVD progression [53,54]. Another underlying mechanism is the negative pressure generated during sleep apnea that leads to considerable pressure gradient and resultant increased cardiac wall strain, which may be a cardinal feature in the development of atrial fibrillation [55].

Several studies have demonstrated these OSA-mediated mechanisms to be the key factors in the development of CVDs such as hypertension, arrhythmias, atrial fibrillation, stroke, heart failure, and ischemic heart disease (Table 1). Furthermore, treatment of OSA has been shown to improve these underlying cardiovascular conditions [56].

Long-term prospective studies have shown OSA to be independently linked with a threefold increase in the incidence of hypertension as compared with healthy subjects [57]. Moreover, treatment of OSA consistently has resulted in a significant decrease in blood pressure [58]. The significance of OSA in the context of hypertension is highlighted by its enlistment as the first treatable cause of hypertension by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

The prevalence of OSA is remarkably high in patients with atrial fibrillation. The risk arises from its association

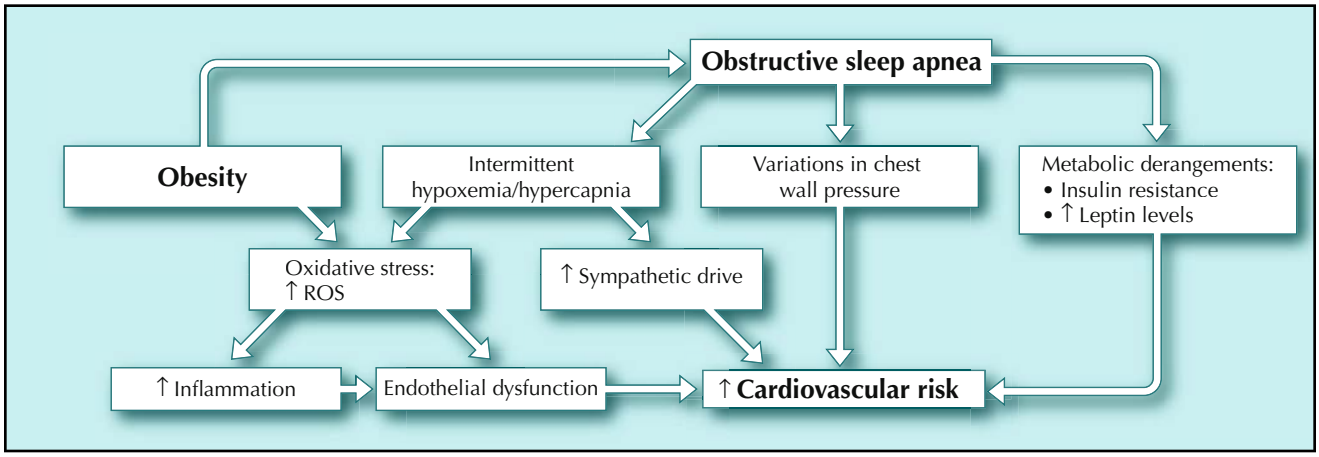

Figure 1. Obstructive sleep apnea and cardiovascular risk mediators. ROS—reactive oxygen species.

with negative intrathoracic pressure, hypoxemia, fluctuations in blood pressure, and sympathetic activation. This may also account for the significantly higher rate of recurrent atrial fibrillation after cardioversion in patients with untreated OSA. Furthermore, Gami et al. [59] found that the presence of OSA predicts the development of atrial fibrillation after coronary artery bypass graft surgery. OSA also has been linked to arrhythmias, specifically bradyarrhythmias. The underlying mechanism is the activation of the peripheral sympathetic system sparing the brain and the heart, leading to coronary and cerebral vasodilation along with increased vagal tone causing bradycardia. The relationship between OSA and bradyarrhythmia is strong, but the link between OSA and ventricular arrhythmia remains unclear because of a lack of well-designed studies.

The 5-year mortality in patients with established coronary artery disease and OSA is considerably higher than in patients with coronary artery disease without OSA. Evidence also suggests that angina is more frequent in patients with severe OSA [60]. Additionally, 14% to 65% of patients with OSA are found to have coronary artery disease. An independent association exists between OSA and development of myocardial ischemia in middle-aged men that is reversed on treatment with CPAP [61•]. Furthermore, coronary artery calcium score, a strong predictor for occlusive coronary artery disease, is directly proportional to the severity of OSA in patients with end-stage renal disease, enhancing the association between OSA and coronary artery disease [62]. Although OSA has not been clearly implicated as an independent risk factor for stroke, OSA has an increased prevalence in patients with stroke and is a predictor of adverse outcomes [63]. Even though OSA only accounts for about 10% of sleep-disordered breathing in patients with heart failure, its impact is remarkable as suggested by studies demonstrating improvement in ejection fraction with CPAP [64].

Although epidemiologic conundrums exist that must be solved to understand the relationship between OSA and CVD, it is established that treatment with CPAP, at least in smaller trials, results in reversal or stabilization of the cardiovascular risk. It is hoped that current larger trials specifically targeting cardiac outcomes will soon lead to an unambiguous picture.

Conclusions

As the obesity epidemic continues to rise, the incidence and prevalence of OSA is also increasing. Accumulating evidence implicates OSA in the pathogenesis of hypertension, stroke, atrial fibrillation, heart failure, and CVD. Increased oxidative stress appears to play a major role in the pathogenesis of OSA together with increased inflammation, adrenergic activity, endothelial dysfunction, and insulin resistance. Treatment of sleep apnea and control of obesity appears to be the prudent strategy in this growing patient population. Further research is needed in sleep apnea to assess the effect of various interventions on the incidence of associated morbidities, particularly cardiovascular events.

Disclosures

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