

Carotid Intima-Medial Thickness in Diagnosis and Prognosis of Atherosclerotic Risk in Obstructive Sleep Apnea Patients

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Abstract

Obstructive Sleep Apnea (OSA) is associated with accelerated atherosclerosis, cardiovascular and cerebrovascular disease. Carotid artery Intima-Medial Thickness (CIMT) measurement has recently evolved as an important non-invasive diagnostic tool in atherosclerosis. In the current review, we have analysed the association of increased CIMT values with OSA, correlation of increased CIMT with the severity of OSA and the role of CIMT measurement as a prognostic marker in monitoring disease progression and response to therapy. Although some studies in the last few years have tried to address this issue, more randomised controlled trials recruiting larger number of patients are required to define its exact role in regular clinical practice.

Keywords: Carotid Intima-Medial Thickness; Obstructive Sleep Apnea; Atherosclerosis

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Obstructive Sleep Apnea (OSA) and Atherosclerosis

Obstructive Sleep Apnea (OSA) and obstructive sleep hypopnoea are sleep related breathing disorders characterised by repeated episodes of upper airway obstruction during sleep. It has been estimated that 4% of middle-aged men and 2% of women have clinically significant symptomatic OSA [1, 2]. The recurrent episodes of upper airway obstruction result in oxyhemoglobin desaturation, sleep fragmentation, impaired cognition and daytime sleepiness [1, 3]. Physiological consequences of OSA include hypoxemia, hypercapnia, systemic and pulmonary vasoconstriction and secondary polycythemia. OSA has also been associated with the sympathetic nervous system activation, systemic inflammation, endothelial dysfunction and accelerated atherosclerosis [4, 5]. These physiologic and biochemical perturbations contribute to an increased incidence of cardiovascular and cerebrovascular disease in these patient population. There has been recent increase in research in the area addressing association of atherosclerosis in OSA patients.

Carotid Intima-Medial Thickness (CIMT) in Atherosclerosis

Calculation of Carotid Intima-Medial Thickness (CIMT) has recently emerged as a simple non-invasive marker of atherosclerosis. It helps to quantify the extent of subclinical disease and monitor change over time. The B-mode ultrasound is used to study the 'double echo' pattern which corresponds to

the combined width of the carotid artery intima and media. The carotid artery runs superficially and courses parallel to the surface of the neck, thereby allowing easy imaging. In ultrasound, the carotid artery may be seen in three separate segments, each approximately 1 cm in length. The most proximal is the 1 cm straight segment of carotid artery immediately prior to the bifurcation (Common Carotid Artery - CCA). Distally, the near and far wall of the CCA diverges as the artery divides into internal and external branches. The widening at the bifurcation extends over approximately 1cm and is called carotid bulb. The final segment is the proximal 1 cm of the Internal Carotid Artery (ICA). The easiest segment to examine by ultrasound is the CCA, making it an attractive target of study. CIMT measurements are devoid of radiation exposure and uses readily available, relatively inexpensive equipment. Several studies have shown a positive correlation between CIMT and future risk of cardiovascular and cerebrovascular diseases [6-9]. In 2003 the 34th Bethesda Conference observed that patients at intermediate risk for cardiovascular event may be considered for further risk stratification by non-invasive atherosclerosis imaging tests and Coronary Artery Calcium (CAC) scoring to assess atherosclerotic burden [10]. The Task Force for the Management of Arterial Hypertension of the

European Society of Hypertension and of the European Society of Cardiology recommended carotid ultrasound in hypertensive patients to provide better risk stratification and to assess vascular hypertrophy and subclinical atherosclerosis [11].

CIMT in OSA patients: Association and Severity

OSA patients are at increased risk of cardiovascular morbidity and mortality, mostly involving systemic hypertension, coronary heart disease, stroke, and heart failure. Repeated hypoxemia followed by re-oxygenation generates oxidative stress which can promote degenerative changes of the arterial walls thereby accelerating the progression of atherosclerosis. The plasma levels of soluble cell adhesion molecules, Vascular Endothelial Growth Factor (VEGF), and fibrinogen are increased in OSA patients. Nasal continuous positive airway pressure therapy has been effective in attenuating the rise of various biomarkers in OSA patients [12-16]. CIMT has been used to assess the underlying atherosclerosis in patients with OSA. Studies have tried to find an association between the severity of OSA and carotid intima-medial thickness. Other studies have tried to focus on oxidative stress and elevated systemic inflammatory markers and their relation to the severity of OSA (Table 1).

Table 1: CIMT in OSA patients vs non-OSA patients

Authors	Study design and Number of patients	Primary outcome	Results
Suzuki et al. (2004)	167 OSA patients	CIMT relation to OSA severity (AHI t90 & mean nadir O2 saturation)	CIMT positively correlated to hypoxemic events
Fox et al. (2014)	37 OSA patients, 105 controls	OSA correlation to subclinical atherosclerosis	OSA independent predictor of atherosclerosis
Silvestrini et al. (2002)	23 severe OSA patients, 23 controls	OSA relation to carotid atherosclerosis	CIMT increased in severe OSA
Nadeem et al. (2013)	Meta-analysis of 16 studies	OSA relation to atherosclerosis	CIMT increased in OSA
Ciccone et al. (2014)	80 OSA patients, 40 controls	CIMT relation to inflammatory markers of atherosclerosis	Positive correlation between CIMT & hsCRP, IL-6, TNF- α and PTX-3

Prejbisz et al. (2014)	121 patients (with/ without OSA)	OSA relation to CVS dysfunction markers	Mod-severe OSA had higher CIMENT ,diastolic dysfunction & wall thickness
Hui et al. (2012)	50 patients with OSA	Effect of CPAP therapy on CIMENT	CPAP therapy associated with decrease in CIMENT in OSA patients

Suzuki et al. studied 167 patients with OSA for underlying atherosclerosis as measured by CIMENT. The study revealed that increased CIMENT was strongly associated with the severity of OSA (Apnoea-Hypopnoea Index, Total time with SpO₂ < 90% {T90}, and mean nadir oxygen saturation). On further analysis the authors found that hypoxemia (T90 and mean nadir oxygen saturation) was more important than frequency of obstructive events as an independent contributor to the severity of carotid artery atherosclerosis [17]. Fox and co-workers included patients aged 40 years or older being investigated for suspected OSA and devoid of established cardiovascular disease or its risk factors (smoking, hypertension, diabetes, hyperlipidemia). CIMENT of OSA patients were compared with controls without known cardiovascular disease or OSA. CIMENT values in OSA patients were significantly higher compared to controls (0.77 mm versus 0.68 mm, p = 0.03). On further analysis it was found that severe OSA patients had much higher CIMENT values relative to controls (0.83mm vs. 0.71 mm) than the CIMENT values of mild-moderate OSA patients as compared to controls (0.71 vs. 0.67 mm). The authors opined that OSA was an independent risk factor for the development of cardiovascular disease [18]. Silvestrini et al conducted a study of twenty-three male patients with severe OSA (respiratory disturbance index > 30). The subjects were compared to 23 control patients matched for age and co-morbidities. CIMENT was measured as a marker of atherosclerosis. Patients with obstructive sleep apnoea syndrome had significantly higher (P<0.0001) CIMENT values than control subjects (1.429±0.34 mm versus 0.976±0.17 mm, P<0.0001) [19].

Prejbisz and co-workers investigated the association between OSA and systemic markers of cardiovascular dysfunction in middle aged patients with essential hypertension. The markers studied were left ventricular structure and function,

CIMENT and urinary albumin excretion. The authors observed that patients with moderate and severe OSA had higher CIMENT (0.74±0.16 vs. 0.60±0.15 mm; P=0.001), urinary albumin excretion, relative wall thickness and a higher degree of diastolic dysfunction as compared with the patients without OSA [20]. A meta-analysis by Nadeem et al. studied the association between OSA and underlying atherosclerosis as measured by CIMENT. While the studies included were low in their quality of evidence, the authors observed that patients with OSA had a higher CIMENT than controls. CIMENT values also increased with the severity of OSA [21]. In another study, correlation between the inflammatory markers of atherosclerosis and Carotid Intima-Medial Thickness (CIMENT) was investigated by Ciccone et al. Serum concentrations of High-sensitive C-Reactive Protein (hsCRP), Interleukin (IL-6), Tumor Necrosis Factor (TNF-α) and Pentraxin (PTX-3) were measured as inflammatory markers of atherosclerosis. Moderate-severe OSA patients had significantly increased CIMENT than mild OSA (p < 0.01) and controls (p < 0.01). hsCRP, IL-6, TNF-α, and PTX-3 in patients with OSA were significantly higher than controls (p < 0.01). Notably in the study, CIMENT in OSA patients had statistically significant positive correlation with serum levels of inflammatory markers [22].

CIMENT in OSA patients: Prognostic significance

CIMENT has also been used to assess the benefits of Continuous Positive Airway Pressure therapy (CPAP) in newly diagnosed patients with OSA. Fifty patients with newly diagnosed OSA were managed either Conservatively (CT) or by CPAP therapy. CPAP group used an average of 4.6 and 4.7 hours/night of CPAP therapy over 6 months and 1 year respectively. CIMENT was measured at baseline, 6 months and at 12 months during follow up. The patients adhering to CPAP therapy showed a significant decrease in CIMENT values during

follow up compared to controls. The changes in mean CIMT between baseline and 6 months were -36.6 (10) versus 9.8 (10) μm for the CPAP and CT group respectively ($p = 0.004$). The changes in mean CIMT between baseline and 12 months were -53 (20) versus 17.7 (10) μm for the CPAP and the CT group respectively ($p = 0.002$) [23]. Tan and co-workers studied the predictors of increased CIMT in OSA patients. Age, fasting plasma glucose, low-density lipoprotein cholesterol, and high-sensitivity C-reactive protein were significantly associated with higher CIMT [24]. The decrease in CIMT over long term follow up has been used for evaluating hypolipidemic drugs, glucose lowering agents, antioxidants, and hormonal replacement therapy in selected subgroups of population without OSA [25-28].

Conclusion

In conclusion, ultrasonographic evaluation of CIMT is a simple, noninvasive, reproducible bedside measure of underlying atherosclerosis. It is an exciting new study tool that can prove to be beneficial in special population subgroups like those with OSA who are predisposed to generalised atherosclerosis. CIMT measurements may be used to detect early stages of atherosclerosis in such patients. This may promote change in lifestyle measures and therapy to halt its progression. Interestingly, the test has shown positive correlation with the severity of OSA and inflammatory molecular markers of atherosclerosis. Furthermore, the test deserves further consideration in OSA patients because it allows objective evaluation of current status of atherosclerosis, risk stratification, monitoring progression of disease and reversal of the disease process with effective therapy.

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