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CLINICAL REVIEW

Carotid IMT Testing: Potential Roles in Prevention and Treatment of Cardiovascular Disease

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Atherosclerotic cardiovascular disease (ASCVD) is not adequately predicted solely by clinical risk factors. Carotid Intima-Media Thickness (CIMT) testing is well-established and if abnormal is an independent CVD risk factor. Many studies reported increased CIMT can identify subclinical atherosclerosis, and have advocated use in conjunction with clinical risk factors as a sensitive tool to predict risk of CVD.

Introduction

Atherosclerosis is a disease of the arteries characterized by development of atherosclerotic plaque throughout and surrounding the arterial walls. ASCVD is a systemic condition, leading to a large group of clinical conditions including myocardial infarction (MI), cerebrovascular disease including ischemic stroke, peripheral artery disease, and chronic kidney disease (CKD).[1] ASCVD is the leading cause of death worldwide.[2] Optimal medical management of ASCVD reduces the risks of cardiovascular disease in asymptomatic patients. Recognition of patients at increased risk allows improved counseling regarding lifestyle factors such as diet, exercise, and smoking cessation and improved use of pharmacotherapies directed at blood pressure and cholesterol lowering. Current guidelines advocate use of risk assessment tools to identify patients with increased risk.[3] However, the sensitivity and specificity of these tools are variable across the total populations.[4] Specifically, some patients at intermediate or high risk may not be identified by these tools and do not receive appropriate treatment. Alternatively, patients with overestimation of cardiovascular risk may receive unnecessary treatment, without improvement in cardiovascular morbidity or mortality.

More direct evaluation of atherosclerotic burden may improve the discrimination of ASCVD risk. CIMT is a noninvasive, relatively low cost technique that is used to detect early ASCVD, allowing for improved risk stratification and medical therapy.

CIMT Testing

CIMT is an assessment of the combined thickness of intima and media layers of the carotid artery, most commonly using by B-mode (bright-mode) ultrasound. This technique measures the thickness of the inner two layers of the carotid artery, the intima and media. Thickening of these layers can identify ASCVD in early, asymptomatic stages by directly visualizing the vessel wall.[5] Visualization of the carotid arteries and carotid bulb also identifies presence of plaques and stenosis. There is variability in CIMT thickness along the carotid arteries, so it is important to follow a standardized sampling protocol when obtaining normative data.

Current Mode of Assessing CV Risk, Its Accuracy and Its Generalizability

Currently, ASCVD risk assessment uses the ASCVD calculator developed by the American Heart Association (AHA) and American College of Cardiology (ACC). Traditional risk factors of age, gender, race, blood pressure, anti-hypertensive treatment, lipid profile, statin treatment, and smoking status are entered to estimate 10-year cardiovascular risk.[6] In a longitudinal study evaluating the accuracy of the ASCVD risks score, 27,542 women aged 45 to 79 years without history of ASCVD events were followed for a median of 10 years. The observed rate of ASCVD events was 2.2%, significantly lower than the 3.6% event rate predicted by the ACC/AHA pooled cohort equation. Overestimation of ASCVD event rates occurred with different risk categories. The ratio of predicted to observed events was 1.90 for those with predicted risk of less than 7.5%, and 1.40 among those with risk of greater than or equal to 7.5%.[7]

Another large study with 307,591 participants evaluated the accuracy of the ASCVD Pooled Cohort Risk Equation within a large multi-ethnic clinical population. Participants included Black, Asian/Pacific Islander and Hispanic patients 40 to 75 years old. The ASCVD risk score overestimated the true risk in this group. There was a five year event rate of 0.20% for those with predicted risk of <2.50%, 0.65% for a predicted risk from 2.50% to <3.75%, 0.90% for a predicted risk from 3.75% to <5.00%, and 1.85% for a predicted risk of 5.00% or greater. Fewer events occurred in each predicted risk category (i.e. sex, race/ethnicity, and socioeconomic status) over the 5-year follow-up period, with similarly poor calibration in both men and women.[8]

CIMT to Assess ASCVD Risk

Several large cohort studies report the association between CIMT measurements and cardiovascular events. An American

study with 13,145 subjects evaluated CHD (coronary heart disease) risk using a number of models. These included TRF (traditional risk factors) only, TRF plus CIMT, and TRF plus CIMT and presence of plaque. The receiver-operating characteristic curve showed a small but statistically significant increased area under the curve (AUC) using the TRF plus CIMT model of 0.755) compared to the TRF-only model, 0.742 suggesting that CIMT improved the accuracy of ASCVD risk independent of TRF alone.[9]

Nambi et al explored the relationship between IMT in carotid arteries and the extent of CAD in the ARIC study. Patients with increasing CAD involving 1, 2, or 3 vessels showed a significant correlation between IMT and advancing CAD. Patients with IMT greater than 1.15 mm had a 94% probability of CAD, with a sensitivity of 65% and a specificity of 80% in high risk CAD.[10] The sensitivity and specificity are not ideal with risks of both false positive and false negative results.

A European study of 3,703 subjects with at least three vascular risk factors without prior clinical ASCVD events were followed for a median of 36.2 months. They reported CIMT was a risk factor for ASCVD independent of vascular risk factors. Additionally, reclassification analysis showed that the use of CIMT along with common carotid artery diameter allowed for improved risk stratification.[11] However, further studies are needed to determine if CIMT measurements can be used to clarify the risk in intermediate risk patients.

Demographic Implications of IMT Testing

Demographics remain important risk factors for ASCVD and need to be considered when using CIMT to assess ASCVD risk.[12] In a study of 939 children, Black African-Caribbean children were found to have an increased CIMT compared to ethnic white Europeans after correction for vascular risk factors. These differences extended to South Asian, other Asian as well as other ethnic groups. Zhao et al demonstrated that in patients with diabetes, male gender and age were associated with increased CIMT.[13] These studies demonstrate the need to include normative data for CIMT based on age and race.

Limitations of IMT testing

The value of CIMT testing has been supported in many large, research based studies, though many studies express concerns and limitations as well.

Accuracy of CIMT measurement is dependent on the location of the assessment. For example, CIMT performed on the common carotid artery (CCA) yields better reproducibility than when performed on internal carotid artery (ICA) or the carotid bifurcation. This is because CCA is more accessible, aligned parallel and closer to the skin surface.[5] Furthermore, variability may exist in assessing the near and far wall of the carotid artery. More study is needed to create a consistent, universal approach for CIMT testing in order to minimize variability, which currently limits generalizability of research findings.

In addition to ASCVD, CIMT may increase due to smooth muscle cell hyperplasia and fibrocellular hypertrophy. Further study is needed to determine if these causes can be differentiated from thickening associated with ASCVD.

Using CIMT as a Surrogate Endpoint in CVD trials

Several studies have looked at the effects of drug treatment on longitudinal changes in CIMT. In the ENHANCE trial involving patients with familial hypercholesterolemia, the combination of ezetimibe 10 mg daily and simvastatin 80 mg daily did not enhance the regression of IMT compared to simvastatin alone, raising doubts about ezetimibe effectiveness.[14] However, a systematic review of the use of ezetimibe, reported modest benefit in cardiovascular events without improvement in mortality.[15] In the SATURN study, patients with coronary artery disease were randomized to maximal dose of rosuvastatin or atorvastatin. After 104 weeks of treatment the LDL levels were lower (62.6 vs. 70.2 mg per dl) and HDL levels were minimally higher (50.4 vs. 48. mg/dl) with the use of rosuvastatin as compared to atorvastatin. There was equal regression of IMT in both arms, raising the question as to whether CIMT is adequate to detect small but meaningful differences in atherosclerotic disease.[16]

In a meta-analysis of randomized-controlled trials using CIMT as an endpoint, a decrease in the progression of CIMT of 0.01 mm per year was associated with an odds ratio for myocardial infarction of 0.82 (95% CI, 0.69 to 0.96; P = .018). However, there was no association of rate of change of CIMT and myocardial infarction in the studies investigating the use of statin therapy.[17] Caution is needed when interpreting studies using changes in CIMT as a primary endpoint.

CIMT and Plaque Assessment Protocols

Various CIMT protocols are used to assess ASCVD. Previous studies have measured IMT of the distal wall only of the right or left CCA or the distal wall of the ICA and CCA of either the left sides, right sides, or both sides. Alternatively, some have utilized the distal wall of the right and left sides of the ICA, ECA (external carotid artery) and CCA as well as the common carotid, bulb and internal carotid artery at various angles. There are several software packages for IMT measurement ranging from caliper IMT measurement to completely automated IMT measurement of still images or a cine loop through an entire cardiac cycle. Considering these alternative methods for measuring IMT, plaque measurement seems to be a relatively quick and straightforward method of atherosclerosis detection. When interpreting results from a CIMT study, results should include the details of the measurement protocol and results should be expressed relative to the norms from that particular study. Because both CIMT and presence of plaque provide incremental prognostic risk, ideally both should be reported.[18]

Discussion

ASCVD is a leading cause of morbidity and mortality in the United States and worldwide. Aggressive risk factor modification is important in reducing the ASCVD. Lifestyle modifications including a heart healthy diet, adequate exercise, smoking cessation should be encouraged in all patients. However, risk assessment is important in targeting pharmacotherapy to patients that will likely benefit and in whom the benefit outweighs the risks of treatment. CIMT can be used to refine ASCVD risk assessment, as an increased CIMT is an independent risk factor for ASCVD. CIMT has several benefits – it can be performed in the ambulatory setting, and compared to CT coronary calcium assessment, is lower cost and without radiation. Utilizing CIMT in conjunction with traditional risk factors can detect early atherosclerosis and has the potential to define the status of cardiovascular events and predict the risk of future cardiovascular events with minimal risk and high efficacy. Further data from randomized trials are needed to determine if CIMT provides useful information relative to ASCVD in improving our accuracy in CV risk detection and whether using information gained from CIMT testing leads to improved cardiovascular outcomes. The potential promising clinical uses make ultrasound CIMT measurement an intriguing diagnostic tool, and further research may confirm CIMT testing's role in improving cardiovascular outcomes.[11,19]

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