Correlation Between Carotid Intimal/Medial Thickness and Atherosclerosis
A Point of View From Pathology
Aloke V. Finn, Frank D. Kolodgie, Renu Virmani

Abstract—A widely adopted surrogate for predicting rates of cardiovascular events involves measure of carotid intimal-medial thickness (CIMT) by B mode ultrasound, a technique available since the mid 1980s. The value of this modality remains in its ability to noninvasively assess cardiovascular risk beyond traditional factors identified by the Framingham risk score, and it is among the few available techniques for monitoring the effectiveness of pharmacotherapy on plaques. There are, however, existing limitations to this methodology. Perhaps the most important distinction is that IM thickness measurements are generally acquired in the common carotid artery, whereas advanced atherosclerotic disease occurs predominantly downstream in the internal carotid. Moreover, primary contributors to IM thickening are age and hypertension, which do not necessarily reflect the atherosclerotic process. Initiation of disease-related plaques begins as what is referred to as pathological intimal thickening; lesions characterized by the formation of lipid pools in the absence of a necrotic core. The eventual development of a necrotic core, however, is considered a key indicator of significant plaque advancement and recognized feature of lesion vulnerability. Necrotic cores are thought to arise from macrophage infiltration of lipid pools followed by secondary necrosis where defective clearance of debris, tissue disruption proteases, and intraplaque hemorrhage, likely contribute to its enlargement. Therefore, one of the primary limitations to CIMT is its inability to distinguish lesions with a necrotic core. Moreover, in most cases measures of plaque area or volume are generally considered better predictors of an inflammatory process consistent with atherosclerotic disease rather than intimal medial thickness. (Arterioscler Thromb Vasc Biol. 2009;29:00-00.)

Key Words: atherosclerosis ■ intimal medial thickness ■ pathology ■ imaging

Traditional risk factors for atherosclerosis are not always reliable predictors of major cardiovascular events (MACE). Noninvasive modalities with the capability of correlating native coronary artery disease and cardiac risk have long been sought for diagnostic use in clinical trials. One widely adopted surrogate for predicting rates of cardiovascular events involves measure of carotid intimal-medial thickness (CIMT) by B mode ultrasound, a technique evaluated and validated in the mid 1980s. Recent clinical trials have relied on CIMT as a diagnostic algorithm for monitoring the effectiveness of pharmacotherapy such as statins to reduce vascular disease progression and cardiovascular risk. The accuracy of CIMT, however, is mired by the fact that age-related thickening of intimal and medial layers of common carotid arteries also occurs in the absence of overt atherosclerosis as shown in humans and animal models.1,2 Important is the fact that pathological changes of medial hypertrophy or intimal thickening in the absence of atherosclerosis are not synonymous with atherosclerosis. Because CIMT and atherosclerosis share common underlying mechanisms for both disease initiation and progression, from a pathologists’ perspective, CIMT may better represent an indicator for overall risk of coronary heart disease as reported in numerous trials, rather than an accurate measure of atherosclerosis per se.

There are recognized differences in the distribution of atherosclerosis relative to the noninflamed smooth muscle-rich plaques recognized as intimal thickening. Common to areas of low shear, carotid atherosclerosis predominantly occurs in the bulb region, which is not easily visible with B mode ultrasound. In contrast, intimal thickening as a response to aging and high shear, as in hypertension, develops in more proximal segments within the common carotid artery near the area of the bifurcation. Dictated by location within the common carotid, intimal thickening is therefore more easily identified by B mode ultrasound as CIMT than atherosclerosis.3

Carotid Plaque Morphology
Morphologically, there are many similarities between atherosclerosis development between carotid and coronary arteries although recognized differences merit discussion. The early
variable and mostly confined to the luminal aspect of the first manifestation of atherosclerosis. Unique to these depending on their location. Based on observational data, intimal xanthomas are generally considered nonprogressive lesions with a tendency to regress.

From our experience, pathological intimal thickening is the first manifestation of atherosclerosis. Unique to these lesions is the presence of lipid pools located in the deeper intima in areas rich in proteoglycan with rare inflammatory cells. Most investigators however, do not consider adaptive intimal thickening as representative of an atherosclerotic disease process. The first recognized lesion of atherosclerosis is the fatty streak or by our classification, the intimal xanthoma, which grossly appears as nonraised yellowish streaks containing intracellular and extracellular lipids and xanthanoma, which contains hemosiderin and collagen matrix with rare inflammatory cells and proteoglycan/collagen matrix with rare inflammatory cells and macrophages (MACs).

The extent of macrophage infiltration in PIT is identified as adaptive intimal thickening, a flow-dependent process, commonly develops early after birth in all vascular beds. These lesions are composed of smooth muscle cells and proteoglycan/collagen matrix with rare inflammatory cells. Most investigators however, do not consider adaptive intimal thickening as representative of an atherosclerotic disease process. The first recognized lesion of atherosclerosis is the fatty streak or by our classification, the intimal xanthoma, which grossly appears as nonraised yellowish streaks containing intracellular and extracellular lipids and foam cells of macrophage and/or smooth muscle cell origin. Based on observational data, intimal xanthomas are generally considered nonprogressive lesions with a tendency to regress depending on their location.

From our experience, pathological intimal thickening is the first manifestation of atherosclerosis. Unique to these lesions is the presence of lipid pools located in the deeper intima in areas rich in proteoglycan with a generalized loss of smooth muscle cells and speckled calcification (Figure). The loss of SMCs within lipid pools is attributed to apoptotic cell death, which is more easily recognized ultrastructurally where a prominent basal lamina around clusters of vesicles is consistent with a smooth muscle cell origin. The extent of macrophage infiltration in PIT is variable and mostly confined to the luminal aspect of the plaque outside the lipid pool. The development of advanced atheromatous plaques with necrotic cores is believed to occur as a result of the invasion of lipid pools by macrophages (Figure). This pivotal step is likely aided by the release of activated proteolytic enzymes such as matrix metalloproteinases (MMPs) and other factors, which degrade the surrounding tissue and together with the apoptotic death of macrophages contribute to formation of the necrotic core. Manifestations of necrotic core expansion and thinning of the fibrous cap are considered critical for the progression toward plaque rupture and acute thrombosis. Therefore, recognition of the necrotic core by whatever modality (ie, B-mode ultrasound, multidetector CT (MDCT), or MRI) may be the best identifier of rupture-prone vulnerable plaques.

Evidence in support of increased necrotic core size and lesion vulnerability comes from both clinical and pathological studies. In a series of 154 patients with carotid disease and follow-up of greater than 1 year, baseline necrotic core size detected by MRI was a significant predictor of subsequent cerebrovascular events. Similarly, in a series of 375 atherosclerotic plaques studied at autopsy, necrotic core size was a significant predictor for the likelihood of plaque rupture (Virmani et al, American Heart Association, 2006). Further validation of these findings, however, is clearly needed in larger population-based patient studies. In addition of its value of predictive risk, the reliable detection of an enlarging necrotic core may identify a class of patients who stand to benefit from therapies targeted at plaque stabilization.

In most large longitudinal studies involving individuals older than 45 years of age, there is a good correlation of CIMT or intimal carotid (IMT) measurement with future cardiac risk. After adjusting for age and sex, however, it is really the last versus first quintile where the relative risk for myocardial infarction and stroke is increased (odds ratio 3.87; 95% confidence interval, 2.72 to 5.51). Previous reports suggest that carotid stenosis only weakly correlates with total risk factors (R²=0.13), whereas a greater correlation is seen for plaque area and volume (R²=0.52). Most impressive is the finding that the adjusted risk of a coronary event is increased by a factor of 7.73 among participants with coronary calcium scores between 101 and 300 relative to participants with no coronary calcium and by a factor of 9.67 among participants with coronary calcium scores above 300 (P<0.001 for both comparisons). Early calcification in coronary arteries occurs in response to the death of smooth muscle cells or macrophages where the extent of calcification (mostly calcified matrix) increases and as plaques advance, particularly in stable lesions. Similarly, calcification in carotid plaques is less frequently correlated with plaque burden, although there is greater calcification in asymptomatic than symptomatic patients.

To our knowledge, only a limited number of published studies have correlated the relationship of internal carotid artery calcification and ischemic cerebrovascular disease. Assessment of intracranial internal carotid artery (ICA) calcification has revealed a good correlation with age, and one
such study reports prevalence of calcification in 36% of
patients with a mean age of 51 years\textsuperscript{14} compared to 67% with
a mean age of 63 years in another study.\textsuperscript{15} Vascular calcifi-
cation is generally more extensive with advancing age,
chronic renal failure, diabetes, and inflammation. Moreover,
calcification of the carotid artery has been correlated with
stable plaque, with plaque calcification of \textgreater 45% of the total
volume in patients with stenosis indicating plaque stability
and absence of symptoms; thus there remains the potential to
noninvasively risk stratify patients with asymptomatic
stenosis.

In general terms, the use of carotid IMT to predict future
events in coronary arteries may be less meaningful consid-
ering greater than 75% of thrombi in the carotid are caused by
rupture with fewer by nodular calcification and rare erosions,
whereas on the contrary 30% to 35% of coronary thrombi are
caused by erosion.\textsuperscript{7} Therefore, relying solely on carotid
plaque indices to predict future coronary events caused by
erosion may not constitute a reliable approach.

### Technical Issues Related to CIMT Measurements

Analysis of CIMT by B-Mode ultrasound is typically
achieved by measuring the common carotid artery (CCA)
rather than bulb, bifurcation, or the internal carotid artery.\textsuperscript{16}
This strategy is supported by its easier accessibility, perpen-
dicular location relative to the transducer beam, and better
reproducibility.\textsuperscript{17,18} Although some investigators have sug-
gested averaging multiple segments to include the common
carotid, bulb, and internal carotid artery, this is not routinely
done, and there remains no clear consensus on which CIMT
measurement constitutes the best measurement of atheroscle-
osis or vascular risk. Consensus recommendations do however
define plaque as a focal structure of at least 0.5 mm or 50%
of the surrounding IMT value, which encroaches into the
arterial lumen, or demonstrates a thickness of \textgreater 1.5-mm as
measured from the media-adventitia interface to the intima-
lumen interface.\textsuperscript{19}

The approach of CIMT has several drawbacks with respect to
the anatomic distribution of carotid atherosclerosis. Pers-
on et al demonstrated that although common carotid artery
(CCA) IMT is higher in subjects with internal carotid artery
plaque rather than those without, considerable overlap exists
between patients and controls.\textsuperscript{20} In the segment of the carotid
where most studies are done, intimal xanthomas and fibrotic
plaques are common but true progressive lesions are rare.\textsuperscript{21,22}
Plaque formation and progression usually occur at sites of
nonlamellar turbulent flow (ie, low shear such as the proximal
internal carotid or at the bifurcation). It is likely that the
pathogenesis of lesions leading to intimal thickening in the
common carotid artery or more the more advanced plaque
phenotypes at or distal bifurcation sites are dissimilar so
measures of CIMT at the CCA might not be representative of
what is occurring at more atherosclerosis-prone locations, (ie,
the bulb and the internal carotid arteries).\textsuperscript{23}

### Autopsy Correlation Between Extent and
Severity of Atherosclerosis and CIMT

Although CIMT has increasingly been used in observational
and interventional studies, only a paucity of data exists about
its relationship to atherosclerosis as measured by the gold
standard, postmortem studies. In an autopsy study of 24
subjects, CIMT measured histopathologically was compared
to atherosclerosis in the femoral artery. The correlation
between mean distal common CIMT and relative plaque area
in the femoral artery was 0.26, which was not statistically
significant.\textsuperscript{24} These findings correlate with earlier autopsy
studies demonstrating only modest correlations between cor-
onary and carotid atherosclerosis.\textsuperscript{25,26} Studies examining the
correlation between CIMT and severity of coronary disease
as measured angiographically have revealed even weaker
correlations ($r=0.26$ for severity and $r=0.23$ for disease
extent).\textsuperscript{27} Although a recent study has reported a greater
correlation comparing CIMT to coronary intimal/medial
thickness measured by intravascular ultrasound (IVUS,
$r=0.49$ to 0.55), the analysis was limited to a small number of
high-risk patients where results need to be confirmed in a
more representative (ie, moderate risk) large patient popula-
tion.\textsuperscript{28} Overall, these correlations remain modest at best, no
matter what technique is used to measure the extent of
atherosclerosis. Notwithstanding however, the regional loca-
tion where IMT measurements are performed may be an
important aspect, because in one study CIMT measured in the
distal wall of the common carotid artery failed to predict
coronary events, whereas measures of CIMT in the bulb
showed a positive association with future cardiac events.\textsuperscript{29}

Although atherosclerosis affects a number of different
diseases, the question remains whether the extent of the
disease correlates across different arterial beds such as in the
coronary and the carotid arteries. In a postmortem study,
Pastekamp and colleagues reported a 5-fold difference in the
extent of atherosclerosis between the common carotid artery
and the coronary arteries and a 3-fold difference between
common carotid artery and the femoral arteries. Thus, the
lack of a strong correlation in the extent of atherosclerosis
among differing vascular beds may explain the modest
relationship between CIMT and coronary atherosclerosis.\textsuperscript{24}

### Relationship of CIMT to Plaque Phenotypes

It is important to emphasize that atherosclerosis is a complex
inflammatory disease comprising multiple plaque phenotypes
with differing risks for future vascular events. Although the
strength of CIMT is its reproducibility, it is in reality a
simplistic measure that fails to capture the complexity of
plaque evolution. For example, plaque grows along the length
of the carotid 2.4 times faster than it thickens,\textsuperscript{30} therefore
serial measurement of CIMT before and after a select therapy
may be insensitive for detection of changes in coronary
plaque progression.\textsuperscript{31} Moreover, the relationship of CIMT to
traditional coronary risk factors remains weak, with the
proportion of CIMT explained by traditional factors ($R^2=0.15$ to 0.17)
with the most important risk factors being age and blood pressure.\textsuperscript{32} On the other hand, the relationship
of coronary risk to total plaque area is markedly greater
($R^2=0.52$).

Although numerous clinical trials have used changes in
CIMT as the primary end point to assess the risk for vascular
events, very few studies have actually examined the relation-
ship between changes in CIMT and risk for future events. The one study addressing this issue included a population of 146 men with coronary disease, aged 40 to 59, with a mean follow-up of 8.8 years. This study demonstrated a 0.03-mm/year increase in CIMT with a 2.2-fold increase in risk for coronary events.\(^\text{33}\) The relative insensitivity of CIMT for prediction of events is illustrated by the fact that articles describing the relationship of baseline CIMT to future clinical events took between 5 and 12 years to publish.\(^\text{22}\)

More reliable quantitative indicators such as plaque area, volume, percent stenosis, degree of calcification, and plaque echolucency may better characterize the distinct lesion phenotypes of atherosclerosis. Along these lines, a 5-year clinical study by Spence et al showed that total plaque area was a strong predictor of cardiovascular syndromes. After adjusting for coronary risk factors and therapy of hypertension and lipids, patients in the top quartile for plaque area have 3.4 times the risk of stroke, death, or myocardial infarction than those in the lowest quartile over a 5-year period.\(^\text{34}\) Further, patients with plaque progression, despite pharmacotherapy, in the first year of follow-up had twice the risk of events after adjusting for risk factors and drug therapy. These findings were further validated in the population-based Tromsø Study in more than 6000 subjects, which showed that plaque area, but not IMT in the far wall of the common carotid, was a stronger predictor of myocardial infarction.\(^\text{20}\) On the contrary, IMT in the carotid bulb, which included plaque thickness, was predictive of coronary risk.\(^\text{29}\) Collectively, these studies and others\(^\text{35}–\text{38}\) emphasize the distinction and greater predictive value of vascular outcomes relying on measures that include plaque area and thickness rather than IMT alone, which is deliberately measured at locations where there is less likelihood of developing plaque.

Recent studies have also described a strong relationship between increasing echolucency of carotid plaque and risk for future clinical adverse events. This surrogate end point was proven to hold significant predictive power for identification of the future risk of MI, in particular in women,\(^\text{39}\) as in the Tromsø Study or as in the study by Groenholt et al, the risk for future stroke.\(^\text{39}\) Histologically, echolucent plaques generally have a higher lipid-content, macrophage density, and hemorrhage.\(^\text{40}\)

### What is the Role of CIMT in Intervention Trials?

As discussed, significant limitations in the assessment of CIMT for prediction of future cardiac events considerably hamper the usefulness of this technology. First, the association between CIMT and that of coronary heart disease is modest at best. Second, CIMT fails to account for the diversity of plaque phenotypes that exist in atherosclerosis, where some are considered high risk and others minimal for predicting clinical events. Third, there is a virtual absence of data demonstrating a link between progression of CIMT and coronary and cerebral events. For these reasons, studies incorporating CIMT as a primary outcome to indicate cardiovascular risk of an intervention are inherently misleading.

The recently published simvastatin with or without ezetimibe Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial best illustrates this point. This investigation failed to show significant group differences in any of several end points with respect to CIMT, despite significant decreases in low-density lipoprotein cholesterol and C-reactive protein.\(^\text{41}\) This study illustrates limitations in the technology, which does not necessarily imply the drugs were ineffective when there was greater reduction in low-density lipoprotein cholesterol in the combined simvastatin plus ezetimide group rather than simvastatin monotherapy alone. Therefore, a more reliable primary outcome consistent with a stronger relationship to atherosclerosis development and progression is needed with an ability to accurately identify an echolucent or attenuated plaque that is representative of the necrotic core.

## Disclosures

None.

### References


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