Measuring Carotid Intima-Media Thickness: Simple Protocols Have Advantages

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Since 1986, ultrasound-based measurement of the carotid artery wall intima-media complex has evolved from a simple pathologic observation to a tool for evaluating responses to cholesterol-lowering therapies and a clinical adjunct for cardiovascular risk assessment.

Many variations of protocols for the measurement of carotid artery intima-media thickness (IMT) now exist, from simple protocols that measure only the common carotid artery on one side of the neck to complex ones with a full bilateral study that includes 30 images.

It is possible that complex IMT measurement protocols might improve the likelihood of detecting differences between treatment and nontreatment arms of cholesterol-lowering intervention trials. However, there are no firm data to support this view, as shown in the next section. The evidence for complex IMT measurement protocols is reviewed in the section that follows.

LACK OF EVIDENCE FROM META-ANALYSES OF CAROTID INTERVENTION TRIALS

Meta-analyses of carotid IMT intervention trials dating back to 2004[1] show large variation in the different protocols used to measure IMT.[2-4] Although some protocols look only at the far wall of the common carotid artery, others sample the different levels of the carotid bifurcation and include images taken from one and often more than one angle. All of these protocols seem to give consistent results. Verification of possible statistical heterogeneity for the aggregate results derived from combining the IMT studies does not control for the IMT measurement protocol. Statistical adjustment is made for cohort size and composition but not for the IMT sampling approach or the IMT measurement protocol.[2-4] The IMT imaging and measurement protocol does not seem to be factored in as important when it comes to detecting differences between the treatment and nontreatment arms of these various cohorts.

A separate argument can be made for sampling at multiple levels of the carotid artery bifurcation. The Atorvastatin and Simvastatin on Atherosclerosis Progression study is a prime example. Results for IMT measurements made at the level of the common carotid artery did not show a statistically significant difference between treatment and nontreatment arms. However, when combined, the aggregate of measurements from multiple levels showed a significant difference.[5] This seems to favor the use of multiple levels for sampling the carotid arteries for IMT measurements, typically the common carotid artery, the bulb, and the internal carotid artery.

However, the adoption of multilevel protocols carries with it the possibility of not visualizing the wall of the carotid bifurcation and the proximal internal carotid artery, thereby leading to sparse IMT data. Selection of individuals in whom carotid artery IMT can be measured is typically done in IMT intervention trials[6,7] and might possibly be biasing the resultant data that compare the results based on the measured IMT changes during the duration of the trial. This issue needs further clarification when reviewing the approaches used in epidemiologic studies in which IMT serves as a marker of subclinical cardiovascular disease.

For intervention trials, there does not seem to be a consensus as to whether one type of IMT protocol is better than another. Sampling from multiple projections versus from one projection does not appear to be worth controlling for in meta-analyses trying to relate change in IMT to cardiovascular outcomes.

THE VALUE OF MULTIPLE-ANGLE SAMPLING IN SPECIFIC STUDIES OF INTIMA-MEDIA THICKNESS

A priori, it would seem logical that sampling from multiple angles is the right approach in epidemiologic studies investigating possible associations among IMT, cardiovascular risk factors, and outcomes. This type of research would seem to require the greatest level of data completeness. However, two questions need to be addressed: (1) If multiple angles of sampling are needed, does this apply equally to all carotid artery segments? (2) If multiple angles are acquired, what is the minimum number needed?

The Common Carotid Artery

Associations with Outcomes. The Atherosclerosis Risk in Communities (ARIC) study is well recognized as the largest epidemiologic study to have looked at associations among IMT, outcomes, and cardiovascular risk factors. The ARIC protocol imaged the common carotid artery from three projections.[8] The data generated from this study are referenced as a set of normative data[9] and shown to be associated with cardiovascular outcomes.[10,11] However, the results show that IMT measurements at the level of the common carotid artery were achieved in only 12,629 of 13,824 participants, for a completeness rate of 91.4%. The use of multiple projections did not seem to yield a 100% success rate. In fact, 1,930 early ultrasound examinations were rejected because they were considered "unreliable."[9] This effectively gives an overall yield of 79.9% for common carotid artery IMT measurements, despite the use of three projections. How does this compare with other studies that followed? The Cardiovascular Health Study protocol relied on only one projection of the common carotid artery, yet the data completeness rate was 99.8% (5,114 of 5,176).[12] The Coronary Artery Risk Development in Young Adults[13] and the Framingham Heart Study[14] sampled one projection of the common carotid artery, yet they showed high completeness rates and strong associations between common carotid artery IMT and cardiovascular risk factors.

Abbreviations

ARIC = Atherosclerosis Risk in Communities

IMT = Intima-media thickness

Published data from the Framingham Heart Study[15] and the Cardiovascular Health Study[16] show that common carotid artery IMT is associated with cardiovascular outcomes despite having been acquired from one projection.

It is hard to argue in favor of using multiple projections of the common carotid artery when data acquired from only one projection show strong associations with risk factors and outcomes.

The differences in completeness rates between ARIC and the other large studies quoted above do not seem to depend on the use of multiple projections but are likely linked to technical factors beyond the scope of this discussion.

Assessment of Atherosclerosis Progression. Does one view of the common carotid artery suffice when it comes to assessing the presence of IMT progression and the possibility of an association of risk factors with progression?

The Monitored Atherosclerosis Regression Study was one of the first IMT progression studies to compare IMT progression rates between an intervention arm and a control arm. The study relied on a protocol whereby only one view of the right common carotid artery was taken and used to measure far-wall carotid artery IMT.[17] This study showed a strong lovastatin-mediated effect in the treatment arm, with a reduction in the rate of IMT progression.[17] The ability to detect differences between treatment and nontreatment arms was repeated in other protocols in which only the common carotid artery was measured. The successful application of the one-projection common carotid artery IMT protocols was well documented by the sequence of Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol trials.[18-20]

Progression and Outcomes. As to outcomes linked to IMT progression, data are sparse. One study suggested that IMT progression might be linked to the risk for stroke,[21] and another study suggested that IMT progression is linked to coronary heart disease outcomes.[22] Both studies used IMT measurements of the far-wall right common carotid artery taken from one projection.

Summary. Is more than one projection of the common carotid artery needed for either risk assessment or evaluation of IMT progression? This seems unlikely on the basis of available data. Proof of the hypothesis that multiple projections of the common carotid artery improve precision of IMT measurements and therefore might have a benefit in intervention trials and cardiovascular risk assessment is lacking.

The Internal Carotid Artery

Perspective. It can readily be argued that IMT measurements centered on the carotid bifurcation will give results somewhat different that those made in the relatively straight segment of the common carotid artery. Lesions of the carotid artery bifurcation are asymmetric, in sharp contrast to the relatively symmetric wall thickening that takes place in the common carotid artery.[23,24] As such, it would make intuitive sense to rely on multiple projections to best evaluate the carotid artery bifurcation and the proximal internal carotid artery.

This concept is applied to the evaluation of lesions that are large enough to cause stenotic lesions of the carotid arteries. Grading of ste-
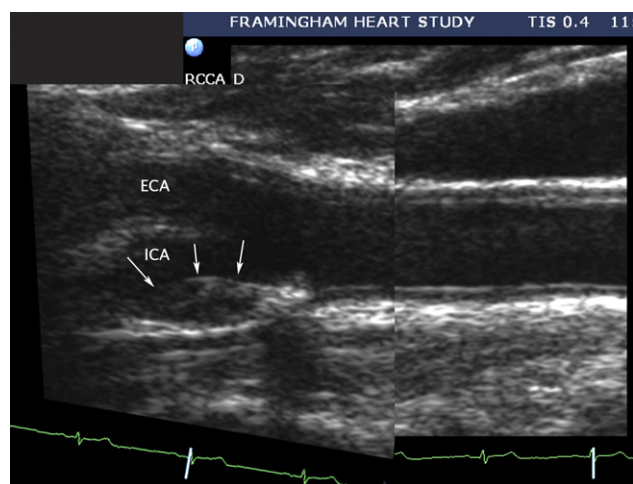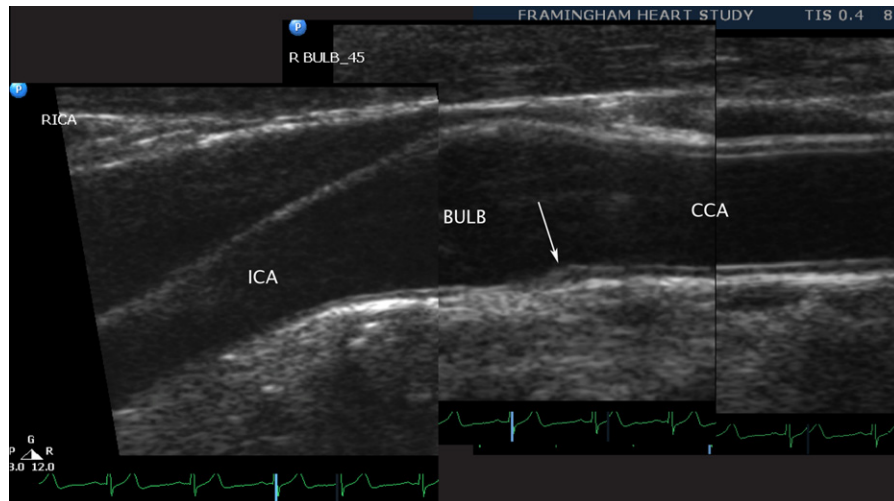

Figure 1 Typical "tuning fork" view of the carotid bifurcation created by superimposing separate views of the common carotid artery and the carotid artery bulb. The external carotid artery (ECA) is situated on top of the internal carotid artery (ICA). The *arrows outline* the surface of an atherosclerotic plaque.

nosis severity is based on imaging techniques that evaluate the extent of luminal diameter narrowing. Although this requires multiple projections, the convention has been to use the projection that shows the greatest degree of narrowing. This approach has been used in large trials that have linked carotid artery interventions to a decrease in the incidence rate of future strokes. Such trials include the North American Symptomatic Carotid Endarterectomy Trial,[25] the European Carotid Surgery Trial,[26] and the Carotid Revascularization Endarterectomy versus Stenting Trial.[27] These large studies did not use an average of multiple projections to assess plaque burden but selected the one best projection showing the greatest degree of narrowing, in essence, the largest or tallest plaque. Such a strategy would seem applicable to IMT measurements.

Carotid bifurcation IMT measurements overlap with the definition of plaque. By ultrasound, plaque is measured as an IMT that is deemed "pathologic." The ultrasound-derived measurements of plaque include the media of the artery wall either as a local protuberance the artery wall of ≥50% compared with contiguous artery wall segments or as an absolute size criterion such as 1.5 mm, or both.[28]

Association with Outcomes. The ARIC protocol relies on a single projection of the carotid artery bulb and internal carotid artery defined within a strict criterion on the basis of a preliminary assessment of the axis of the carotid artery. On this one view, the internal and external carotid arteries are in the same imaging plane, the "optimal angle"[8] or so-called tuning fork view (Figure 1). However, this one projection is difficult to obtain (Figure 2).[29] The ARIC protocol was constrained to this one view. The data completeness for evaluation of the carotid bifurcation was <43%, because up to 57% of carotid bifurcation images in ARIC could not be used for the evaluation of IMT or plaque.[30] However, associations between plaque and outcomes were significant, based mostly on subjective evaluations of plaque and by imputation of missing data.[30,31]

Summary. Protocols that rely on three views of the carotid artery show associations between carotid bifurcation IMT and events. Hybrid protocols in which more than one view is taken but the sonographer selects the one projection of the carotid bifurcation that best

Figure 2 Standard view of the carotid bifurcation obtained at 45° from the horizontal. The external carotid artery is not in this imaging plane, because a "tuning fork" view could not be obtained. The internal carotid artery (ICA), the carotid bulb, and the common carotid artery (CCA) are aligned. The *arrow points* to an early plaque.

shows the greatest IMT have also shown associations between internal carotid artery IMT and events.[14,15]

ASSESSMENT OF ATHEROSCLEROSIS PROGRESSION

Atherosclerosis progression, by its nature, requires careful attention to technique and strict adherence to imaging and IMT measurement protocols.

The Issues

There are obvious statistical advantages for relying on multiple projections when measuring IMT progression at the level of the carotid artery bifurcation. Data derived from intervention trials and epidemiologic studies typically average IMT values obtained from multiple projections. Differences in progression rates have been shown for targeted intervention trials as well in targeted population studies.

Is this a better approach than obtaining measurements from only one projection? This is not clear, because plaque area measurements from one projection are a valid measure of IMT.[32] The one caveat is the following: the projection where plaque is estimated is selected.[33] The process implicitly considers a global evaluation of the carotid bifurcation and the selection of a reliable location and then imaging in one plane.

As of this writing, there are no solid data anchoring the progression of carotid bifurcation IMT with cardiovascular outcomes. It is therefore difficult to speculate as to whether a single view or multiple views would be more reliable for this task.

Summary

The asymmetric nature of intima-media thickening in the carotid bifurcation obviously requires that consideration be given to sampling, by ultrasound, from multiple projections. What is not clear, however, is whether an average measurement of IMT taken from these projections should be used instead of a preselected imaging plane that best displays the pathologic change.

COST-EFFECTIVENESS ISSUES

Are multiple imaging planes and sampling of the carotid bifurcation needed in IMT-based intervention trials? Probably not if one examines the results of the Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin study. Five projections were taken at three levels and included the near-wall and far-wall measurements, for a total of 60 measurements per patient at each time point to show a difference in IMT progression between the rosuvastatin arm and the nontreatment arm.[34] However, an analysis published by the same group but this time restricted to one projection of the common carotid artery, with measurements only of the far wall, for a total of four measurements per patient, achieved the same result.[35] It is therefore very difficult to argue in favor of complex protocols.

Are multiple projections needed for the clinical evaluations of IMT? The clinical imaging protocols used to evaluate the carotid artery for stenotic lesions typically sample the common carotid artery and the internal carotid artery from one projection. Although transverse images are used to document the presence of eccentric plaque at the level of the bifurcation, the best imaging plane remains in an axis parallel to the long axis of the artery segment. Great reliance is given to the imaging skill of the sonographers and their ability to best demonstrate lesions in the carotid arteries. This approach of selective sampling also seems to work when applied to measurements of internal carotid artery IMT.[14] In the Framingham Heart Study, a trained sonographer picked the one best projection for IMT measurements in up to 54% of instances.[14]

CONCLUSIONS

Common carotid artery IMT, by virtue of being a symmetric process, can be estimated from only one projection.

The evaluation of pathologic changes in the carotid artery bifurcation is more complete when data from multiple imaging planes are integrated. However, these data need not be averaged, but the presence of more significant areas of intima-media thickening can be identified and used as a sole measurement to estimate the severity of carotid artery plaque.

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