Published in final edited form as:

J Am Soc Echocardiogr. 2009 May ; 22(5): 505–507. doi:10.1016/j.echo.2009.03.019.

IMT as a Risk Marker: The Plot Thickens

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Atherosclerotic cardiovascular diseases (myocardial infarction, stroke, peripheral arterial disease) remain the leading causes of morbidity, mortality and disability in industrialized countries. The pathogenesis and progression of atherosclerosis involve complex interactions between the arterial wall and inflammatory, dietary, hemodynamic, genetic, environmental, and lifestyle factors. From a primary prevention standpoint, there is heightened interest in the ability to identify individuals without clinically manifest atherosclerosis who are at increased risk for adverse events. The hope is that these individuals could be targeted for more aggressive intervention strategies that would mitigate the adverse clinical outcomes associated with atherosclerotic diseases.

Atherosclerosis is a systemic disease involving the deposition of lipids in the arterial intima (initially) and the infiltration of inflammatory cells, predominantly in large and medium sized arteries. Whereas catheter-based angiographic techniques are diagnostically very useful in the advanced stages of atherosclerosis, they are of limited utility in the early stages of disease. This is because angiography is unable to detect (or underestimates the burden of) atherosclerotic plaques that have limited encroachment into the vascular lumen, due, in part, to the compensatory Glagov remodeling of the arteries. Thus, the cornerstone of imaging early atherosclerosis has relied on modalities that assess structural properties of the arterial wall.

Imaging of the Arterial Wall

Intravascular ultrasound allows a detailed examination of the arterial wall for the presence of an atherosclerotic plaque. This modality also allows the measurement of the plaque size, and the monitoring of its progression or regression over time. Thus, intravascular ultrasound has proven particularly useful in clinical research studies evaluating the effects of interventions on atherosclerotic plaques. However, the invasive nature of this procedure precludes its widespread use as a screening tool for primary prevention. Computed tomography (CT) is increasingly used as a means to assess the atherosclerotic burden non-invasively, particularly in the coronary arteries. Traditionally, the goal of CT in risk assessment was not to image the atherosclerotic plaque directly (although luminal plaque can now be assessed with CT angiography), but to quantify the amount of calcium in the coronary arteries. The deposition of calcium in the vasculature is a complex and regulated process (1). In the coronary arteries, calcium deposits occur almost exclusively in atherosclerotic plaques, and they can be rapidly and reproducibly measured with CT. Another imaging modality that is often used to evaluate the arterial wall is high-resolution ultrasound. Ultrasound is a safe and non-invasive imaging

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modality that does not involve any exposure to ionizing radiation or to nephrotoxic contrast agents, and it will be the focus of the remainder of this article.

The common carotid artery (CCA) provides a convenient window to study the structure and function of elastic arteries because of its size, its superficial location, ease of accessibility and limited movement. Histologically, the arterial wall of the common carotid artery is composed of 3 layers. The tunica intima usually consists of a single continuous layer of endothelial cells, a sub-endothelial space containing connective tissue rich in proteoglycans and scattered macrophages, and a collagenous inner layer with abundant elastic fibers and smooth muscle cells (2). The tunica media consists of concentric layers of fenestrated sheets of elastin separated by collagenous connective tissue, and smooth muscle cells. The tunica adventitia consists mainly of fibroblasts, collagen and small vasa vasorum.

IMT

Ultrasonography provides a convenient, reproducible, and non-invasive means to image the CCA with acceptable resolution. During ultrasound imaging of the far wall of the CCA, 2 echogenic lines are usually visualized. In situ anatomic and in vitro histologic studies have validated these lines as corresponding to the lumen-intima interface, and the media-adventitia interface (3–5). With existing ultrasound technology, it is difficult to discern the intima-media interface reliably. Thus, ultrasound imaging studies have focused on measuring the combined thickness of the intimal and medial layers (IMT) of the far wall. Some studies include plaques in the measurement of IMT, whereas others measure IMT in areas devoid of plaques and report the presence of plaques separately. Some investigators also measure the IMT of the near wall. However, this measurement is less accurate than the IMT of the far wall, because the ultrasound beam is traveling from more echogenic to less echogenic layers at the adventitia-media and intima-lumen interfaces of the near wall. In one study, the ultrasound measurement of the near wall IMT was 20% lower than the corresponding histologic measurement (5).

The clinical importance of IMT is underscored by a growing body of literature showing that traditional cardiovascular risk factors and prevalent cardiovascular diseases are usually associated with higher IMT. Furthermore, longitudinal studies have shown that IMT is a potent predictor of adverse cardiovascular outcomes (e.g., myocardial infarction, stroke), independent of other traditional cardiovascular risk factors (6). Thus, measurement of IMT is increasingly recognized as a valuable adjunct in cardiovascular risk assessment. In addition, IMT is often used as a surrogate marker for atherosclerosis, particularly in clinical studies of pharmacologic interventions (e.g., lipid lowering medications) that evaluate the effects of these interventions on IMT progression and/or regression. A detailed description of the measurement techniques and clinical applications of IMT is provided in a report from the American Society of Echocardiography and the Society of Vascular Medicine and Biology (7). A statement from the American Society of Echocardiography also provides consensus recommendations for the use of carotid ultrasound in clinical practice, such as the selection of the imaging protocol to be used, and the selection of patients who might benefit from this test (8).

Because it is difficult to discern the intimal-medial interface by ultrasound, the measurement of IMT encompasses the thicknesses of both the intimal and medial layers. However, a large number of investigators have assumed that a higher IMT is due to thickening of the intima, and have attributed this thickening to atherosclerosis, overlooking the possibility that a higher IMT may reflect non-atherosclerosis related thickening of the intimal layer (see below) and/or hypertrophy of the medial layer. Medial hypertrophy, in turn, could represent an adaptive response to changes in flow, tension, or lumen diameter (9,10). Blood pressure is a known determinant of IMT, and antihypertensive medications can attenuate the rate of progression of IMT (11). In this issue of the Journal, Meijs et al. examine the association between IMT and

left ventricular mass (LVM) in 525 hypertensive subjects with extra-cardiac atherosclerotic disease or with risk factors for atherosclerosis (12). IMT was measured on the baseline visit by B-mode ultrasound. LVM was determined by cardiac MRI, which was performed approximately four and a half years after the baseline visit. In age- and sex-adjusted models, LVM was found to be significantly associated with IMT. This relationship was strengthened when the models were adjusted for height and weight, which are known determinants of LVM. However, the association between LVM and IMT was not altered when the models were further adjusted for markers of atherosclerosis, namely previous stroke or transient ischemic attack, previous peripheral arterial disease, lipid lowering medications, presence of albuminuria and current smoking. In contrast, this association was attenuated by 19% when the models were adjusted for blood pressure parameters (systolic blood pressure, diastolic blood pressure, and blood pressure lowering medications), which are known determinants of LV hypertrophy and arterial wall hypertrophy. Thus, the relationship between IMT and LVM does not appear to be influenced by atherosclerosis. Instead, a substantial portion of this relationship can be attributed to factors known to influence the hypertrophy of both the left ventricle and the arterial wall. This should serve as a reminder that variables other than atherosclerosis can also influence IMT. How then do we reconcile the fact that IMT is a potent predictor of cardiovascular outcomes, if it can be impacted by factors other than atherosclerosis?

Beyond atherosclerosis and blood pressure, several other factors are known to influence IMT. In particular, age is one of the most potent determinants of IMT. Carotid IMT increases nearly threefold between the 3rd and 10th decade of life (13). Post-mortem studies have indicated that this age-associated increase in thickening is caused mainly by an increase in intimal thickening (14). This thickening is due to a multitude of age-associated morphologic, cellular, enzymatic and biochemical changes in the arterial wall (reviewed in reference 15). These alterations have been well characterized in animal models of aging, particularly in species that do not develop atherosclerosis with aging, where the age-associated alterations that are observed can be confidently attributed to aging and not to superimposed atherosclerosis.

IMT and Aging

In both rodent and non-human primate models of aging, advancing age is accompanied by diffuse thickening and increased cellularity of the intimal layer, even though these animals do not usually develop atherosclerosis. The intimal thickening is due to increased formation of extracellular matrix, which includes increased secretion and deposition of proteins, and increased expression and activity of growth factors and enzymes that regulate the synthesis and degradation of extracellular matrix components (16,17). Endothelial cells also exhibit morphological, structural and functional alterations. These cells produce more vaso-constricting growth factors (e.g., Angiotensin II, endothelin-1) and less vaso-dilating factors (e.g., nitric oxide). Several features indicate that one of the hallmarks of the thickened intima is its evolution towards a pro-inflammatory state. For example, in the thickened intima, the levels of inflammatory chemokines are increased (18), and endothelial cells exhibit increased expression of intimal adhesion molecules and enhanced adherence of monocytes to their surface (19). Furthermore, the bioavailability of nitric oxide is decreased with aging, whereas the production of reactive oxygen species is increased (20), and these can lead to peroxidation of lipids and oxidative modifications of proteins. Thus the thickened intima of the aged artery is not an inert structural alteration, but rather a surprisingly hyperactive cellular, enzymatic and metabolic milieu.

It is worth emphasizing that these age-associated structural and functional alterations in the arterial wall are observed in animal models of aging that are devoid of atherosclerosis. Yet these alterations include several of the key features that have been implicated in the pathogenesis and progression of atherosclerosis, such as endothelial dysfunction, pro-

inflammatory state and oxidative stress (21). In other words, the cellular, biochemical and metabolic profiles of the aging arterial wall constitute a fertile substrate that is conducive to the initiation and/or progression of atherosclerosis (22). Indeed, in an experimental model of atherogenesis, the manifestation of atherosclerosis was more severe in older vs. younger animals in spite of an equivalent exposure to the duration and intensity of the atherogenic stimulus (23), suggesting a pivotal role for the age-associated alterations of the arteries in modulating the severity of disease.

In summary, intimal medial thickening of the carotid artery can be modulated by several factors beyond atherosclerosis (e.g., aging, hypertension). Therefore, IMT should not be construed as synonymous with “subclinical *atherosclerosis*”, particularly in the absence of plaques. Nonetheless, because the factors that modulate intimal medial thickening are the very same ones that have been implicated in the genesis of various cardiovascular diseases (and not just atherosclerosis), IMT provides a useful gauge of the impact of these factors on the arterial wall. As such, IMT remains a very useful marker of “subclinical *vascular disease*”.

Acknowledgments

This work was supported by the intramural research program of the National Institutes of Health, National Institute on Aging

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