Noninvasive tests of vascular function and structure: Why and how to perform them

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Background Early atherosclerosis involves the endothelium of many arteries. Information about peripheral arterial anatomy and function derived from vascular imaging studies such as brachial artery reactivity (BAR) and carotid intima media thickness (IMT) may be pertinent to the coronary circulation. The prevention and early treatment of atherosclerosis is gaining more attention, and these tests might be used as indicators or perhaps guides to the effectiveness of therapy, but their application in clinical practice has been limited. This review seeks to define the anatomy and pathophysiology underlying these investigations, their methodology, the significance of their findings, and the issues that must be resolved before their application.

Methods The literature on BAR and IMT is extensively reviewed, especially in relation to clinical use.

Results Abnormal flow-mediated dilation is present in atherosclerotic vessels, is associated with cardiovascular risk factors, and may be a marker of preclinical disease. Treatment of known atherosclerotic risk factors has been shown to improve flow-mediated dilation, and some data suggest that vascular responsiveness is related to outcome. Carotid IMT is associated with cardiovascular risk factors, and increased levels can predict myocardial infarction and stroke. Aggressive risk factor management can decrease IMT.

Conclusions BAR and IMT are functional and structural markers of the atherosclerotic process. The clinical use of BAR has been limited by varying reproducibility and the influence by exogenous factors, but IMT exhibits less variability. A desirable next step in the development of BAR and IMT as useful clinical tools would be to show an association of improvement in response to treatment with improvement in prognosis. (Am Heart J 2001;141:694-703.)

Significance of vascular structure and function to cardiologists

Coronary angiography and standard functional tests have been the cornerstone of the diagnosis and management of coronary artery disease for decades. However, as the emphasis of cardiovascular care moves progressively toward prevention and regression of earlier disease, these tools may become less effective in diagnosing early subclinical disease, in which the greatest potential gain exists. Functional tests identify disease in the setting of significant coronary stenoses, which implies the presence of advanced disease. Coronary angiography may be used to identify earlier lesions but is restricted to analyzing the lumen and does not directly assess the vessel wall. Furthermore, it is ill suited to sequential follow-up, and, being an invasive study, carries the potential of significant adverse effects.

Given that early atherosclerosis involves the endothelium of many arteries, several noninvasive tests may provide information about peripheral arterial anatomy and function that may be pertinent to the coronary arteries. The application of these tests in clinical practice has been limited by a number of factors including limited data (especially regarding flow-mediated vasodilation), technical considerations, and in part by the field of vascular imaging being outside the standard repertoire of cardiologists. However, as the prevention and early treatment of disease gains more attention, these tools may become important as indications or perhaps guides to the effectiveness of therapy. This review seeks to define the anatomy and pathophysiology underlying these investigations, their methodology, the significance of their findings, and the factors that must be defined before their clinical application.

Vascular function and early atherosclerosis

Endothelial dysfunction in relation to imaging protocols

Since the landmark 4S study, many investigations have shown cholesterol lowering to be associated with a marked decrease in cardiac events and mortality rates,
yet the actual improvement in coronary vasculature as assessed by angiography has been small. Other mechanisms to explain this discrepancy have been suggested, including a direct beneficial effect on endothelial function. Moreover, vascular dysfunction associated with vascular injury has been postulated as the precursor of atherosclerosis. Impaired endothelial function has been exhibited in asymptomatic children and young adults who have risk factors for atherosclerosis including hypercholesterolemia and cigarette smoking. The implications of this are significant. Tests of endothelial function may be used to diagnose early disease and track the response to various treatments that cause disease regression. Endothelial dysfunction may indeed predict outcome; therefore its reversal may have important clinical implications.

The primary agent used to assess coronary endothelial function in the coronary circulation is selective intracoronary infusion of acetylcholine (10^{-8} to 10^{-6} mol/L). In the normal coronary vasculature, acetylcholine releases nitric oxide (NO) and causes vasodilation, but in the presence of atherosclerosis, associated with reduced NO release, acetylcholine causes a paradoxical vasoconstriction secondary to a net muscarinic smooth muscle cell activation. This is in contrast to the normal vasodilator response to glyceryl trinitrate, which provides an exogenous NO source.

Peripheral tests of vascular function

Methodology. Direct measurements of coronary flow responses are invasive and not readily repeatable. In patients with chest pain, impaired brachial artery flow-mediated vasodilation (FMD) has been reported in patients with an abnormal coronary endothelial function as compared with those with normal coronary endothelial function (FMD, 4.8% ± 5.5% vs 9.7% ± 8.1%, P < .02). Peripheral tests have therefore been applied as a surrogate for coronary reactivity.

Vasodilator responses in the peripheral vessels have traditionally been evaluated with plethysmography. In this test, a strain gauge is placed around the forearm, cuffs are then placed at the wrist and the upper arm, and the wrist cuff is inflated to 200 mm Hg to prevent blood circulation in the hand. After the upper arm cuff is inflated to 40 mm Hg, venous occlusion causes forearm engorgement, which is then recorded on the plethysmograph to derive measurement of resting blood flow. After this, the cuff is inflated to suprasystolic pressures for between 4 and 10 minutes and then deflated, thereby measuring hyperemic blood flow. However, plethysmography remains technically difficult, and the recognition of a good waveform is somewhat subjective; it is not likely to develop into a standard clinical tool.

The most widely used alternative to invasive, direct testing of the coronary vasculature is a noninvasive method of testing brachial and femoral artery endothelial function, based on the technique described by Celermajer et al. Attention to detail is important: Patients are studied in the fasting state; caffeine and cigarette smoking are prohibited on the morning of the study because of their documented acute influences on vascular physiology. Similarly, vasoactive medications including angiotensin-converting enzymes, calcium entry blockers, and β-blockers are withheld for 24 hours before the study, assuming the patient is stable from a cardiovascular viewpoint. After the patient had been lying at rest for 5 minutes, the brachial artery is located above the elbow. To standardize the technique and reduce variability, we use the right brachial artery whenever possible. Longitudinal images of 6 to 8 cm are optimized, and a resting scan is taken, including a 10-second measurement of Doppler flow. Complete occlusion of the artery is needed for the duration of the scan. The cuff is placed on the forearm and inflated to 300 mm Hg for a duration of 4.5 minutes. The cuff is deflated, and after 15 seconds of hyperemic Doppler flow, the second or hyperemic scan is obtained at approximately 1 minute after deflation, when peak brachial artery dilation occurs. The patient is allowed to rest for 15 minutes, and a second resting scan is then acquired. Three minutes after administration of 400 µg of sublingual nitroglycerin, a fourth scan is obtained (Figure 1). Celermajer et al found an FMD of approximately 10% in a control group between 8 and 57 years of age, with no classic risk factors for coronary artery disease.

Correlates of endothelial dysfunction. Although present in established cardiovascular disease, impaired FMD is also a marker of the preclinical phase of overt vascular disease. In a study of 500 clinically well, nonhypertensive subjects, 5 to 73 years of age, lower levels of FMD were associated with univariate analysis with hypercholesterolemia, cigarette smoking, hypertension, male sex, larger vessel size, and family history of premature vascular disease.

Several cardiovascular risk factors have been associated with abnormalities of endothelial function. In a comparison of femoral artery FMD in 16 patients (42 ± 4 years of age) with primary hypercholesterolemia who had no overt cardiovascular disease with 16 normocholesterolemic control patients (35 ± 3 years of age), Arcaro et al demonstrated a statistically significant difference in the area under the curve of the time-dependent femoral artery diameter change. Gerhard et al studied endothelial function of 119 healthy volunteers 19 to 69 years of age with no clinical cardiovascular disease by using venous occlusion plethysmography. Brachial artery metacholine infusion was used for assessment of endothelium-dependent vasodilation and intra-arterial sodium nitroprusside infusion for endothelium-independent vasodilation. The slope of the meta-
Choline–blood flow response was indicative of endothelium-dependent vasodilation and exhibited a progressive decline with each decade increase in age. Similar results have been shown with brachial artery infusions of an NO synthase inhibitor, \(N^G\)-monomethyl-L-arginine (L-NMMA). The response of groups with documented vascular disease is similar: In an older population with symptomatic peripheral vascular disease, impaired FMD has been reported in comparison with age-matched control patients without peripheral vascular disease.

Other correlates of impaired FMD include the extent of coronary artery disease, the maximum percent diameter stenosis in any of the major coronary arteries, and brachial artery diameter. Impaired FMD in the brachial artery has been shown to correlate with the angiographic extent of coronary artery disease in 74 patients with angina pectoris when a cutoff of \(\geq 30\%\) diameter was used. It should be noted that this cutoff value should be distinguished from “significant” coronary artery disease.

In a pilot study, Schroeder et al proposed that endothelial dysfunction as quantified by FMD could be used as a screening test for coronary artery disease. One hundred twenty-two consecutive patients with a clinical suspicion of coronary artery disease who had no previous invasive investigations underwent coronary angiography as well as a stress modality (either exercise electrocardiography or myocardial perfusion imaging). Of these patients, 101 were found to have the presence of any angiographically detectable disease of any severity. FMD of the brachial artery was better in the group with no coronary artery disease (7.0% ± 3.5%) as opposed to the group with coronary artery disease (3.8% ± 4.1%, \(P < .001\)). However, FMD could not significantly differentiate between the various grades of severity of coronary artery disease. FMD demonstrated a sensitivity of 71% and a specificity of 81% in predicting any coronary artery disease. Receiver operating characteristic analysis found the optimal cutoff point for FMD in terms of sensitivity and specificity in predicting coronary artery disease as being \(\leq 4.5\%\). It should be noted that this value is different from those of previous studies and probably is related to different patient group selection.

Response of vascular reactivity to interventions that alter endothelial dysfunction. Endothelium-mediated responses of the coronary arteries have been shown to improve in response to treatment of atherosclerotic risk factors. Aggressive lipid lowering with lovastatin has been shown to cause a significant improvement in the endothelium-mediated response of the coronary arteries in 23 patients 30 to 81 years of age with coronary artery disease requiring angioplasty, as assessed by serial examinations with intracoronary acetylcholine at baseline and at 6 months. After 6 months, patients receiving placebo had \(-18\% ± 5\%\) change in coronary artery diameter as compared with those receiving lovastatin, who had \(0\% ± 3\%\) change in response to acetylcholine at a dose of \(10^{-6}\) mol/L. Similarly, the use of probucol confers improved coronary vascular function when added to standard lipid therapy. Gould et al demonstrated improved myocardial perfusion by using a PET scanner as early as 3 months after commencement of treatment.

The correlation of coronary and peripheral reactivity suggests that peripheral parameters might also be used to track treatment responses. Indeed, even a single episode of low-density lipoprotein (LDL) apheresis can improve endothelial function, as measured by forearm plethysmography and local acetylcholine infusion.
10 patients with hypercholesterolemia (serum cholesterol between 6.0 and 10.0 mmol/L), the use of simvastatin has been shown to improve forearm vasodilator response to acetylcholine within 4 weeks of commencement. Finally, in a group of patients with acute myocardial infarction or unstable angina pectoris and a total cholesterol level ≥5.2 mmol/L or LDL ≥3.4 mmol/L, Dupuis et al demonstrated a 42% relative increase (from 4.93% ± 0.81% to 7.0% ± 0.79%) in brachial FMD in the group of patients treated with 40 mg pravastatin daily as compared with those who received placebo after 6 weeks.

A number of other interventions have also been shown to influence vascular function, measured by FMD and other techniques. Endothelial NO production appears to be related to the renin-angiotensin system, and a number of studies have examined this link at the basic and clinical levels. In the TREND study, angiotensin-converting enzyme inhibition with quinapril was associated with improved coronary endothelial function in a normotensive group of 129 patients with 1- or 2-vessel coronary artery disease requiring nonsurgical revascularization with no evidence of severe hyperlipidemia or overt cardiac failure. More recently, Anderson et al compared quinapril, enalapril, losartan, and amlodipine on brachial FMD in 80 patients (mean age, 58 ± 0.9 years) in a crossover design. These patients had ≥50% stenosis in a major epicardial vessel on angiography in the preceding 6 months. From the baseline FMD of 7.3% ± 0.6%, quinapril resulted in a statistically significant increase in absolute FMD of 1.8% ± 1% (P < .02). The changes with the other medications were not significant. Other studies of angiotensin-converting enzyme inhibition have produced more variable findings, perhaps reflecting some variability in the group.

O’Driscoll et al assessed FMD with forearm plethysmography in a group of 10 men (mean age, 60 ± 3 years) with non–insulin-dependent diabetes mellitus who were treated with 10 mg enalapril twice daily or placebo for 4 weeks. Vasodilation as assessed by forearm blood flow ratio (ratio of flow in infused to noninfused arm) in response to acetylcholine was greater in those receiving enalapril (3.60 ± 0.55 vs placebo, 2.63 ± 0.34 at infusion rate of 40 µg/min acetylcholine; P < .02). In a similar study by Cheatham et al of a group of 9 patients (mean age, 54 ± 2 years) with uncomplicated non–insulin-dependent diabetes mellitus, the use of losartan, an angiotensin type 1 receptor antagonist at a dose of 50 mg per day, demonstrated improved forearm blood flow compared with those receiving placebo. Not all studies have shown a positive result. In a young group of insulin-dependent diabetic patients (mean age, 30.9 years), 6 months of treatment with 20 mg enalapril once daily did not result in a significant difference in brachial artery FMD.

Vasodilator reserve correlates with circulating levels of estradiol-17β, and postmenopausal women have impaired forearm blood flow and vasodilator capacity. The latter has been shown to improve with administration of estrogen. In a study of 17 postmenopausal women (mean age, 60 years) with no clinical manifestation of cardiovascular disease, the introduction of estradiol was associated with an improved brachial artery FMD (from 4.7% ± 0.06% to 11.1% ± 1.0%, P < .001) with no statistical difference when progesterone is added to estradiol therapy. Finally, improved endothelial function has been previously exhibited with the administration of L-arginine. Intravenous administration of L-arginine has been shown to significantly improve FMD in both hypercholesterolemic patients as well as in smokers but not in a diabetic subset.

Finally, there is evidence that vascular responsiveness correlates with outcome. In 147 patients who were followed for a median of 7.7 years, Schächinger et al demonstrated significantly increased cardiovascular events (cardiovascular death, unstable angina, myocardial infarction, revascularization, and ischemic stroke) in patients with an abnormal coronary vascular response to acetylcholine or nitroglycerin and thus gave the first evidence of the prognostic significance of coronary vascular dysfunction. Suwaidi et al followed 157 patients with mild coronary artery disease (lesions ≤40% stenosis) over a period of 28 months. They demonstrated no cardiac events (cardiac death, myocardial infarction, and revascularization) in those with normal or mild coronary endothelial dysfunction with coronary artery acetylcholine infusion (percent change in coronary blood flow between 0% and 50%). However, those with severe endothelial dysfunction (percent change in coronary blood flow <0%) had a 14% cardiac event rate (P < .05 compared with those with normal or mildly decreased endothelial function). Because FMD correlates with coronary reactivity, analogous results might be anticipated, but this remains speculative.

**Barriers to application of brachial reactivity as a clinical tool.** Although impaired FMD is often seen in patients with coronary artery disease, its specificity for significant stenoses is poor, probably because of a strong correlation with atherosclerotic risk factors and mild disease. It may perhaps have value as a screening test in that coronary disease might be unlikely in the presence of a normal test, but there is insufficient evidence to apply this currently. This test would be more likely to find application in determining the response of the endothelium to various interventions if the degree of change were greater than would be expected with the innate variability of this test. However, the main limitation in this respect is likely to be the reproducibility of the test. Sorensen et al calculated that in clinical trials, a mean improvement of FMD of ≥2% is necessary to detect treatment
benefit and that for any one individual, a difference of 4% to 8% was necessary to account for natural variability. However, the level of variation reported in the original studies may have been colored by the means of expressing this variability, and subsequent workers have reported greater variations. In a study of normal adults 20 to 70 years of age (mean, 46.5) studied a mean of 2.5 weeks apart, Liang et al reported a mean FMD of 10.8%, with a coefficient of variability of 10.8% and an $r$ value of 0.70. The cause of this variation is multifactorial; to some extent, it may reflect variability in the sampling site and inconsistency in drawing the lumen-endothelium interface, which could be improved by automated methods of drawing the borders (Figure 2). To a large extent, it may reflect the exquisite short-term sensitivity of this parameter to various stimuli, including diet; for example, transient decreases in FMD in normal volunteers have been exhibited with fatty meals and even a diet high in olive oil.

Vascular structure and atherosclerotic burden

Background

Early lesions consistent with atherosclerosis have been documented in young adults and even children and progress with aging. Ultrasonography of the peripheral vessels (as opposed to angiography) is an accurate investigation for the extent of atherosclerosis because early lesions may progress with no decrease in intraluminal diameter because of concomitant vessel wall dilation. Magnetic resonance imaging and intravascular and transesophageal ultrasound techniques have been applied to the evaluation of plaque burden. Newer techniques such as electron-beam computed tomography and spiral computed tomography have recently been applied in the investigation of atherosclerotic burden but as yet have an ill-defined role in clinical practice. However, the measurement of carotid intima-medial thickness (IMT) is highly feasible and appears to reflect the early stages of atherosclerosis. Because it is noninvasive and does not expose the patient to radiation, it can be used in asymptomatic patients, and serial measurements can be readily obtained, although further work is needed to establish its role in clinical practice.

Technical aspects of measurement of IMT

Scanning of the extracranial carotid arteries is performed with the patient lying supine, the head directed away from the side of interest, and the neck extended slightly. Both the left and right common carotid arteries are imaged at the level of the carotid bifurcation in anterior, lateral, and posterior planes. The focal zone is set at or just below the far wall, which is scanned perpendicular to the transducer face.

On a longitudinal B-mode image of the carotid artery, a series of echogenic “lines” and nonechogenic “spaces” is displayed (Figure 3). An echogenic line is produced when the beam passes through an acoustic interface, which generates a “leading” edge echo as well as a “trailing” edge, which is gain dependent. The distance between two leading edges can be reliably measured, but because the trailing edge is gain dependent, it does not always correspond anatomically to any structure, hence the unreliability and large error in near-wall measurements. In Figure 3, the leading edge
of the first echogenic line corresponds to the adventitia interface, followed by the leading edge of the intima. From here, the leading edge of the next echogenic line corresponds to the lumen-intima interface (far wall of the lumen), which is then followed by the leading edge of the media-adventitia interface, both of which define the IMT of the far wall.\textsuperscript{43} The intimal layer must be differentiated from plaque, which often exhibits calcification (bright echo) or localized protrusion into the lumen.

Although various investigators have measured the common, internal, and external carotid vessels, the most reliable measurements are obtained from the distal 2 cm of the common carotid artery, proximal to its bifurcation.\textsuperscript{44} This region has advantages in being close to the skin surface and being relatively parallel to it.

Clinical significance of measurements of IMT
Carotid IMT may have clinical application as a marker of atherosclerosis development in the setting of various risk factors, a marker of response to therapy for atherosclerosis, a predictor of events, and a marker of advanced vascular disease in the peripheral, carotid, and coronary circulations. Hashimoto et al\textsuperscript{45} compared the IMT and brachial FMD of 34 men with atherosclerosis with 33 age-matched men without clinical atherosclerosis. There was a significantly smaller percentage of FMD in those patients with atherosclerosis than those without (2.78\% vs 5.10\%, \(P < .05\)). In all 67 patients, IMT was inversely related to FMD (\(r = -0.36, P < .01\)), and after accounting for covariables in a multivariate analysis, IMT remained inversely related to percent FMD (\(r = -0.29, P = .03\)).

A number of large studies have demonstrated the strong relation between IMT and cardiovascular risk factors. Increased carotid IMT has been associated with diabetes, fibrinogen level, body mass index, and clinically overt atherosclerosis.\textsuperscript{46} Other studies have associated IMT with abnormal glucose metabolism, abdominal adiposity, and fasting plasma insulin levels in patients without cardiovascular disease.\textsuperscript{47,48} Lower levels of increased IMT probably reflect the early stages of vessel involvement, whereas the vessel enlarges before lumenal narrowing occurs. In a study of 1715 patients \(>55\) years of age, inner and outer lumen diameter increased gradually up to an IMT of 1.0 to 1.1 mm, after which there was a decrease in the inner lumen diameter suggesting the presence of atherosclerotic thickening.\textsuperscript{49} Indeed, it is thought that IMT rather than localized plaque may be a good marker of the total body atherosclerotic burden.\textsuperscript{49,50} Variable annual rates of increase in IMT have been described, probably reflecting racial differences in the progression of atherosclerosis. Salonen and Salonen\textsuperscript{51} found in 100 Finnish men (between 42 and 60 years of age) over a period of 24 months a mean increase in IMT of 0.12 ± 0.20 mm. Hodis et al\textsuperscript{52} investigated the annual rate of change of IMT in 146 American men 40 to 59 years of age who had previous coronary bypass grafting. Patients on dietary management had an annual

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**Figure 3**

Carotid IMT measurement. Trailing edge of first echogenic line (1) corresponds to adventitia interface followed by leading edge of intima (2), which defines beginning of measured lumen. From here, leading edge of next echogenic line corresponds to lumen-intima interface (3, far wall of lumen), which is then followed by leading edge of media-adventitia interface (4), both of which define IMT of far wall.\textsuperscript{43}
increase in IMT of 0.021 ± 0.02 mm, whereas those receiving dietary plus colestipol-niacin therapy had an annual decrease in IMT of -0.024 ± 0.03 mm. The strongest predictors of the 2-year increase in carotid IMT in 128 Finnish men included age, LDL, smoking, and platelet aggregability. Lipid lowering has been shown to slow the progression of IMT. In a study of 151 patients with documented coronary artery disease, treatment with pravastatin resulted in a relative reduction in IMT progression of 35% compared with the placebo group (0.0295 mm/y vs 0.0456 mm/y, \( P = .03 \)).

Reduction in the progression of peripheral atherosclerosis has been shown to correlate with parallel trends in the coronary vasculature, as addressed by quantitative coronary angiography. There is growing evidence that IMT may predict myocardial infarction and stroke prospectively. Increasing levels of common carotid IMT are associated with an incremental risk of stroke and myocardial infarction. In one study, 5858 patients >65 years of age with no preexisting cardiovascular disease were separated into quintiles on the basis of maximal common carotid artery IMT and followed for a mean period of 6.2 years. Over this period, 47 of 897 patients in the lowest quintile of IMT (<0.87 mm) had a stroke or myocardial infarction. In comparison, those in the highest quintile of IMT (≥1.18 mm) had 167 events. This equated to an age- and sex-adjusted relative risk of 2.85.

Carotid IMT has been used as a marker of advanced atherosclerosis of other vessels. Sørensen et al56 performed postmortem comparison of histologic grading of atherosclerosis of the brachial, coronary, and carotid arteries, in which atherosclerotic change was classified as fatty streak, fibrous plaque, or advanced lesion in 52 consecutive patients between 21 and 79 years of age. They demonstrated significant correlations of the grade of lesion severity in the brachial and coronary (\( r = 0.41, P = .003 \)), the brachial and carotid (\( r = 0.53, P = .0001 \)), and the carotid and coronary arteries (\( r = 0.69, P = .0001 \)). In a prospective study of 1000 patients ≥55 years of age, Bots et al57 demonstrated an inverse relation between carotid IMT and the ankle-brachial index. Linear regression analysis, corrected for age and sex, revealed that for each 0.1-mm increase in carotid IMT, there existed a decrease in the ankle-brachial index of 0.026, suggesting that carotid IMT is indicative of arterial disease in different vascular beds. Finally, in 276 patients referred for ultrasound examination of carotid arteries, Gnasso et al58 demonstrated an increased prevalence of carotid atherosclerosis (defined as plaque with IMT ≥2.0 mm or Doppler evidence of stenosis) with each increase in IMT tertile. For men, 19% in the lowest tertile had carotid atherosclerosis as opposed to 50% in the highest tertile (\( P < .02 \)).

A relation between carotid and coronary atherosclerosis has long been known, but the ability of IMT to act as a surrogate marker for coronary artery disease is debatable. A significant overlap exists between patients with and those without coronary artery disease (luminal stenosis ≥70%) and elevated IMT. In a study of 350 patients undergoing coronary angiography, mean carotid IMT was only weakly correlated to both severity and extent of coronary artery disease (\( r = 0.26, P < .001 \)). Nonetheless, a significant association between asymptomatic exercise-induced myocardial ischemia and increased carotid IMT has been reported. A graded increase in IMT was shown from community-based patients with no coronary artery disease (\( n = 397 \); age, 58.5 ± 15.8 years), possible coronary artery disease in which exercise electrocardiography revealed ≥1 mm of horizontal or downsloping ST-segment depression (\( n = 72 \); age, 66.1 ± years), and definite coronary artery disease (\( n = 38 \); age 77.4 ± 7.8 years). Furthermore, a subset of those with possible coronary artery disease underwent exercise thallium scintigraphy, subdividing this group into low and high risk by a negative or positive result. Common carotid artery IMT progressively increased in the patients with no coronary artery disease (0.52 ± 0.14 mm) to possible (low-risk) coronary artery disease (0.61 ± 0.12 mm) to possible (high-risk) coronary artery disease (0.74 ± 0.10 mm) to definite coronary artery disease (0.75 ± 0.16 mm). Regression analysis revealed that for each 0.1-mm increase in IMT, there is an associated 1.91-times increased risk of a positive exercise stress test or clinically manifest coronary artery disease, even by controlling for the effects of age, hypertension, and lipid-lowering medication.

**Barriers to application of IMT as a clinical tool**

The literature regarding IMT has been derived from groups of patients, and an evidence base regarding its application in individuals is still to be developed. Nonetheless, the test is more reliable than FMD, in the sense of being less influenced by acute changes in the patient’s milieu. Stensland-Bugge et al62 have shown that the measurement of carotid IMT is reproducible and that measurement error is more likely with increasing levels of IMT. Reliable serial IMT was demonstrated in the large ACAPS study (Asymptomatic Carotid Artery Progression Study), which involved 919 participants.63 Smaller studies have given acceptable results in terms of interobserver and intra-observer variabilities.64 The recent development of automated techniques to measure IMT may improve the reliability of this measurement in less expert readers. In a study that used a mobile field scanner, Dwyer et al65 exhibited a within-sonographer mean absolute difference between baseline and follow-up scans of the common carotid artery IMT of 0.027 mm and a coefficient of variation of 4.2%.
The between-sonographer (both within and between visit) mean absolute difference was 0.041 mm, with a coefficient of variation of 6.1%.

Requirements for clinical application

The current treatment of atherosclerosis involves biochemical targets, the selection of which is based on a large evidence base of outcome studies such as the 4S study.66,67 Nonetheless, this approach neglects the continuum of risk, even at “normal” lipid levels, and the interaction with other risk factors. A means of quantifying atherosclerotic burden or the adverse effects of risk factors on vascular function may be of value in decision-making regarding the initiation of treatment in patients with borderline lipid values, in guiding the addition of other agents, and in providing information to patients regarding the efficacy of treatment. Moreover, these investigations may be used as a surrogate of outcome in research studies.

The current application of these investigations has been across populations and in tightly controlled research groups. Although increased IMT has been shown to prospectively predict myocardial infarction and stroke55 and abnormal coronary endothelial function has been shown to be predictive of cardiovascular events,55,56 this has not yet been validated with regard to peripheral arterial reactivity. Furthermore, although a number of studies have been described in which the introduction of an intervention has improved either FMD or IMT, prospective studies are required that exhibit that the improved FMD or IMT is also associated with improved cardiovascular events or prognosis.

Before these investigations can be applied to individual patients, more automated and reproducible measurement approaches are needed. Recent developments in border recognition may facilitate automated approaches that reduce test-retest variation and move the tests into routine clinical practice.

References

thickness is only weakly correlated with the extent and severity of coronary artery disease. Circulation 1995;92:2127-34.


