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Measurement of subclinical atherosclerosis: beyond risk factor assessment

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Abstract

Purpose of review Assessment of subclinical atherosclerosis using the current available noninvasive imaging modalities holds promise for individual cardiovascular risk management and monitoring efficacy of therapeutic interventions (i.e. surrogate end-points). The present review addresses benefits and limitations of flow-mediated dilatation, intima-media thickness, electron-beam computed tomography and magnetic resonance coronary angiography.

Recent findings Both carotid intima-media thickness and peripheral flow-mediated dilatation correlate inversely with cardiovascular risk factors and coronary artery disease. They have been shown to carry predictive value for future cardiovascular events, but clinical application of both intima-media thickness and flow-mediated dilatation demands further methodological maturation of these techniques. Intima thickening has been successfully targeted in numerous intervention trials, but determination of an explicit threshold value beyond which cardiovascular risk significantly increases will facilitate its utility as a routine clinical tool. Electron-beam computed tomography can accurately detect and quantify coronary artery calcification (an established marker of the total coronary plaque burden). However, lack of evidence of its additional predictive power for future coronary events warrants for further research. Finally, magnetic resonance coronary angiography appears to be a promising technique, integrating both functional and anatomical aspects of coronary artery disease. Properly designed studies are needed to determine its value in clinical practice.

Summary Various noninvasive imaging techniques have recently emerged that may find applications in clinical research. However, before widespread clinical utilization, further technical refinement of all of the cited imaging modalities is mandatory. It will be a challenge over the coming few years to clarify whether improvements in surrogate end-points can directly be translated into improved outcomes.
Introduction

During the past few decades advances in drug development and widespread implementation of guidelines for individual risk factor management have resulted in a substantial reduction in cardiovascular morbidity and mortality. Despite these achievements, cardiovascular disease remains the leading cause of death worldwide, and new strategies are needed to improve these outcomes. Both improved management of traditional cardiovascular risk factors and the discovery of novel therapeutic agents, driven by the observation that only 50% of cardiovascular disease can be attributed to established risk factors, underscore the necessity of noninvasive diagnostic procedures. Such procedures are needed not only to assist in recruitment of subjects who are at intermediate/high risk for coronary artery disease (CAD) but also to provide us with reliable intermediate end-points that can be used to evaluate promising therapeutic strategies.

In addition, these procedures have great potential to become part of our routine diagnostic arsenal for assessment of individual cardiovascular risk and tailored therapies. Efficient preselection can assist in reducing the number needed to treat, thus enhancing macro-economic feasibility of prevention programmes. In the present review we highlight recent advances in noninvasive assessment of subclinical atherosclerosis, including measurement of intima-media thickness (IMT), electron-beam computed tomography (EBCT) and magnetic resonance coronary angiography (MRCA), as well as ultrasound assessment of flow-mediated dilatation (FMD).

Measurement of functional changes

It is widely recognized that abnormal endothelial function plays a key role in the pathogenesis of atherosclerosis, preceding structural wall alteration. The endothelium normally performs several homeostatic functions to maintain vascular tone and blood fluidity, and to inhibit inflammation, platelet aggregation, adherence of inflammatory cells to the vascular surface and smooth muscle cell proliferation. During long-term exposure to established cardiovascular risk factors the endothelium loses some of its properties, which initially results in an impaired endothelium-dependent vasodilatation. Over the past decade a noninvasive technique has evolved that enables assessment of these earlier stages of atherosclerosis.

Flow-mediated dilatation

An increase in forearm blood flow during reactive hyperaemia provokes the endothelium to release nitric oxide, which mediates vasodilatation of the brachial artery. Numerous factors, including food intake, smoking, vasoactive medication and menstrual cycle, can affect FMD. Therefore, careful standardization of both subject ‘preparation’ and ultrasound protocol are mandatory. In healthy persons FMD is usually more than 10% if upper-arm occlusion is used and more than 6% if forearm occlusion is used. Ultrasound imaging can be done either using B mode or M mode (wall tracking). In trained ultrasound technicians, the intrasession variation coefficient for baseline diameter is approximately 1%.
In contrast, the variation coefficient for intersession FMD varies from 15 to 30%\textsuperscript{17,25,26}. Based on these data, a significant (absolute) change in FMD in excess of 2% may be found in 20-30 persons using a crossover design\textsuperscript{27-29} (Wilmink CVR 2001) versus 40-60 patients using a parallel group design\textsuperscript{21,24}.

Relation to cardiovascular disease
All major cardiovascular risk factors are associated with endothelial dysfunction (i.e. impaired FMD response), including hypertension\textsuperscript{30,31}, hypercholesterolaemia\textsuperscript{32,33}, diabetes\textsuperscript{34,35}, smoking\textsuperscript{20,36}, hyperhomocysteinaemia\textsuperscript{37,38} and positive family history of premature CAD\textsuperscript{39,40}. Several studies have evaluated FMD as a screening test for CAD. Schroeder et al.\textsuperscript{41} measured FMD in 122 patients who were scheduled for coronary angiography. Using FMD below 4.5% as cut-off value, a sensitivity of 71% and a specificity of 81% were calculated for predicting the presence of CAD. Teragawa et al.\textsuperscript{42} found a sensitivity of 93% and a specificity of 88% in 81 patients with suspected CAD, using FMD below 6% as cut-off value. Kuvin et al.\textsuperscript{14} evaluated 94 persons who were scheduled for exercise myocardial perfusion imaging. Using FMD below 10% as a cut-off value (upper-arm occlusion cuff), a sensitivity of 91% and a specificity of 54% were calculated for predicting a positive exercise myocardial perfusion imaging test.

Endothelial dysfunction, which is usually assessed using coronary angiography, has also emerged as an independent predictor of cardiovascular events. In 157 patients with mild CAD, who were classified on the basis of their endothelial function, Suwaidi et al.\textsuperscript{43} found that after an average follow-up of 28 months all coronary events occurred in the group with severe endothelial dysfunction. Of note, there were no differences in vessel, lumen or plaque areas at baseline, refuting the suggestion that endothelial dysfunction merely reflects the severity of atherosclerotic disease. These findings were in accordance with those of a study conducted by Schachinger et al.\textsuperscript{44} in 147 CAD patients over an average 7.7 years of follow-up. In view of the correlation between endothelium-dependent vasodilatation of the coronary and brachial arteries - ranging from $r = 0.36$\textsuperscript{45,46} to 0.75\textsuperscript{47}, analogous results may be expected for peripheral FMD assessment. Neunteufl et al.\textsuperscript{48} evaluated the predictive value of FMD in 73 CAD patients after 5 years of follow-up. Using FMD below 10% as the cut-off (upper-arm occlusion), sensitivity between 75 and 90% and specificity between 39 and 51% were calculated for the occurrence of CAD events. However, in that study the relation between FMD and outcome disappeared after adjustment for the extent of CAD at baseline. More recently, Gokce et al.\textsuperscript{49} followed 187 patients who had undergone vascular surgery for 30 days after surgery. Using FMD below 8.1% as the cut-off value (upper-arm occlusion), FMD exhibited a sensitivity of 95% and a specificity of 37% for predicting cardiovascular events.

Clinical perspective of flow-mediated dilatation
FMD testing has emerged as a noninvasive, easily applicable test. FMD response correlates with all established CAD risk factors and with the presence and severity of CAD, as well as with risk for future cardiovascular events. It is readily reversible, facilitating the use of FMD in short-term intervention trials. However, several issues need closer attention before inte-
gration into clinical practice can be justified. First, careful standardization of the protocol, including subject preparation, should minimize variation in FMD. Moreover, technical advances will assist in progressive reduction in technical variation. Second, the large impact of individual risk factors on FMD compromises its use as a screening tool for CAD in the presence of multiple risk factors. In this respect, FMD may have particular relevance in 'younger' persons who lack clustering of risk factors or, in view of its high negative predictive value, a normal FMD may be used to indicate the absence of cardiovascular disease. Third, most studies on the value of FMD have been performed in small cohorts with a high pretest probability for CAD. These results are not readily applicable to the general population that is at low/intermediate cardiovascular risk.

Figure 1 FMD, flow-mediated dilation

**Measurement of structural changes**

Improved insight into the progression of atherosclerosis in human arteries suggests that the very early morphological changes in the vessel wall, observable using B-mode ultrasonography, may precede development of atherosclerotic lesions. At present, measurement of carotid wall thickening is widely believed to be a measurable index of the presence of atherosclerosis. Alternative noninvasive imaging modalities include EBCT and MRCA.

**Ultrasonographic measurement of intima-media thickness in carotid artery**

Measurement of carotid IMT has emerged as a major research tool since the early 1980s. Ultrasonographic visualization (high-resolution) of the distance between the lumen-intima and media-adventitia interfaces (defining IMT) truly reflects arterial wall characteristics, as indicated by earlier histopathologic studies. More recently, alternative ultrasound biomarkers such as carotid plaque volume and arterial wall properties (compliance and distensibility) are being evaluated with regard to their predictive value for cardiovascular disease.
Recent advances in IMT methodology are confined to the number of carotid segments that may be measured (distal carotid versus multiple sites; far wall versus near plus far wall; bilaterally versus unilaterally), the method of image analysis (automatic detection versus manual cursor placement) and the type of measure (mean of several maximum or randomly selected IMT measures). Combined efforts to improve reproducibility resulted in two main approaches. These include IMT measurement at multiple carotid sites (and multidirectional), which appears to add further to its predictive value for future cardiovascular disease \(^{55,56}\). The second approach, which is now widespread, is application of software-guided evaluation, which consists of automatic detection of the interface distance, resulting in acceptable interobserver and intraobserver variation coefficients \(^{57-60}\).

**Relationship to cardiovascular disease**

Many established CAD risk factors are related to IMT, as indicated by numerous cross-sectional studies\(^ {61-72}\). Clustering of these risk factors correlates with progressive intima thickening. Moreover, IMT has been associated with angiographically assessed CAD\(^ {73}\) and left ventricular hypertrophy\(^ {74-76}\).

A number of prospective studies addressed the issue of whether increased IMT in asymptomatic persons has predictive value for future cardiovascular events. The Kuopio Ischemic Heart Disease (KIHD) study\(^ {77}\) demonstrated a twofold increase in risk for myocardial infarction over 3 years associated with an IMT greater than 1 mm. Concordantly, the Atherosclerosis Risk in Communities study (follow-up period of 4-7 years)\(^ {78}\) reported that an IMT of 1 mm or greater was accompanied by increased risk ratios for coronary events of 5.07 (95% confidence interval (CI) 3.08-8.36) and 1.85 (95% CI 1.28-2.69) in women and men, respectively. These findings were complemented by those of the Cardiovascular Health Study\(^ {79}\) and the Rotterdam Study\(^ {80}\), both of which were conducted in elderly persons over 3-6 years. Finally, one secondary prevention study with a follow-up of 8 years (the Cholesterol Lowering Atherosclerosis Study\(^ {81}\)) demonstrated that, for each 0.03-mm increase per year in IMT, the relative risk for any coronary event was 3.1 (95% CI 2.1-4.5). Overall, the predictive value of increased IMT for future cardiovascular events is clearly emphasized by all cited studies, but IMT is most reliable when measured at multiple carotid sites.

Over the past decade numerous well designed trials that evaluated the effect of lipid-lowering agents on IMT have shown retardation of IMT progression after a follow-up of 2-4 years\(^ {82-86}\). In the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) study\(^ {87}\), conducted in 325 familial hypercholesterolaemia patients for 2 years, IMT regression was demonstrated in the atorvastatin (80 mg) group (-0.031 mm, 95% CI (-0.007 to -0.055) as compared with conventional treatment. Concordantly, the findings of trials evaluating the effect of antihypertensive compounds on IMT (i.e. angiotensin-converting enzyme inhibitors and calcium channel blockers) were similar although less pronounced\(^ {88-90}\).
Clinical perspective of intima-media thickness measurement

Carotid IMT measurement has proven to be a safe, inexpensive and easily applicable test. Evidence has accumulated to show a highly significant correlation between intima thickening and cardiovascular risk factors, established CAD and future cardiovascular events. In more than 15 therapeutic trials, IMT has successfully been used as a surrogate end-point. Because structural changes are evaluated, long-term follow-up for a minimum of around 2 years is required. However, before broader application can be advocated, several methodological obstacles must be overcome, including further standardization of the ultrasound protocols and definition of a potential threshold (adjustments for race, sex or age) above which cardiovascular risk increases significantly.

Figure 2 B-mode ultrasound image (intima-media thickness) of the common carotid artery

Electron-beam computed tomography

EBCT allows rapid and noninvasive quantification of coronary artery calcification, which reflects total coronary atherosclerotic burden. Given that arterial remodelling to maintain luminal integrity precedes significant luminal stenoses, measurement of CAC in the selection of at-risk individuals may prove superior to conventional coronary angiography (which assesses the coronary artery lumen only).

By this method, the entire arterial tree may be visualized in only 15 min, using an electron X-ray source and four stationary tungsten targets. The individual CAC score is then calculated according to Agatston’s method. Over the past few years, reproducibility in improvement in calcium score has been achieved with advances in hardware, scoring methods and imaging algorithms. Nonetheless, EBCT has limitations with regard to reliable visualization.
Relation to cardiovascular disease
Quantification of CAC provides a valid noninvasive surrogate for coronary atherosclerosis, as indicated by several histopathological and angiographical studies. Because extensive CAC reflects more advanced atherogenic stages, evidence of its relationship with traditional risk factors is still conflicting. This is illustrated by the fact that, in young patients with familial hypercholesterolaemia, CAC is absent, whereas increased IMT or impaired FMD already can be identified in such individuals.

Many established risk factors appear to correlate with CAC quantity. However, the overall predictive potential of EBCT for hard coronary events in asymptomatic persons remains a topic of debate. Whereas some studies failed to demonstrate its additional predictive value in primary risk stratification, others reported a higher incidence of hard coronary events in persons with advanced CAC scores. Complementary, rapid progression of the CAC score might predict future cardiovascular events.

A few therapeutic trials have addressed the effect of lipid-lowering therapy on EBCT findings and demonstrated minor favourable changes in CAC. These findings are consistent with a strong attenuation of CAC after initiating the antihypertensive agent nifedipine - a calcium channel blocker. In contrast, cardiovascular outcome remained unaffected by nifedipine. Hence, further data are awaited. Both the American Heart Association prevention V report and the American Heart Association/American College of Cardiology report on EBCT emphasized the need for additional, appropriately designed studies to define clearly which patients could benefit from EBCT and patient follow-up for assessing progression or regression of CAD in response to pharmaceutical intervention.

Clinical perspective of electron-beam computed tomography
EBCT is a promising imaging technique for diagnosing obstructive CAD but it is not sufficiently robust to replace invasive coronary angiography. Absence of an accurate prediction of risk argues against its integration into individual CAD risk management. Moreover, misuse of EBCT might lead to unnecessarily invasive cardiodiagnostic tests and aggressive therapeutic intervention.

Magnetic resonance coronary angiography
Invasive coronary angiography has been the ‘gold standard’ for identification of clinically significant coronary stenoses (>50% reduction in diameter). However, its failure to identify early lesions (luminology), laboriousness, major complication rate of 0.3-1.1% and high costs mandate development of alternative diagnostic approaches. MRCA has developed rapidly as a noninvasive method to assess both subclinical and symptomatic coronary atherosclerosis. Recent technical/methodological advances, comprising respiratory gating (imaging while the patient is breathing freely) and standardization of scanning protocols (and hardware and software), led to enhanced spatial resolution and minimal patient discomfort. Currently, accuracy remains poor for detection of CAD in small-diameter vessels (left circumflex) or if extensive calcifications are present. Apart from visualization of cardiovascular anatomy.
in any desired plane, MRCA facilitates simultaneous assessment of functional parameters (left ventricular function measurements, coronary flow reserve and flow velocity). Moreover, MRCA offers the benefits of high spatial resolution, providing detailed information on perfusion heterogeneity within the myocardium, and on the composition and microanatomy of the atherosclerotic plaque in order to identify lesions that are prone to rupture. Importantly, MRCA does not involve the use of ionizing radiation.

**Relation to cardiovascular disease**

Thus far, the association between conventional CAD risk factors and MRCA outcome has not been evaluated. In a recent prospective study\(^{122}\), noncontrast MRCA was compared with invasive coronary angiography in 109 patients who were referred for elective angiography. MRCA appeared to have a high sensitivity and negative predictive value for detecting CAD, but reliability was limited to the left main coronary artery or three-vessel disease. These findings are in agreement with those of another study\(^{121}\), which was conducted in 31 patients with a history of percutaneous transluminal angioplasty with stent implantation. Evidence of the predictive value of MRCA for future cardiovascular events in asymptomatic persons is lacking.

**Clinical perspective of magnetic resonance coronary angiography**

MRCA is developing rapidly as an alternative for invasive conventional angiography in diagnosing CAD. However, the relationship between MRCA findings and traditional cardiovascular risk factors and its predictive value in asymptomatic persons are still unknown. Nevertheless, MRCA appears to be a promising technique for assessment of subclinical atherosclerosis\(^ {124}\), and limitations are confined to restricted image quality and high costs.

**Conclusion**

Individualization of cardiovascular risk management and monitoring of efficacy of novel therapeutic strategies, as well as evaluation of individual response to instituted therapy increasingly call for incorporation of intermediate end-points both in the diagnostic and therapeutic work-up of populations at risk for CAD.

Assessment of FMD constitutes an attractive biomarker for the following reasons: abnormalities can be detected early in the course of atherogenesis, indicating a reversible state; changes in FMD (after initiating therapy) can be analyzed after a short period; and functional changes may provide further insight into lesser-known areas such as plaque stabilization. Remaining issues of concern regarding FMD testing are lack of methodological standardization and its reproducibility. During advanced stages of atherogenesis IMT measurement may be of major relevance because early structural alterations can be detected with good reproducibility and progression rate reflects the interaction of multiple risk factors. Issues of
concern for IMT assessment are further methodological standardization and refinement of the value of IMT for individuals (e.g. upper value indicating increased cardiovascular risk). Finally, MRCA and EBCT are rapidly emerging as tools with which to detect manifest macrovascular disease. Expectations for magnetic resonance imaging of the coronaries are high, and we await further evolution of technical capabilities.

The use of noninvasive techniques as surrogate end-points in intervention trials is rapidly gaining ground, but their use in the individual patient, both for diagnosis and during follow-up, is still trailing behind. In view of ongoing efforts, however, it can be anticipated that clinical implementation of one or various noninvasive measurements will allow more careful selection of 'intermediate/high-risk' persons who are in need of aggressive therapeutic interventions.

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