Noninvasive Ultrasound Techniques for the Assessment of Atherosclerosis in Coronary Artery Disease

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Atherosclerosis is a generalized arterial disease that begins decades before the onset of clinical symptoms, such as angina pectoris, myocardial infarction or stroke, and it is this preclinical lag phase that provides the opportunity for the presymptomatic detection of disease, the identification of high-risk subjects, and initiation of appropriate preventive strategies. The most innovative imaging techniques currently used include vascular sonography, electron-beam and multislice computed tomography (CT), and magnetic resonance imaging (MRI). Noninvasive ultrasonography (US) has been used to detect early signs of atherogenesis, such as impaired endothelial function, increased arterial wall thickness and decreased arterial distensibility, as well as atherosclerotic lesions reflecting a more advanced state of disease.

Atherosclerotic Lesions

Background and Methods

The earliest and most extensive atherosclerotic lesions usually occur in the aorta, and later in the coronary and carotid vessels. In a population-based study involving a large cohort (60,393 women, 55,916 men) aortic arch calcification detected by chest X-ray was not only associated with traditional cardiovascular risk factors, but also independently related to increased risk of coronary artery disease (CAD) in both sexes. However, the low resolution of X-ray studies limits the possibility of detecting atherosclerotic plaque in the aorta and makes it difficult to draw conclusions about the coexistence of CAD. In contrast, transesophageal echocardiography (TEE) offers high resolution imaging for evaluation of diseases of the thoracic aorta with high interobserver and interreader reproducibilities. Transesophageal echocardiography (TEE) has also been used to visualize plaque in the ascending aorta and aortic arch, but because the resolution of images obtained by TEE is currently not as high as that of images obtained with a transducer in the esophagus, TEE is the procedure of choice for the detection, measurement and characterization of thoracic aortic atheromas. In patients with CAD, atherosclerotic plaques were found predominantly in the descending aorta (93%) and in the aortic arch (80%), whereas the ascending aorta was the least involved (37%).

Cardiovascular Risk Factors

Not surprisingly, coronary and aortic atherosclerosis share the same risk factors. Age, male gender, smoking, diabetes, hypercholesterolemia, and hypertension have been shown to be independent predictors of thoracic atherosclerotic plaque. In addition to these ‘traditional’ risk factors, both fibrinogen and homocysteine concentrations have been positively correlated with aortic atherosclerosis. Moreover, age, smoking, hypercholesterolemia, diabetes, and hypertension are related to the extent and severity of thoracic aortic atherosclerosis.

Predictors of CAD

Atherosclerotic plaques in the aorta and femoral arteries and, to a lesser extent, in the carotid arteries are strong predictors of CAD. Studies in highly selected patient groups, as well as in the general population, have demonstrated an association between aortic atherosclerosis as determined by TEE and angiographically defined CAD. Aortic atherosclerosis correlates with the angiographic extent of CAD and is predictive of obstructive CAD even after adjusting for conventional CAD risk factors. However, in patients over the age of 70 years the presence of atherosclerotic lesions of the thoracic aorta failed to predict CAD and, conversely, the lack of aortic plaque on TEE is predictive of the absence of CAD. In patients with valvular heart disease it has been suggested that the absence of aortic plaque, based on TEE, should be added to the criteria for deciding not to perform coronary arteriography.

Prognostic Value

The ‘French Study of Aortic Plaques in Stroke’ group demonstrated that atherosclerotic plaques in the aortic arch that are greater than 4 mm in thickness determined by TEE are a strong independent predictor of vascular events (including cerebral infarctions, myocardial infarctions, peripheral embolisms, and vascular deaths) in patients 60 years or older who were consecutively admitted with ischemic stroke. Interestingly, the results of the British Regional Heart Study (BRHS) suggest that the presence of plaque rather than increased intima media thickness (IMT) is the major criterion of high risk of disease in patients who have been followed up for mortality and nonfatal cardiovascular disease events. However, these findings need to be confirmed by prospective studies.

In addition to quantitative analysis, qualitative analysis of plaque can be determined by surface and transesophageal US. Hypoechoic heterogeneous plaque is associated with both intraplaque hemorrhage and lipids, whereas hyperechoic homogeneous plaque is mostly fibrous. The risk of vascular events associated with aortic plaque thickness (≥24 mm) is markedly increased in the absence of plaque calcification. Ultrasonic contrast agents have been introduced to improve image resolution and specificity for example, acoustically reflective liposomes conjugated with monoclonal antibodies have been used for...
targeted imaging of plaque components. However, further studies elucidating the composition of plaque using US textural analysis are required and moreover, the role of qualitative analysis of noncoronary atherosclerotic lesions in the management of patients at risk of CAD needs to be determined.

In summary, aortic atherosclerotic plaques may serve as a good marker of severe generalized atherosclerotic disease that could be used to select patients at high risk for cardiovascular events and to evaluate the regression or progression of atherosclerosis related to therapeutic interventions.

Therapeutic Interventions

To date, little is known about the impact of therapeutic interventions on thoracic aortic atherosclerosis determined by TEE; however, the observations of a 2-year follow-up study of 16 newly diagnosed patients with heterozygous familial hypercholesterolemia support the hypothesis that lipid-lowering therapy may favorably affect the course of thoracic aortic atherosclerosis.

IMT

Background and Methods

As atherosclerosis develops in the coronary arteries, the lumen of the artery initially does not narrow but rather enlarges. The same is true of the common carotid artery. Stenosis develops in a very small number of patients with advanced atherosclerosis and therefore is an extremely insensitive index of atherosclerosis. Carotid 2-dimensional US has been shown to be a valid and reliable indicator of wall thickness of the extracranial carotid arteries. IMT is defined as the distance between the lumen–intima interface and the media–adventitia interface, but because of the physical principles of diagnostic US, the measurement is reliable only at the far arterial wall and does not indicate whether the thickening is caused by intima or media infiltration and/or hypertrophy. Both the new digital systems as well as the more widely used analogue system have been used for IMT evaluation and showed comparable reproducibility. Interestingly, pathologic examinations have shown that the relationship between atherosclerosis of the carotid and coronary arteries is as strong as that between any 2 coronary arteries.

Cardiovascular Risk Factors

Many risk factors (ie, age, gender, diabetes, blood pressure, active and passive smoking, elevated concentrations of low-density lipoprotein cholesterol and low concentrations of high-density lipoprotein cholesterol, homocysteine, and chlamydia) that are associated with clinical coronary artery disease are also associated with a larger diameter and IMT of the extracranial carotid arteries. Moreover, IMT values of carotid arteries were associated with the number of atherosclerotic risk factors, and so it has been suggested that IMT reflects an individual’s past exposure to risk factors.

Predictor of CAD

The IMT of the carotid, aortic, femoral and brachial arteries were significantly higher in patients with CAD compared with controls and moreover, the IMT of the common carotid artery is increased in older subjects with asymptomatic myocardial ischemia as evidenced by exercise ECG alone or in combination with thallium scan. Thus, it has been suggested that carotid US may help to identify asymptomatic individuals with CAD. However, carotid IMT is only weakly correlated with the extent and severity of CAD although interestingly, the authors of the BRHS reported that the common carotid IMT and bifurcation IMT correlated with each other but showed differing patterns of association with risk factors and prevalent disease. Bifurcation IMT and plaque showed very similar patterns of association with cardiovascular risk factors and disease, whereas common carotid IMT appears to be more strongly associated with risk factors for stroke (ie, blood pressure and FEV1). However, bifurcation IMT values in the BRHS were higher than in other populations which seems to be related to a high prevalence of plaques in the BRHS patients.

Two large epidemiologic studies, the Atherosclerosis Risk in Communities (ARIC) study and the Cardiovascular Health study (CHS) clearly demonstrated an association of IMT with CAD prevalence in middle-aged (45–65 years) and elderly subjects (>65 years), respectively. The usefulness of quantitative carotid IMT and thoracic aorta IMT measurements in excluding significant CAD in patients scheduled for heart valve surgery was recently evaluated and demonstrated that carotid IMT less than 0.55 mm and thoracic aorta IMT less than 3 mm had an excellent negative predictive value for excluding significant CAD, suggesting that IMT measurements may be useful in selecting patients who do not require coronary angiography before heart valve surgery.

Prognostic Value

IMT may also be a useful marker of CAD progression. The ARIC study showed that mean carotid IMT is a noninvasive predictor of future CAD events and the CHS demonstrated that carotid IMT is associated with the incidence of new myocardial infarction or stroke. In accordance with those findings, the Rotterdam Study revealed significant relationships between disease events (ie, stroke and acute myocardial infarction) and common carotid artery IMT, but after adjustment for other risk factors, these fell to insignificant levels for MI and were of only borderline significance for stroke.

Therapeutic Interventions

Intervention studies have reported changes in both bifurcation and/or hypertrophy (Fig 1). Both the new digital systems as well as the more widely used analogue system have been used for IMT evaluation and showed comparable reproducibility. Interestingly, pathologic examinations have shown that the relationship between atherosclerosis of the carotid and coronary arteries is as strong as that between any 2 coronary arteries.

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cation and common carotid IMT as surrogate end-points for trials of antihypertensives, cholesterol-lowering drugs, antioxidant vitamins, and estrogen. Several studies demonstrated a beneficial effect of cholesterol-lowering treatment on IMT after 1 year of treatment. In addition, a follow up study of the CLAS trial demonstrated a prospective relation between the rate of IMT progression and the appearance of cardiovascular events: the relative risk was 2.2 for myocardial death or coronary event, and 3.1 for any coronary event per IMT progression rate of 0.03 mm per year. No evidence was found for changes in IMT as a marker for alterations of atherosclerosis in coronary arteries. In the Multicenter Iraspidine Diuretic Atherosclerosis Study (MIDAS) there was no difference in the rate of progression of mean maximum IMT between iraspidine and hydrochlorothiazide over 3 years in patients with mild to moderate hypertension. Small changes in the carotid IMT were found in the Verapamil in Hypertension and Atherosclerosis Study (VHAS) in patients receiving verapamil as well as in those receiving chlorthalidone, but a lower rate of IMT progression and less cardiovascular events were observed in the verapamil group. The SECURE trial, a substudy of the HOPE study, showed that long-term angiotensin converting enzyme inhibitor therapy retards the progression of human atherosclerosis in patients who had vascular disease or diabetes and at least one additional cardiovascular risk factor. The beneficial effect of ramipril on atherosclerosis remained statistically significant after adjusting for a history of hypertension and for blood pressure changes, suggesting the benefit is not fully explained by lowering the blood pressure and may be related to a direct vascular protective effect. Healthy postmenopausal women without preexisting cardiovascular disease who randomly received unopposed estrogen replacement therapy with 17β-estradiol had less progression of common carotid artery IMT, than did those who received placebo; in subgroup analysis, this result was seen only in women not receiving lipid-lowering medication. Controversial results have been obtained with antioxidant vitamins. In non smoking 40–59-year old men with previous coronary artery bypass graft surgery, supplementary vitamin E intake (≥100 IU per day) appears to be effective in reducing the progression of IMT in subjects not treated with lipid lowering drugs (colestipol/niacin) and a subgroup analysis of the Atherosclerosis Prevention (ASAP) study found benefit in hypercholesterolemic men who smoked and received combined supplementation of vitamins E and C. Very little support for an association between antioxidant intake and/or plasma concentrations and early carotid atherosclerosis has been provided by the CUDAS trial. Dietary vitamin E intake was found to have an inverse relationship with carotid IMT in men; however, this relationship was very weak and explained only 1% of the variance in measured IMT in men. Finally, in the SECURE trial, administration of vitamin E (400 IU per day) had a neutral effect on carotid IMT progression in high-risk patients. In summary, any association between individual antioxidant vitamins and early atherosclerosis, if present, is likely to be modest.

### Elastic Properties

**Background and Methods**

Atherosclerotic changes in the arterial wall include smooth muscle cell proliferation, deposition of lipid, and accumulation of collagen, elastin and proteoglycans. Elastin and collagen are responsible for elastic behavior, which allows systolic wall distension (strain) under pulse pressure (stress), and the elastic properties of each wall component can be described by the slope of their stress–strain relationship. This slope, known as Young’s modulus for linear deformation, is much steeper for collagen (1.000×10⁶ dynes/cm² at 100% elongation) than for elastin (3×10⁶ dynes/cm²). In addition, reduced flow in the vasa vasorum, which for the ascending aorta originates from the coronary arteries, might contribute to abnormal elastic properties of the ascending aorta in patients with CAD.

### Table 1 Methods of Estimating Aortic Elastic Properties

<table>
<thead>
<tr>
<th>Strain (S)</th>
<th>( S = Dd - Dd/Dd )</th>
<th>( Dd = \text{diastolic diameter}, Ds = \text{systolic diameter} )</th>
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</thead>
<tbody>
<tr>
<td>Elastic modulus (Ep)</td>
<td>( Ep = (Ps - Pd)/S )</td>
<td>( Ps = \text{systolic pressure}, Pd = \text{diastolic pressure}, S = \text{strain} )</td>
</tr>
<tr>
<td>Beta index (β)</td>
<td>( \beta = \ln[(Ps/Pd) + (Ds - Dd)/Dd] )</td>
<td>( \beta = \text{natural logarithm} )</td>
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<tr>
<td>Elastic modulus (E)</td>
<td>( E = \pi P/\pi De, 2De Di(1 - \beta^2)/De^2 - Di^2 )</td>
<td>( P = \text{changes of intravascular pressure}, \beta = \text{changes of the external diameter}, Di = \text{changes of the internal diameter}, \alpha = \text{constant with a value for blood vessels of approximately 0.5} )</td>
</tr>
<tr>
<td>Intermental elastic modulus (Eim)</td>
<td>( E_{\text{im}}(\beta) = 0.75 )</td>
<td>( Rm = \text{midwall radius}, \omega = \text{aortic midwall stress} )</td>
</tr>
<tr>
<td>Distensibility (D)</td>
<td>( D = 1/E(H/Dd) )</td>
<td>( Dd = \text{diastolic diameter}, H = \text{thickness of the vessel} )</td>
</tr>
<tr>
<td>Distensibility (D) [vessels with thin walls]</td>
<td>( D = 2(Ds - Dd)/Dd )</td>
<td>( Dd = \text{diastolic diameter}, Ds = \text{systolic diameter}, Ps = \text{systolic pressure}, Pd = \text{diastolic pressure} )</td>
</tr>
<tr>
<td>Compliance (CC)</td>
<td>( CC = H D (Ds - Dd)/2(Ps - Pd) )</td>
<td>( Dd = \text{diastolic diameter}, Ds = \text{systolic diameter}, Ps = \text{systolic pressure}, Pd = \text{diastolic pressure} )</td>
</tr>
<tr>
<td>Pulse wave velocity (PWV)</td>
<td>( PWV = ZO \omega \cdot ro )</td>
<td>( ZO = \text{characteristic impedance}, ro = \text{blood density} )</td>
</tr>
<tr>
<td>Acceleration index (Acut)</td>
<td>( V_{\text{max}}/T_p )</td>
<td>( V_{\text{max}} = \text{maximal velocity}, T_p = \text{time to peak} )</td>
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</table>
Various methods have been used to determine the mechanical properties of the aorta, but 2 main types of stiffness index are easily applicable to noninvasive US; that is, indices derived from classical moduli of biomechanics relating strain to stress\(^{65-67}\) and indices derived from Doppler measurements based on the changes in aortic flow acceleration\(^{68}\). However, consensus on the preferred ‘stiffness index’ has not been established (Table 1).

**Cardiovascular Risk Factors**

The stiffness of the thoracic aorta rises sharply with advancing age. Interestingly, the slope relating U index to age was less steep for symptom-free subjects with hypercholesterolemia than for their counterparts with normal serum cholesterol\(^{69}\). Age and cardiovascular risk factors, such as arterial hypertension, diabetes mellitus and hypercholesterolemia, are accompanied by disturbances in collagen metabolism and are associated with decreased distensibility, which is the ability of the artery to expand in response to pulse pressure\(^{69-77}\). Moreover, in habitual smokers, smoking one cigarette causes short-term decreases in distensibility of both the carotid and brachial arteries, leading the authors of that study to speculate that short-term increases in arterial wall stiffness might be harmful to the artery and increase the risk for plaque rupture\(^{78}\). Invasive studies have demonstrated that both passive and active smoking were associated with changes in the aortic pressure–diameter relationship\(^{79}\). In patients who already had vascular disease or atherosclerotic risk factors, the risk scores increased nearly linearly with decreasing common carotid distensibility\(^{80}\). Thus, arterial stiffness seems to be an index of the cumulative effect of all risk factors on the elastic properties of the arterial wall.

**Predictor of CAD**

Patients with CAD have markedly lower distensibility of the ascending aorta than normal subjects, as shown by both invasive and non-invasive techniques\(^{64}\). Moreover, the stiffness index of both the abdominal aorta and the carotid arteries, determined noninvasively by US in patients with 2- or 1-vessel disease, was lower than those in patients with 3-vessel disease. Thus, it has been suggested that serial evaluation of the arterial stiffness may allow the early detection of pathologic acceleration of the aging process and may be useful for prevention of CAD\(^{81}\).

**Prognostic Value**

A wide pulse pressure in men is an independent predictor of cardiovascular and especially coronary mortality in both hypertensives and normotensives\(^{82,83}\). However, pulse pressure does not take into account all parameters of elastic properties. Increased arterial stiffness, determined by both aortic pulse wave velocity (PWV) as well as carotid incremental elastic modulus ($E_{inc}$), is a strong independent predictor of cardiovascular mortality in end-stage renal disease\(^{84,85}\). In patients with ischemic heart disease, both invasive (aortic stiffness constant) as well as noninvasive (aortic root distensibility) measures of aortic elastic properties predicted recurrent acute coronary events. Thus, aortic stiffness measurements might help in the evaluation of the individual risk during secondary prevention\(^{86}\).

**Therapeutic Interventions**

Cholesterol-lowering therapy with statins in patients with familial hypercholesterolemia has been shown to decrease the arterial wall stiffness in the common femoral artery\(^{87}\). Nifedipine increased the aortic distensibility in both normal subjects and patients with CAD in a semi-invasive study that measured aortic diameters by echocardiography and aortic pressures directly by catheterization of the ascending aorta\(^{88}\). Administration of a combination of trandolapril and verapamil to hypertensive subjects decreased mean arterial and pulse pressures more than each compound alone. The blood pressure reduction was associated with significant increases in carotid, brachial, and abdominal aorta distensibility. Thus, there is no doubt that mechanical factors have a major role in the increase of distensibility. Nevertheless, such changes in distensibility were observed even after adjustment for the percent decrease in mean arterial pressure, suggesting a significant contributive role of nonpressure mechanisms\(^{89}\). In patients with Marfan syndrome a heterogeneous response (normalizing or worsening) has been observed in both the aortic stiffness index and distensibility to $\beta$-adrenergic blockade, with possible implications for their prognosis\(^{90,91}\). These data are in accordance with the fact that $\beta$-blockers do not inhibit aortic root dilatation in all patients with Marfan syndrome. Long-term folic acid treatment showed no major effect on carotid artery stiffness in chronic dialysis patients using a non-invasive vessel wall movement detector system\(^{92}\).

**Flow-Mediated Dilation (FMD)**

**Background and Methods**

The endothelium plays a key role in vascular homeostasis through the release of a variety of autocrine and para-
Cardiovascular Risk Factors

Endothelial dysfunction has been demonstrated in asymptomatic children and young adults with risk factors for atherosclerosis,94 hypercholesterolemia is associated with endothelial dysfunction in children as young as 7 years old. Impaired FMD has been independently correlated with low density lipoprotein (LDL)-cholesterol as well as lipoprotein(a).96 and active as well as passive cigarette smoking has been shown to be associated with impaired FMD, which is partially reversible after smoking cessation.97-99 Cigarette smoke contains large amounts of free radicals, which may degrade the NO released from the endothelium and also produce highly reactive intermediates, resulting in endothelial injury. Interestingly, administration of nicotine nasal spray containing 1 mg of nicotine also causes acute endothelial dysfunction in the brachial artery of chronic smokers suggesting that nicotine itself contributes to the acute endothelial dysfunction after cigarette smoking.100 Further modifiable cardiovascular risk factors associated with impaired endothelial-dependent vasodilation in the preclinical phase of vascular disease are diabetes, hypertension, and hyperhomocysteinemia.101-103 Regarding arterial hypertension, one large study using plethysmography failed to confirm this finding104 although that does not argue against evidence that basal release of NO is abnormal in the forearm vasculature of these patients, but does call into question evidence of abnormal responsiveness of this vascular bed to acetylcholine or other muscarinic agonists. Aging, too, is associated with progressive endothelial dysfunction in both genders, although the age-related impairment in endothelial function appears to occur earlier in men than women, consistent with a protective effect of physiological concentrations of estrogen on endothelial function.105 Furthermore, even young adults with a family history of premature CAD, but no additional risk factors, show impaired FMD, suggesting a direct inherited influence on arterial function from an early age.106

Predictor of CAD

Several studies have shown impaired FMD in the brachial artery of patients with CAD104,107-113 but it is still point of discussion whether the functional response of the brachial artery reflects the presence and perhaps stage of CAD or only the number and intensity of risk factors. Previous studies examining FMD in patients undergoing coronary angiography for the evaluation of chest pain have reported that the impairment of FMD is an independent predictor for the presence of angiographically detectable CAD.10-112 However, a recent study of 179 patients undergoing coronary angiography for the evaluation of chest pain failed to demonstrate an impairment of FMD in patients with CAD (≥30% diameter stenosis in more than 1 major branch) compared with patients with chest pain but smooth coronary arteries.113 Differences in the degree and duration of risk factors, differences in lifestyle, differences in the stage of CAD as well as methodological differences might have been responsible for this discrepancy. Interestingly, individuals with CAD defined by nuclear imaging showed lower FMD than those with normal exercise myocardial perfusion imaging.114 Because of an excellent negative predictive value for CAD the authors of that study speculated that the assessment of FMD with brachial US might be useful as a screening tool to exclude CAD in low-risk subjects undergoing evaluation for suspected CAD.

Prognostic Value

Some studies assessing coronary endothelial dysfunction strongly suggest that impaired vascular function relates to the pathogenesis of cardiovascular disease.115-117 With regard to brachial artery US we have previously demonstrated that the impairment of FMD is a predictor of combined cardiac events, including coronary angioplasty, coronary bypass and acute MI, in patients presenting with chest pain.118 More recently, Gokce et al have shown that impaired FMD of the brachial artery independently predicts short-term cardiovascular events in patients undergoing vascular surgery.119 Both studies showed a strong negative predictive value of preserved FMD.

Therapeutic Interventions

US-based study methods have documented improvement of FMD in CAD patients and patients at risk of CAD with the use of lipid-lowering therapy (in particular statins), antioxidant vitamins (vitamins C and E), folic acid treatment, ACE inhibitors, angiotensin-receptor antagonists, calcium antagonists, hormone replacement therapy, L-arginine, tetrahydrobiopterin etc.120-130 However, the important question for the clinician is what to do with these findings. Consistent data have been obtained with regard to lipid-lowering therapy. Improvement of endothelial function in the forearm vasculature of patients with hypercholesterolemia was observed after a single session of LDL apheresis131 and within 1 month of statin therapy.132 Moreover, statin therapy has been shown to be associated with sustained improvement of FMD for up to 10 months in patients with CAD in whom statin therapy was newly established.121 In contrast, controversial results have been obtained with regard to the effects of antioxidant vitamins on endothelial function. In a previous study we demonstrated that oral supplementation of vitamin E can attenuate the transient impairment of endothelial function after heavy smoking, but cannot restore chronic endothelial dysfunction within 4 weeks in healthy male smokers.122 Furthermore, Raitakari
et al showed that oral vitamin C therapy improves endothelial dysfunction in healthy young smokers within 2h, but has no beneficial long-term effect, despite sustained elevation of plasma ascorbate concentrations. The reason for this lack of effect is unclear, but may indicate the reduction in the bioactivity of vitamin C associated with prolonged therapy. In summary, these studies demonstrate that therapeutic strategies resulting in acute improvement of endothelial function do not necessarily affect chronic endothelial dysfunction. Thus, randomized clinical trials are needed to critically examine whether (acute and/or sustained) improvement of FMD in the brachial artery is associated with a better clinical outcome.

**Summary and Conclusions**

Noninvasive US has been shown to detect morphologic, mechanical and functional signs of atherosclerosis in the preclinical phase of CAD and has brought new insights into the pathophysiology and treatment of CAD. However, to be considered a surrogate marker for both the diagnosis of CAD and therapeutic monitoring, a test must have the ability to predict risk of CAD, and improvement of the marker must correlate with improvement of the atherosclerotic process. A recent study suggests that morphological parameters predict the presence of angiographically evident CAD more accurately than functional and mechanical parameters determined by noninvasive US. Although there is some correlative evidence that the presence of atherosclerotic lesions in the aorta, increased aortic stiffness, impaired FMD in the brachial artery and increased IMT of the carotid artery are associated with increased risk of cardiovascular events, a prospective study investigating the relationship between the rate of progression of the surrogate marker and the appearance of cardiovascular events has so far only been demonstrated for IMT. Studies examining IMT or FMD in selected patient groups demonstrated a strong negative predictive value for excluding angiographically evident CAD and suggest that these parameters may be useful in the management of patients undergoing heart valve surgery and in patients at low risk for CAD, respectively. Furthermore, patients undergoing vascular surgery with relatively preserved FMD had a very low risk of postoperative cardiovascular events. However, the positive predictive values of these markers for the detection of CAD as well as for identifying patients at high risk of cardiovascular events were low. A combined evaluation of morphological, mechanical and functional sonographic parameters might result in a more accurate identification of patients at risk of CAD who would benefit from appropriate preventive strategies. Some studies have shown that aortic atherosclerosis, carotid IMT, aortic/carotid elastic properties, and FMD of the brachial artery are related to the severity of CAD; however, their specificity for significant stenoses is poor, probably because of a strong correlation with atherosclerotic risk factors and mild disease. Thus, the detection of significant CAD remains the domain of noninvasive tests for myocardial ischemia such as exercise electrocardiography, myocardial scintigraphy, and stress echocardiography.

Electron-beam and multislice CT allow noninvasive assessment of coronary atherosclerosis and both methods have been demonstrated to accurately detect and quantify coronary calcification, confirming the presence of a coronary atherosclerotic plaque. The extent of calcium predicts the angiographic extent of CAD, in particular the number of vessels involved and the likelihood of the presence of significant stenosis. A high calcium score (eg, Agatston score >400) may be consistent with moderate to high risk of cardiovascular events within the next 2–5 years, whereas if no calcium is present, the angiographic features are likely to be normal. However, because of the lack of specificity and low statistical power of available studies this procedure has not been recommended yet as a screening test for CAD in asymptomatic patients. Recent studies indicate the potential of contrast-enhanced CT to detect and quantify stenotic lesions and furthermore, the composition of the atherosclerotic plaques within the coronary vessel wall can be characterized.

MRI has the ability to image atherosclerotic plaque and to determine plaque morphology in human carotid arteries in vivo with high sensitivity and specificity. It may also have the potential to measure wall thickness of the coronary arteries and to detect clinically significant lesions in vivo. However, although promising results have been reported for both coronary CT and coronary MRI, their usefulness for disease management and their impact on patient outcome have yet to be demonstrated.

In conclusion, noninvasive imaging techniques, including US, have diagnostic value, but the role and indication for the clinical use of noninvasive surrogate markers of atherosclerosis is still a matter of debate and investigation. Large cohort studies, such as the Multiethnic Studies of Atherosclerosis (MESA) in which FMD, carotid IMT, and vascular compliance are measured cross-sectionally in 6,500 patients and then observed prospectively for 10 years are underway, and should help define the future role of noninvasive US in clinical practice.

**References**


Burton AC. Relation of structure to function of tissues of the wall of blood vessels. Physiol Rev 1954; 34: 619 – 642.


Arentz DK, Evans GW, Riley WA. Arterial stiffness: A new cardio-

Fuertes A, Laurent S, Boutouyrie PH, Safar ME. Arteri-


Saloman V, Riley W, Kark JD, Nardo C, Folsom AR. Non-insulin- dependent diabetes mellitus and fasting glucose and insulin concentra-


Riley WA, Freedman DS, Higgs NA, Barnes RW, Zinkgraf SA, Berenson GS. Decreased arterial elasticity associated with cardio-


Mitchell GF, Moye LA, Braunwald E, Rouleau JL, Bernstein V, Gittman EM, et al. Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function: SAVE investigators (Survival and Ventricular Enlarge-

Madhavan S, Ooi WL, Cohen H, Alderman M. Relation of pulse pressure and blood pressure reduction to the incidence of myocar-

Blacher J, Gaerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal dis-


Topouchian J, Asmar R, Sayegh F, Rudnicki A, Benetos A, Barci AM, et al. Changes in arterial structure and function under tran-

Haouzi A, Berglund H, Pelikan PC, Maurer G, Siegel RJ. Heteroge-


128. O’Driscoll G, Green D, Taylor RR, Sinnvastan, an HMG-coenzyme A reductase inhibitor, improves endothelial function within I.


150. Barth JD. Which tools are in your cardiac workshop? Carotid ultrasound, endothelial function, and magnetic resonance imaging. Am J Cardiol 2001; 87: 8A – 14A.