Arterial Ultrasonography and Tonometry as Adjuncts to Cardiovascular Risk Stratification

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Myocardial infarction and stroke often occur without prior warning in asymptomatic individuals. Identifying individuals at risk is important for cost-effective use of preventive therapies. Algorithms based on risk factors statistically associated with cardiovascular events classify individuals into high-risk, intermediate-risk, or low-risk categories. However, more than one-third of adults in the U.S. are in the intermediate-risk category, and decisions regarding therapy are challenging in this subset. Testing for alterations in arterial function and structure that predate cardiovascular events may help refine cardiovascular risk assessment in the intermediate-risk group and identify candidates for aggressive therapy. Vascular ultrasonography and tonometry are promising test modalities for assessment of arterial function and structure in asymptomatic subjects. Several prospective studies have shown that measures of arterial function and structure provide prognostic information incremental to conventional risk factors. Standardization of methodology and establishment of quality control standards in the performance of these tests could facilitate their integration into clinical practice as adjuncts to existing cardiovascular risk stratification algorithms. (J Am Coll Cardiol 2007;49:1413–26) © 2007 by the American College of Cardiology Foundation

Every year, 1.2 million Americans suffer a coronary event (approximately 1 event every 26 s and 1 death every min) and 700,000 develop a stroke (approximately 1 event every 45 s, causing 1 death every 3 min) (1). These events are most often related to atherosclerotic vascular disease and frequently occur without warning (2). Assessment of conventional risk factor burden is necessary but may not accurately estimate risk of cardiovascular disease (3). Most patients in whom myocardial infarction or ischemic stroke develops have one or more conventional risk factors for atherosclerosis, but these risk factors are also prevalent in the general population. As a result, the predictive value of algorithms based on conventional risk factors is unsatisfactory (4,5). Nearly 40% of adults in the U.S. may be at intermediate risk for a future cardiovascular event when assessed with current algorithms (6), and these individuals may benefit from further risk stratification. The available screening and diagnostic tests have limitations; cardiac stress tests detect only advanced, hemodynamically significant lesions, and conventional coronary angiography is invasive, provides only a “luminogram,” and does not identify vulnerable or unstable plaque. Tests for early detection of atherosclerotic vascular disease are therefore needed to better assess cardiovascular risk in asymptomatic individuals, the main focus of primary prevention.

Noninvasive arterial testing for cardiovascular risk assessment is based on several important considerations. Alterations in arterial function and structure predate clinical manifestations of occlusive atherosclerotic disease; changes tend to be widespread and are not limited to a single arterial bed. These alterations result from the cumulative effects of known and unknown vascular risk factors that promote formation and progression of atherosclerotic lesions and may also increase the propensity for atherosclerotic plaque rupture (Fig. 1). Identification of such abnormalities in accessible peripheral arteries provides a means for early detection of presymptomatic vascular disease and improved cardiovascular risk stratification.

Arterial ultrasonography and tonometry are attractive modalities for detecting early disease because they are noninvasive and relatively inexpensive. High-resolution ultrasonography can assess arterial dilatation in response to shear stress or pharmacological stimuli (a function that may be compromised early in atherogenesis) and directly examine the arterial wall for early atherosclerotic changes preceding luminal compromise. Arterial tonometry can be used to acquire arterial pulse waveforms to assess arterial stiffness and wave reflection, measures that have been associated with the presence and extent of atherosclerotic vascular disease and cardiovascular events. In this article, we review the potential use of vascular ultrasonography and tonometry for noninvasive assessment of arterial function and structure.
as adjuncts to cardiovascular risk stratification. Although ultrasonography and tonometry have been used in research settings to investigate the effect of risk factors and risk factor intervention on arterial function, this review focuses on their potential clinical utility in cardiovascular risk assessment.

**Ultrasonography to Assess Conduit Artery and Microcirculatory Function**

Functional abnormalities of the endothelium precede development of atherosclerotic plaque and may also be involved in its progression and clinical expression (7,8). Endothelial dysfunction reflects the cumulative effect of conventional and novel risk factors for atherosclerosis. A key feature of endothelial dysfunction is reduced bioavailability of nitric oxide, an endothelium-derived vasodilator with antiatherogenic properties (9). Arterial vasodilatation in response to shear stress produced by increased flow is mediated predominantly by endothelium-derived nitric oxide (10,11), and hence, flow-mediated dilatation (FMD) is considered a biomarker of endothelial function (12,13). At present, FMD is commonly assessed by high-resolution ultrasonography of the brachial artery.

Because endothelial dysfunction is associated with cardiovascular events (14), measurement of brachial artery FMD may help to identify patients at risk. The prognostic value of brachial artery FMD has been shown in several patient populations (15–24) (Table 1). Chan et al. (20) showed that in patients with coronary heart disease (CHD), impaired baseline FMD and its further decrease over time predicted the occurrence of adverse cardiovascular events. In patients with peripheral arterial disease, impaired FMD was predictive of early and late adverse cardiovascular events after vascular surgery, even after accounting for risk factors and the ankle-brachial index (16,18). In patients undergoing evaluation for chest pain, impaired FMD was predictive of adverse cardiac events in the near term and long term (15). Two recent studies (23,24) showed FMD to be predictive of increased mortality and the need for cardiac transplantation in patients with congestive heart failure.

Data about the incremental prognostic value of FMD in asymptomatic subjects are limited. In a study of 444 subjects at increased cardiovascular risk (21), the incidence of adverse cardiovascular events and all-cause mortality over a median follow-up period of 2 years was significantly higher in subjects with FMD <2% compared with those with FMD >2%. However, FMD was not an independent predictor of these events after adjustment for conventional risk factors. Whether an improvement in FMD translates into improved clinical outcome is yet to be established, although in a study of 400 hypertensive postmenopausal women, failure to improve FMD after 6 months of optimal antihypertensive therapy was associated with increased risk of nonfatal cardiovascular events over a mean follow-up of 67 months (17).

In addition to FMD, brachial artery ultrasound also provides a means of assessing other measures of arterial function that may be associated with cardiovascular risk. For example, impaired brachial artery dilatation to sublingually administered nitroglycerin, an “endothelium-independent” response that reflects arterial smooth muscle function (25), has been noted to be impaired in the presence of cardiovascular disease (26,27) as well as in asymptomatic subjects with risk factors (28,29). Brachial artery ultrasound can be combined with pulsed Doppler to measure forearm blood flow at rest and during the phase of hyperemia after transient forearm occlusion; both measures reflect microvascular function. Several cardiovascular risk factors have been found to be associated with higher resting forearm blood flow (30,31) and a blunted reactive hyperemic response (31–33). Postischemic reactive hyperemia is mainly mediated by local release of ischemia-induced vasodilator substances from forearm resistance vessels (34,35), although myogenic response (36) and endothelial nitric oxide (32,37) likely play a role. Further studies are needed to investigate whether nitroglycerin-mediated dilatation of the brachial artery and reactive hyperemia in the forearm are associated with increased cardiovascular risk.

Thus, arterial dysfunction related to atherosclerosis and its risk factors may manifest as impaired conduit artery responsiveness to endothelium-dependent and
Table 1  
Studies Investigating the Association of Brachial Arterial Flow-Mediated Dilatation With Cardiovascular Events

<table>
<thead>
<tr>
<th>Reference</th>
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<th>End Points Assessed</th>
<th>Risk Estimate (95% Confidence Interval)</th>
<th>Conclusion</th>
</tr>
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<tbody>
<tr>
<td>Neunteufl et al. (15)</td>
<td>73 patients (51 yrs)* with chest pain</td>
<td>5 yrs</td>
<td>Death, CHD events</td>
<td>FMD &lt; 10% had PPV of 52% and NPV of 85%</td>
<td>Preserved FMD in patients with chest pain was predictive of low risk of CHD events.</td>
</tr>
<tr>
<td>Gokce et al. (16)</td>
<td>187 patients (65 yrs)* undergoing vascular surgery</td>
<td>1 month</td>
<td>Fatal and nonfatal CHD events, stroke</td>
<td>Adjusted OR for FMD ≤8.1% vs. &gt;8.1% was 9.0 (1.2–68); PPV 32%, NPV 92%</td>
<td>Impaired FMD was an independent predictor of postoperative CV events.</td>
</tr>
<tr>
<td>Modena et al. (17)</td>
<td>400 hypertensive postmenopausal women (57 yrs)*</td>
<td>67 months</td>
<td>Nonfatal CV events needing hospitalization</td>
<td>Adjusted incidence rate ratio for women with FMD &lt;10% after 6 months vs. those with FMD ≥10% = 7.3 (3.8–14.2)</td>
<td>Failure to improve FMD after 6 months of antihypertensive therapy was an independent predictor of CV events.</td>
</tr>
<tr>
<td>Gokce et al. (18)</td>
<td>199 patients (66 yrs)* undergoing vascular surgery</td>
<td>1.2 yrs</td>
<td>Fatal and nonfatal CHD events, stroke</td>
<td>Adjusted OR for FMD ≤8.1% vs. &gt;8.1% = 9.5 (2.3–40)</td>
<td>Impaired FMD was an independent predictor of CV events.</td>
</tr>
<tr>
<td>Brevetti et al. (19)</td>
<td>131 patients (64 yrs)* with PAD</td>
<td>23 months</td>
<td>Fatal and nonfatal CHD, cerebrovascular or peripheral vascular events</td>
<td>RR for FMD, ABI, or both &lt; median vs. both &gt; median = 4.8 (1.1–23.3), 6.4 (1.4–29.1), and 13.0 (3.0–56.1), respectively</td>
<td>FMD and ABI had additive prognostic value for prediction of CV events.</td>
</tr>
<tr>
<td>Chan et al. (20)</td>
<td>152 patients (56 yrs) with CHD</td>
<td>34 months</td>
<td>Fatal or nonfatal CHD, cerebrovascular or peripheral vascular events</td>
<td>Baseline FMD/NMD ratio (p &lt; 0.0001) and change in FMD (p = 0.05) on follow-up were associated with CV events</td>
<td>Lower FMD and decrease in FMD over time were independently predictive of CV events. The predictive values of FMD and carotid plaque were additive.</td>
</tr>
<tr>
<td>Fathi et al. (21)</td>
<td>444 patients (58 yrs) at high risk of CHD</td>
<td>24 months (median)</td>
<td>Fatal and nonfatal CHD events, stroke</td>
<td>Event rate was higher in patients with FMD ≤2% vs. those with FMD &gt;2% but not after adjustment for baseline risk</td>
<td>FMD was lower for patients with CV events but not an independent predictor of events.</td>
</tr>
<tr>
<td>Frick et al. (22)</td>
<td>398 men (54 yrs) with chest pain</td>
<td>39 months</td>
<td>Fatal or nonfatal CHD events</td>
<td>Event-free survival for patients with FMD &lt; median was not different from those with FMD &gt; median (p = 0.47)</td>
<td>FMD was not independently predictive of CHD events.</td>
</tr>
<tr>
<td>Meyer et al. (23)</td>
<td>75 CHF patients (56 yrs),* UNOS status 2</td>
<td>Up to 3 yrs</td>
<td>Conversion to UNOS status 1 or death</td>
<td>FMD predicted combined end point after adjustment for functional class, beta-blocker use, mean BP, and brain natriuretic peptide levels (p = 0.0007)</td>
<td>Impaired FMD was independent predictor of conversion to UNOS status 1 or death.</td>
</tr>
<tr>
<td>Katz et al. (24)</td>
<td>149 CHF patients (54 yrs), NYHA functional class II–III</td>
<td>28 months (median)</td>
<td>Death, urgent cardiac transplantation</td>
<td>Adjusted HR was 1.2 (1.03–1.45) for each 1% decrease in FMD</td>
<td>Lower FMD was associated with higher mortality risk after adjustment for known prognostic factors.</td>
</tr>
</tbody>
</table>

Mean age (in parentheses) and follow-up are shown unless indicated otherwise. *The mean age was calculated as the weighted mean of the groups because the overall mean age was not reported in the original study.

ABI = ankle-brachial index; BP = blood pressure; CHD = coronary heart disease; CHF = congestive heart failure; CV = cardiovascular; FMD = flow-mediated dilatation; HR = hazard ratio; IMT = intima-media thickness; NMD = nitroglycerin-mediated dilatation; NPV = negative predictive value; NYHA = New York Heart Association; OR = odds ratio; PAD = peripheral arterial disease; PPV = positive predictive value; RR = relative risk; UNOS = United Network of Organ Sharing.
endothelium-independent stimuli as well as reduced microvascular reactivity. Assessment of conduit artery and microcirculatory function using ultrasonography could be useful in refining cardiovascular risk estimates, choosing appropriate risk-reduction therapy, and assessing the effect of therapeutic interventions. However, brachial vasoreactivity testing has significant test–to-test variability and requires a skilled ultrasonography technician. Although edge-detection software may improve precision and reproducibility and decrease dependence on operator skill (38,39), there remains a need for standardizing of measurement technique across laboratories and establishing cutoff values that differentiate normal from abnormal. Prospective studies that assess the independent predictive value of brachial vasoreactivity testing in asymptomatic subjects are awaited.

Ultrasonography For Assessing Subclinical Atherosclerosis: Carotid Intima-Media Thickness (IMT)

The combined thickness of carotid artery intima and media is measured noninvasively by high-resolution ultrasonography. Although atherosclerosis is predominantly a disease of the intima, carotid IMT correlates with the degree of carotid atherosclerosis measured at autopsy (40), and the latter, in turn, has been found to correlate with atherosclerotic vascular disease in other arterial beds (41). Thus, ultrasound-derived carotid IMT is considered a surrogate for systemic atherosclerotic disease burden. In addition to IMT, carotid ultrasonography also provides information about the presence of plaque, lumen stenosis, and arterial remodeling. Increased carotid IMT is associated with cardiovascular risk factors (42,43), prevalent cardiovascular disease (44,45), coronary artery calcification on computed tomography (46), presence and extent of angiographically determined coronary atherosclerosis (47,48), and plaque burden on intracoronary ultrasound (49). Carotid IMT has been used in research settings to identify patients with subclinical atherosclerosis and as an intermediate outcome variable in epidemiologic studies and intervention trials of disease progression (50–53).

Several studies show that increased carotid IMT is predictive of cardiovascular events in asymptomatic individuals (54–59) (Table 2) and recurrent events in patients with known cardiovascular disease (60,61), independent of conventional risk factors. Increased IMT was associated with risk of myocardial infarction, stroke, and death in several large prospective studies with different study designs, sample characteristics, and IMT measurement protocols. In the ARIC (Atherosclerosis Risk in Communities) study (55), a mean carotid IMT of ≥1.0 mm was associated with a hazard ratio for incident CHD events of 5.07 in women and 1.85 in men. After adjustment for risk factors, the hazard ratio associated with increased IMT was attenuated but remained statistically significant. In another study (54), a 0.1-mm increase in common carotid artery IMT was associated with an 11% increase in the risk of myocardial infarction, and the association remained significant after adjustment for several cardiovascular risk factors. In the Cardiovascular Health Study (56), 4,476 subjects were followed over a median period of 6.2 years, and the baseline carotid IMT was associated with cumulative survival free of myocardial infarction or stroke. For a 1-SD increase in baseline IMT, the age- and gender-adjusted relative risk for the combined end point increased by 35% to 44% and remained significantly elevated after adjustment for risk factors. In CAPS (Carotid Atherosclerosis Progression Study) (59), 5,056 members of a German primary health care scheme were followed for a mean of 4.2 years. A higher common carotid IMT was associated with increased risk of incident myocardial infarction, stroke, and the combined end point of myocardial infarction, stroke, or death even after adjustment for conventional risk factors.

Given that carotid IMT is associated with coronary atherosclerosis and cardiovascular events, it may be useful in refining risk stratification of individual patients, especially those assigned to an intermediate-risk category. A limitation of the Framingham cardiovascular risk equations (62–64) is that these are heavily influenced by patient age without taking into account the heterogeneity of atherosclerotic burden. Researchers have proposed replacing chronological age in the Framingham risk algorithms with vascular age derived from the composite carotid IMT score (65–67). Using such an approach, nearly one-half of the individuals assigned to the intermediate-risk category by the original Framingham CHD risk algorithm were reclassified into higher- or lower-risk categories (65). Computerized algorithms may be used to integrate IMT values with demographic and other relevant clinical information to determine the vascular age of the individual and recalculate the cardiovascular risk (65).

The reported median values of carotid IMT have varied, although a value of 1.2 mm or higher for an adult would be considered clearly abnormal (68,69). Progression of IMT in asymptomatic individuals is estimated to be ≤0.03 mm/year (4), but this rate is accelerated in the presence of cardiovascular risk factors (70–72). A higher progression rate is associated with increased risk of myocardial infarction and stroke (55,56,73,74); therefore, serial measurements may provide greater prognostic information than a single measurement.

Distinct from diffuse intimal-medial thickening is atherosclerotic plaque, which is typically seen as a focal thickening often with mineralization and protrusion into lumen. Some studies suggest that plaque area or volume may be a better predictor of cardiovascular events than IMT (74–77), particularly in diabetics (78,79), but the evidence is mixed (58,80). Although carotid IMT needs to be interpreted in the context of age and gender of an individual, presence of a carotid plaque is always abnormal. However, plaques develop late in atherogenesis (81), whereas IMT can be measured at any age and may be a better marker of systemic
## Table 2  
Studies Investigating the Association of Carotid IMT With Cardiovascular Events in Asymptomatic Subjects

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Sample</th>
<th>Follow-Up</th>
<th>End Points Assessed</th>
<th>Risk Estimate (95% Confidence Interval)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salonen et al. (54)</td>
<td>1,257 middle-aged eastern Finnish men</td>
<td>1 month to 2.5 yrs</td>
<td>Fatal and nonfatal MI</td>
<td>A 0.1-mm increase in IMT was associated with an 11% (6%–16%) increase in risk; the association remained significant after adjustment for several risk factors</td>
<td>Presence of increased carotid IMT or plaque was associated with increased risk of MI.</td>
</tr>
<tr>
<td>Chambless et al. (55)</td>
<td>12,841 subjects (45–64 yrs)</td>
<td>4–7 yrs</td>
<td>Fatal and nonfatal CHD events</td>
<td>For IMT ≥ 1 vs. &lt; 1 mm, HR adjusted for age, race, and study center = 1.8 (1.3–2.7) in men and 5.1 (3.1–8.4) in women; the strength of association was attenuated but remained significant after adjustment for CV risk factors</td>
<td>Higher baseline IMT was associated with increased risk of CHD events in both men and women.</td>
</tr>
<tr>
<td>O'Leary et al. (56)</td>
<td>4,476 subjects (≥65 yrs)</td>
<td>6.2 yrs (median)</td>
<td>MI, stroke, combined end point (MI or stroke)</td>
<td>RR of the combined end point (adjusted for age, gender, SBP, DBP, smoking, diabetes, and presence of atrial fibrillation): 3.2 (2.2–4.5) for the highest vs. the lowest quintile of IMT; similar results for MI and stroke considered separately</td>
<td>Increased carotid IMT was independently predictive of MI and stroke in older adults.</td>
</tr>
<tr>
<td>Iglesias del Sol et al. (57)</td>
<td>2,073 subjects (≥55 yrs)</td>
<td>4.6 yrs</td>
<td>Fatal and nonfatal MI</td>
<td>RR (adjusted for risk factors) for IMT ≥ 1.12 vs. &lt; 0.88 mm = 4.8 (2.6–9.4); history of prior MI or stroke did not significantly affect the increased RR</td>
<td>Increased carotid IMT was an independent predictor of future MI.</td>
</tr>
<tr>
<td>Rosval et al. (58)</td>
<td>5,163 subjects (58 yrs)</td>
<td>7 yrs (median)</td>
<td>Fatal and nonfatal stroke</td>
<td>Adjusted HR was 2.54 (1.20–5.40) for IMT ≥ 0.81 vs. ≤ 0.69 mm and 1.26 (0.76–2.10) for the presence vs. absence of carotid plaque</td>
<td>Carotid IMT was associated with incident stroke independent of CV risk factors and carotid plaque.</td>
</tr>
<tr>
<td>Lorenz et al. (59)</td>
<td>5,056 subjects (19–90 yrs)</td>
<td>4.2 yrs</td>
<td>MI, stroke, combined end point (MI, stroke, or death)</td>
<td>HR (adjusted for risk factors) for IMT ≥ 0.79 vs. &lt; 0.63 mm was 1.8 (0.97–3.4), 1.8 (0.64–5.2), and 1.8 (1.1–3.2) for MI, stroke, and the combined end point, respectively</td>
<td>Increased carotid IMT independently predicted CV events. The predictive value of increased IMT seemed to be higher in the younger (&lt;50 yrs) individuals.</td>
</tr>
</tbody>
</table>

Mean age (in parentheses) and follow-up are shown unless indicated otherwise.  
DBP = diastolic blood pressure; MI = myocardial infarction; SBP = systolic blood pressure; other abbreviations as in Table 1.
Atherosclerosis (82,83). The predictive value of carotid plaques may be greater in patients with known cardiovascular disease, whereas carotid IMT may be a better prognostic marker in asymptomatic individuals. However, in a recent study (84), both carotid IMT and plaque were independently predictive of stroke risk, and the predictive value of IMT was higher in the absence than in the presence of plaque. In another recent study (58) of 5,163 apparently healthy middle-aged Swedish men and women, carotid IMT was associated with incident stroke, even after adjustment for presence of carotid plaque and conventional risk factors.

Ultrasonographic measurement of carotid IMT is a safe, inexpensive, and reproducible measure of atherosclerotic burden associated with prevalent and incident cardiovascular disease. Carotid IMT also can be used as a marker of efficacy of therapies intended to achieve regression of atherosclerosis (85). Integration of carotid IMT measurement into routine cardiovascular risk assessment may improve risk stratification of individual subjects. The American Heart Association has concluded that among asymptomatic persons >45 years old, measurement of carotid IMT in experienced laboratories could be considered for further clarification of CHD risk (86). Automated computerized edge-detection software (87,88) and intravascular contrast agents (89) may decrease variability and improve precision in IMT measurement. Development of guidelines for quality control, standardization of measurements, and establishment of thresholds for different risk categories will help optimize the use of carotid IMT in clinical practice.

**Arterial Tonometry for the Assessment of Arterial Stiffness**

Arterial stiffening is a manifestation of atherosclerosis, a process characterized by thickening and loss of elasticity of the arterial wall. Capacitance and conduit arteries are predominantly affected, and histopathological features include fractured and damaged elastin fibers and increased collagen deposition (90). Not only is increased arterial stiffness a marker of vascular aging; it also predicts target-organ damage and cardiovascular events. Increased arterial stiffness impairs the cushioning function of the central arterial reservoir with adverse consequences for cardiac performance and organ perfusion. The resulting hemodynamic abnormalities (e.g., increased systolic blood pressure [BP] and pulse pressure and reduced diastolic BP) increase cardiovascular morbidity and mortality (91–93). Systolic hypertension increases cardiac workload and leads to myocardial hypertrophy (94), whereas reduced diastolic BP may compromise coronary perfusion and increase vulnerability to ischemia (95). Stiffening of the aorta and its major branches may reduce or eliminate the normal elastic gradient between the central and peripheral segments of the arterial tree; the resulting increase in distal transmission of pressure pulse energy is deleterious to the microvascular beds of many organs and tissues (96). The pulsatile stress associated with increased pulse pressure may also induce arterial remodeling (97), contribute to plaque formation and progression (98,99), and alter hemodynamic forces acting on the plaque surface, all of which could increase the propensity for plaque rupture (100).

Several indexes of arterial stiffness have been proposed (101,102). However, 2 measures have been studied extensively: 1) the velocity of arterial pulse wave transmission across an arterial segment, and 2) analysis of the arterial waveforms to estimate augmentation of systolic pressure by peripheral wave reflection. Both measures may be assessed conveniently and reproducibly by using commercially available devices based on the principle of applanation tonometry (103).

**Aortic pulse wave velocity (aPWV).** Because blood is a noncompressible fluid, transmission of the arterial pressure wave occurs along the arterial wall and is influenced by the biomechanical properties of the arterial wall. The velocity of the pressure wave transmission (pulse wave velocity [PWV]) provides a robust estimate of arterial stiffness (104) and is described by the Moens–Korteweg equation:

\[
PWV = \sqrt{\frac{Yh}{2pR}}
\]

where \(Y\) is the Young's modulus of the arterial wall, \(h\) is wall thickness, \(R\) is arterial radius at the end of diastole, and \(p\) is blood density (102). Central arterial stiffness is most commonly estimated by measuring carotid–femoral PWV (aPWV) because the common carotid and femoral arteries are located superficially and because the distance between them spans most of the length of aorta, the arterial segment particularly prone to stiffening. Applanation tonometry (vide infra) provides a convenient method for measuring aPWV, although Doppler ultrasonography (105) and magnetic resonance imaging (106) also may be used. The latter allows accurate assessment of aortic length and provides separate estimates of PWV for the proximal and distal segments of aorta (107), but cost and logistics hinder its use as a screening tool. In healthy adults, aPWV generally ranges from 5 to 7 m/s (108).

Aortic PWV increases with age and with the cumulative effect of risk factors on arterial wall physiology and structure. Increased aPWV is associated with the presence and extent of atherosclerotic disease in the coronary arteries (109–112) and other vascular beds (113). Aortic PWV is associated with cardiovascular risk factors (114–117) and correlates with estimates of cardiovascular risk based on conventional risk factor algorithms (104). A growing body of evidence indicates that aPWV itself may have prognostic value. Several studies have shown an independent and significant association between aPWV and cardiovascular events in different populations (118–124) (Table 3), including patients with end-stage renal disease (118), hypertension (120), and the elderly (119,121).
<table>
<thead>
<tr>
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<th>Conclusion</th>
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</thead>
<tbody>
<tr>
<td>Blacher et al. (118)</td>
<td>241 patients on hemodialysis with ESRD (52 yrs)</td>
<td>72 months</td>
<td>All-cause and CV mortality</td>
<td>OR (adjusted for age, time on dialysis, DBP, and hemoglobin) for aPWV &gt;12.0 vs. &lt;9.4 m/s: 5.4 (2.4–11.9) for all-cause mortality and 5.9 (2.3–15.5) for CV mortality</td>
<td>aPWV was an independent predictor of all-cause and CV mortality in patients with ESRD.</td>
</tr>
<tr>
<td>Meaume et al. (119)</td>
<td>141 subjects (70–100 yrs)</td>
<td>30 months</td>
<td>CV mortality</td>
<td>OR (adjusted for several factors including SBP and prior CV disease) = 4.6 (1.4–15.7) for aPWV &gt;17.7 vs. ≤17.7 m/s</td>
<td>aPWV was the major independent predictor of CV death.</td>
</tr>
<tr>
<td>Boutouyrie et al. (120)</td>
<td>1,045 asymptomatic hypertensives (51 yrs)</td>
<td>5.7 yrs</td>
<td>Fatal and nonfatal CHD events, all CV events</td>
<td>Adjusted RR for CHD events = 2.8 (1.3–5.9) for subjects in the highest (&gt;12.3 m/s) vs. lowest (&lt;10.0 m/s) tertile of aPWV; similar RR for all CV events</td>
<td>aPWV was a more powerful predictor of events than Framingham risk score, especially in subjects classified as low-risk.</td>
</tr>
<tr>
<td>Sutton-Tyrrell et al. (121)</td>
<td>2,488 community-based subjects (73 yrs)</td>
<td>4.6 yrs</td>
<td>Total mortality, fatal and nonfatal CV events</td>
<td>Unadjusted RR for the highest vs. lowest quartiles of aPWV = 1.7 (1.2–2.5) for all-cause mortality, 2.3 (1.2–4.3) for CV mortality, 1.5 (1.1–2.1) for CHD, and 3.6 (1.8–7.2) for stroke</td>
<td>Increased aPWV was associated with elevated risk of CHD, stroke, and all CV events, even after adjustment for age, gender, race, and SBP.</td>
</tr>
<tr>
<td>Laurent et al. (122)</td>
<td>1,980 patients with essential hypertension (50 yrs)</td>
<td>112 months</td>
<td>All-cause and CV mortality</td>
<td>Adjusted OR for a 5 m/s increase in aPWV = 1.3 (1.04–1.7) for all-cause mortality and 1.5 (1.1–2.1) for CV mortality</td>
<td>aPWV was associated with all-cause and CV mortality, independent of previous CV disease, age, heart rate, or diabetes.</td>
</tr>
<tr>
<td>Willum-Hansen et al. (123)</td>
<td>1,678 subjects (40–70 yrs), no prior MI or stroke</td>
<td>9.4 yrs (median)</td>
<td>Fatal and nonfatal CHD events, stroke, CV death</td>
<td>HR per 1-SD increment in aPWV = 1.2 (1.01–1.4) for CV mortality, 1.2 (1.0–1.4) for CHD, and 1.2 (1.04–1.3) for composite end point</td>
<td>aPWV was a predictor of CV outcome in a Danish population, independent of age, gender, BMI, smoking, alcohol intake, and mean BP.</td>
</tr>
<tr>
<td>Mattace-Raso et al. (124)</td>
<td>2,835 apparently healthy subjects (72 yrs)</td>
<td>CHD, 4.1 yrs; stroke, 3.2 yrs</td>
<td>Fatal and nonfatal CV events</td>
<td>HR of CV disease (adjusted for risk factors, carotid IMT, ABI, and pulse pressure) for the highest vs. lowest tertile of aPWV = 1.9 (1.2–3.2)</td>
<td>aPWV provided prognostic information about CHD and stroke incremental to that provided by risk factors, pulse pressure, and measures of atherosclerosis.</td>
</tr>
</tbody>
</table>

Mean age (in parentheses) and follow-up duration are shown unless indicated otherwise.
aPWV = aortic pulse wave velocity; BMI = body mass index; ESRD = end-stage renal disease; other abbreviations as in Tables 1 and 2.
Two recent studies have shown that aPWV provides incremental information about cardiovascular risk in asymptomatic individuals from the general population. In a community-based study of 1,678 Danes (123), aPWV predicted incident cardiovascular events over a median follow-up period of 9.4 years. After adjustment for conventional risk factors and average 24-h ambulatory BP, a 3.4-m/s increase in aPWV was associated with a 16% to 20% increase in the risk of an adverse cardiovascular event. In the Rotterdam Study (124), aPWV was a predictor of CHD and stroke, independent of conventional risk factors, measures of atherosclerosis (carotid IMT and ankle-brachial index), and pulse pressure. The age- and gender-adjusted hazard ratio for incident cardiovascular disease in subjects with aPWV in the highest tertile compared to those with aPWV in the lowest tertile was 2.40 (95% confidence interval 1.51 to 3.83).

To summarize, aPWV is a robust measure of central arterial stiffness that may be a useful adjunct to cardiovascular risk stratification. A recent consensus document (125) described aPWV as the gold-standard measure of arterial stiffness. Analogous to carotid IMT, aPWV could also be used to assess vascular age. The case for incorporating aPWV into routine clinical practice is strengthened by the evidence supporting its independent prognostic value and the availability of user-friendly devices for rapid, reliable, and reproducible measurement.

**Pulse wave analysis.** Pulse wave analysis is based on the principle that the forward-moving pressure wave generated with each cardiac pulse is partially reflected back toward the aorta at points of impedance mismatch along the arterial tree (bifurcations, branch points, arterioles, and other sites of discontinuity in arterial elasticity); this reflection increases (augments) the central aortic pressure (102). Applanation tonometry is a simple and reproducible method of pulse wave analysis. The technique involves partial flattening (applanation) of a superficial artery against an underlying bone using a handheld external pressure sensor; the sensor eliminates tangential pressures and determines pressure within the artery (102). A correctly obtained noninvasive pressure waveform is virtually identical to a waveform recorded by intra-arterial transducers (126,127). The radial artery pressure waveform is used to derive a central aortic pressure waveform using a mathematical transfer function that has been validated under several different conditions (128–131), although some investigators have questioned the generalizability of the transfer function (132–135). Tonometry of the carotid artery (136) may obviate the need of a transfer function but requires a higher degree of technical expertise, particularly in obese subjects (137).

Analysis of arterial pulse waveforms provides information about several hemodynamic characteristics related to arterial wave reflection. Augmentation pressure is defined as the degree of augmentation of central systolic BP by the reflected pressure wave. It is generally expressed as a fraction of the central pulse pressure (aortic augmentation index [AIx]), and it is affected by several factors, including the velocity of the reflected wave. When arteries are relatively compliant (e.g., in a young healthy adult), PWV is low; the reflected wave arrives at the ascending aorta after closure of the aortic valve and augments diastolic BP, thereby increasing coronary perfusion. With increasing arterial stiffness, the reflected wave is transmitted at a higher velocity and arrives in systole, resulting in augmentation of systolic pressure, increased cardiac workload, loss of augmentation of diastolic pressure, and decreased coronary perfusion. Whereas aPWV represents a measure of aortic stiffness, AIx reflects the overall interaction between the arterial tree and the left ventricle (138).

Like carotid IMT and aPWV, AIx has been proposed as a measure of vascular age, albeit only in individuals younger than 60 years (139). This is because AIx plateaus at or may even decrease after the age of 60 (96,139,140). The decrease in AIx in older individuals could be caused by a proportionally greater effect of the reflected wave in reducing flow at the aortic valve than in augmenting the systolic BP in the aorta (141). Further, the preferential increase in central arterial stiffness with aging and resulting changes in the normal centrifugal gradient of arterial stiffness may result in reduced amplitude, despite earlier timing of pressure wave reflection, and decrease AIx (96).

Higher AIx is associated with increased left ventricular mass in normotensive (142) and hypertensive adults (143), with lower cardiorespiratory fitness in asymptomatic men (144), and with lower walking distance in patients with peripheral arterial disease (145). The AIx has also been associated with higher C-reactive protein levels in asymptomatic adults (146,147) and with several cardiovascular risk factors (148–152). However, AIx is lower in men compared with women (102), it is inversely related to body mass index (147,153), and it may not be a reliable measure of arterial stiffness in diabetic patients (154–156).

Cross-sectional studies have shown AIx to be associated with the presence and extent of angiographic coronary artery disease in patients with end-stage renal disease (111) and in men <60 years of age undergoing diagnostic coronary angiography (157). Whether AIx is associated with cardiovascular risk in community-based cohorts is not known, although several small studies have also shown AIx to be predictive of adverse cardiovascular events in select populations (158–162) (Table 4), such as patients with end-stage renal failure (158), patients with angiographically documented coronary artery disease (161), and patients undergoing coronary revascularization (159,160). A recent study did not find AIx to be predictive of cardiovascular events in elderly hypertensive women (162).

Pulse wave analysis also can be used to estimate central systolic and pulse pressures from the radial artery- derived aortic pressure waveform. Because of progressive amplification of the pressure waveform from the central arteries to the peripheral arteries, systolic BP and pulse pressure from brachial artery cuff measurements may not accurately reflect...
### Table 4: Studies Evaluating the Association of Aortic Augmentation Index With Cardiovascular Events

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Sample</th>
<th>Follow-Up</th>
<th>End Points Assessed</th>
<th>Risk Estimate (95% Confidence Interval)</th>
<th>Conclusion</th>
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<tr>
<td>London et al. (158)</td>
<td>180 patients with ESRD (54 yrs)</td>
<td>52 months</td>
<td>All-cause mortality, CV mortality</td>
<td>Adjusted RR for each 10% increase in AIx was 1.5 (1.2–1.9) for all-cause mortality and 1.5 (1.2–1.9) for CV mortality</td>
<td>AIx was a significant predictor of events in ESRD patients, independent of CV risk factors and aPWW.</td>
</tr>
<tr>
<td>Ueda et al. (159)</td>
<td>103 patients (34–82 yrs undergoing PCI)</td>
<td>6 months</td>
<td>In-stent restenosis</td>
<td>Adjusted OR of restenosis was 7.0 (1.9–25.1) for the highest vs. lowest tertile of AIx and 1.7 (1.2–2.5) for a 10% increase in AIx</td>
<td>Higher AIx at baseline predicted increased rate of restenosis after PCI, independent of CV risk factors, stent size, and heart rate.</td>
</tr>
<tr>
<td>Weber et al. (160)</td>
<td>262 patients (66 yrs) undergoing PCI</td>
<td>Up to 24 months</td>
<td>All-cause mortality, MI, clinical restenosis</td>
<td>Adjusted RR for the combined end point was 1.8 (1.2–2.8) per increase in tertile and 1.04 (1.01–1.1) per unit of heart rate-corrected AIx</td>
<td>Increased AIx was a significant predictor of CV events, independent of risk factors, angiographic variables, and medication use.</td>
</tr>
<tr>
<td>Chirinos et al. (161)</td>
<td>297 men (64 yrs) undergoing coronary angiography</td>
<td>3.2 yrs</td>
<td>Any MACE, all-cause mortality</td>
<td>For MACE, adjusted HR was 1.2 (1.1–1.3) for each 10mm Hg increase in AP and 1.3 (1.1–1.5) for each 10% increase in AIx</td>
<td>In patients with CHD, higher AIx and AP were predictive of CV events, independent of risk factors, CHF history, angiographic severity, and medications.</td>
</tr>
<tr>
<td>Dart et al. (162)</td>
<td>484 hypertensive women (65–84 yrs)</td>
<td>4.1 yrs median</td>
<td>Fatal and nonfatal CV events</td>
<td>HR (adjusted for age, cholesterol, and smoking history) for carotid augmentation index &gt;38.4% vs. &lt;38.4% was 0.8 (0.4–1.5)</td>
<td>BP at the brachial artery, but not central BP, carotid augmentation index, or systemic arterial compliance derived from carotid artery tonometry, predicted CV events.</td>
</tr>
</tbody>
</table>

Mean age (in parentheses) and follow-up duration are shown unless indicated otherwise. *MACE included all-cause mortality, MI, unstable angina, coronary revascularization, or stroke. AIx = aortic augmentation index; AP = augmentation pressure; aPWW = aortic pulse wave velocity; MACE = major adverse cardiovascular events; PCI = percutaneous coronary intervention; other abbreviations as in Tables 1 and 3.
studies have shown that carotid plaque burden and brachial artery FMD independently and additively predict occurrence of cardiovascular events (20) and that aPWV may be a predictor of CHD and stroke, independent of carotid IMT (124). Thus, different arterial tests may provide complementary information about arterial structure and function, and a combination of the tests might be superior to any single test used alone. Further, because some arterial changes (e.g., impaired FMD) may be discernible earlier than others (e.g., increase in carotid IMT or aPWV), an absence of abnormality in one testing domain would not rule out an abnormality in other domains.

The relative utility of various modalities and tests as adjuncts to cardiovascular risk assessment depends on several factors. Tonometry has an advantage over ultrasonography in that it can be performed after minimal training using a relatively low-cost portable device, whereas ultrasound assessment of IMT and FMD require relatively expensive equipment and considerable operator skill. Carotid IMT and aPWV are predictive of cardiovascular events in community-based cohorts, independent of conventional risk factors, whereas brachial artery FMD and AIx have been shown to be associated with cardiovascular events in select groups of patients.

Summary

Although office-based assessment of cardiovascular risk using conventional risk factor algorithms is important for initial risk stratification, it may not always answer the key questions of whether and how aggressively an asymptomatic individual should be treated. Identification of preclinical alterations in arterial function and structure may refine cardiovascular risk stratification and decrease the chances of misclassification of cardiovascular risk. Arterial ultrasonography and tonometry are 2 promising testing modalities in this regard. For noninvasive tests of arterial function and structure to be incorporated into clinical practice, measurement protocols need to be standardized, quality control procedures established, and risk-defining threshold values identified. Further technological advances might improve reproducibility and decrease operator-dependence, making these tests more resource-efficient and potentially more widely available.

Noninvasive tests should be performed solely to improve risk assessment; they should supplement (but not replace) the standard risk assessment algorithms and should not be used to make a diagnosis of cardiovascular disease. A potential algorithm for noninvasive arterial testing (Fig. 2) incorporates both ultrasonography and tonometry in intermediate-risk and select low-risk subjects. Abnormal findings from one or more of these tests may change the risk category assigned to an individual and could be used to modify treatment thresholds and therapeutic targets for risk-reduction therapy. Further, noninvasive testing may be useful for longitudinal follow-up to monitor vascular disease progression and the effect of therapy. Detection and monitoring of early arterial abnormalities could become part of a paradigm shift in the care of individuals at risk for cardiovascular events, with emphasis on prevention of such events.

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