In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Santos et al report from a large Brazilian study (n=9792) that factors they analyzed explained a higher proportion of carotid intima-media thickness (IMT; ie, gave a higher $R^2$ in multiple regression) than reported in previous studies.

As pointed out by Inaba et al, it is crucial to distinguish between IMT measured according to the Mannheim consensus (in the far wall of the distal common carotid where there is no plaque) and methods that include plaque thickness in numerous locations, including the carotid bulb (the Atherosclerosis Risk in Communities [ARIC] and related protocols). IMT measured according to the Mannheim consensus does not represent atherosclerosis; it is another phenotype. Studies that include plaque thickness in the measurement of IMT, and then analyze participants with and without plaque as if they were the same, confuse the issue by conflating the 2 kinds of IMT.

Carotid ultrasound phenotypes are different: compensatory enlargement (positive remodeling) results in enlargement of the artery to accommodate plaque progression, without narrowing of the lumen. Thus, plaque burden represents the effects of oxidative stress and a lifetime’s exposure to coronary risk factors, whereas stenosis reflects factors that cause plaque rupture and thrombosis. An illustration of this principle is the differential relationship between Lp(a), a clotting factor, with carotid stenosis and occlusion, but not plaque burden.

Plaque thickness predicts cardiovascular risk. It is likely for that reason that the studies of IMT that include plaque thickness predicted cardiovascular risk, particularly in the elderly. In the ARIC study, the increment in risk above coronary risk factors gave an area under the curve of 0.08 with IMT, which increased to 0.17 with addition of the presence of plaque. However, meta-analyses found that IMT measured without plaque is a weak predictor of cardiovascular risk, and progression of IMT did not predict cardiovascular risk nor did regression of IMT. A meta-analysis by Inaba et al concluded that plaque area was a stronger predictor of risk than IMT. Adam and Bojara also found, in a workplace health program study in >4000 participants, that plaque area and plaque type, but not IMT, predicted coronary stenosis and cardiovascular risk.

A report from the Multi-Ethnic Study of Atherosclerosis (MESA) indicated that coronary calcium, but not IMT, predicted cardiovascular risk in the overall population. Brook et al reported that carotid total plaque area was more specific for exclusion of coronary artery stenosis that either IMT or coronary calcium score. Chan et al found that both total plaque area and impaired flow-mediated vasodilation predicted risk among patients with coronary artery disease; in that study, IMT without plaque did not correlate with either IMT or flow-mediated vasodilation, and did not predict risk. In a study of residual risk after statin response among patients with coronary artery disease, carotid plaque echolucency, but not IMT, predicted cardiovascular risk.

The largest population-based study in which both IMT and plaque burden were measured was the Tromsø study, in >6000 participants. In the 7-year follow-up report of that study, IMT in the common carotid did not predict coronary risk, IMT in the carotid bulb (including plaque thickness) was a weak predictor, and total plaque area was a strong predictor of coronary risk. In a 10-year follow-up report, IMT did not predict stroke, whereas total plaque area was a strong predictor of stroke. In the Tromsø study, total cholesterol, systolic blood pressure, and smoking were stronger predictors of progression of TPA than of IMT; whereas sex and age were stronger predictors of IMT.

Previous studies have reported that traditional coronary risk factors explained 52% to 57% of total plaque area, but only 13% of carotid stenosis. O’Leary et al reported, in a study using IMT methods that included plaque thickness, that 17% of IMT in the common carotid and 18% of IMT in the bulb were explained by coronary risk factors. In the Northern Manhattan Study, only 11% of IMT was explained by traditional risk factors; age and male sex accounted for most of the explained variance; glucose and smoking (pack-years) also contributed, and low-density lipoprotein cholesterol was a marginally significant factor. An extended model, including inflammatory biomarkers, adiponectin, homocysteine, and renal function, explained 16% of the variance in carotid intima-media thickness (cIMT); only adiponectin was an additional significant contributor to the variance in cIMT.

In the study of Santos et al, factors such as race, pulse pressure, and neck circumference made a greater contribution to the prediction of IMT (ie, had higher beta values) than to the traditional coronary risk factors. IMT was predicted less strongly among participants with a predicted coronary risk >10%. Thus, the authors have expanded the explained variance of IMT, by including additional predictors of IMT.

Besides assessment of cardiovascular risk, ultrasound phenotypes of atherosclerosis are useful for genetic studies and for evaluation of new therapies. As would be expected, genetic factors for IMT are different from those for plaque burden. It would be expected that genetic factors affecting...
stenosis would again be different, as they would preferentially affect plaque rupture and thrombosis. Similarly, genetic factors affecting coronary calcium scores would be expected to be different, preferentially affecting calcification.26

Ultrasound phenotypes of atherosclerosis are also importantly different with regard to studies of new therapies. Recommended sample sizes for IMT studies of a therapy causing a 30% difference between placebo and active therapy are ≈300 participants per group, followed for 2 years.27 This large sample size and duration of study are because of the small magnitude of average progression of IMT (≈0.15 mm/y) in relation to the spatial resolution of carotid ultrasound (≈0.3 mm).

Two-dimensional (2D, total plaque area) and 3D (total plaque volume [TPV]) measurement of plaque burden, however, change by much greater quantities in relation to the spatial resolution of carotid ultrasound, so are much more sensitive to effects of therapy (Figure).

Early work in 3D ultrasound by Delcker and Diener,28 Hennerici et al.,29 and Fenster’s group30–32 led to increasingly automated methods for measuring TPV33–35 and vessel wall volume (VWV).

Total plaque area changes by ≈10 mm²/y, and 3D TPV by ≈50 to 100 mm³/y, so it is much easier to measure change in these quantities.36,37 It was possible to show a significant change in carotid plaque volume with atorvastatin in only 3 months, in only ≈20 patients per group.38 In patients randomized to placebo, TPV increased by 16.81±74.10 mm³; on atorvastatin, it regresses by −90.25±85.12 mm³ (P<0.001). Progression of TPV, but not of IMT or plaque area, predicted cardiovascular events among patients attending vascular prevention clinics.39

For patients or study participants without plaque, it is possible to measure VWV,40 which also changes by quantities easy to measure in small samples over short durations. Atorvastatin significantly reduced VWV in 3 months in ≈20 patients per group.41 Even weight loss and blood pressure reduction by diet was sufficient to show significant changes in VWV in 2 years with a mean reduction in VWV by −58.1 mm³ (95% confidence interval, −81.0 to −35.1 mm³; P<0.001).

A systematic review42 of intravascular ultrasound and other methods concluded that regression of atherosclerotic plaque using statin therapy in those studies documenting regression occurred after an average time of 19.7 months. This suggests that patients should undergo ≈2 years of aggressive lipid reduction before considering a reduction of statin therapy. However, because carotid plaque is focal, it is much more sensitive to effects of treatment than coronary plaque volume on intravascular ultrasound. Carotid plaques change in length, along the axis of flow, 2.4× faster than they thicken.43 Plaques also grow and regress circumferentially, so they can change in 3 dimensions: thickness, length, and circumferential extent. Coronary plaques, in contrast, extend around the entire circumference of the artery and along the entire length of the pullback, so they are not focal. Thus, the change over time reduces to a single dimension: average thickness.44

Santos et al.1 have shown that traditional coronary risk factors explain only a small fraction of IMT, and adding neck circumference, race, and pulse pressure brought the proportion

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**Figure.** Ultrasound images used for determinations of right carotid anatomy in 1, 2, and 3 dimensions from 2 study subjects. Three top panels are images from one subject and 3 bottom panels are images from the other. The left panels show typical images used to determine intima-media thickness (IMT), with arrows at the far carotid wall showing where IMT was determined. Both subjects had IMT of ≈1 mm. The middle panels show images used to determine total plaque area (PA) of the shaded plaques, with values shown for each subject. The right panels show images used to determine total plaque volume (PV) of the colored regions, with values shown. Reproduced from Al-Shali et al.45 with permission of the publisher. Copyright © 2005, Elsevier.
of explained variance (the $R^2$) up to only 0.3. This illustrates again the differences between IMT and plaque burden.

Ultrasound phenotypes of the carotid arteries thus differ in their relation to coronary risk factors and genetic factors and in response to therapy. Stenosis, IMT, and plaque burden are biologically distinct.

Sources of Funding

Dr Spence has received grants from the Canadian Institutes of Health Research, Heart & Stroke Foundation of Canada (Ontario), National Institutes of Health (National Institutes for Nervous Diseases and Stroke), and grants from industry for investigator-initiated research projects (Pitzer and Merck). Lecture honoraria/travel support/consulting fees were provided by Bayer, Merck, and Boehringer-Ingelheim. Contract research was conducted with all of the above pharma companies and Takeda Pharmaceuticals, Bristol-Myers Squibb, Servier, Wyeth, Miles, Roussel-Uclaf, and AstraZeneca, as well as with manufacturers of devices for percutaneous closure of patent foramen ovale (NMT, AGA, and Gore).

Disclosures

Dr Spence is a member of the Editorial Boards of Hypertension, Stroke and Atherosclerosis, Thrombosis and Vascular Biology. He receives royalties on books from Vanderbilt University Press and McGraw-Hill Medical. He is a shareholder and officer of Vascularis Inc.

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Carotid Ultrasound Phenotypes Are Biologically Distinct
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Arterioscler Thromb Vasc Biol. 2015;35:1910-1913
doi: 10.1161/ATVBAHA.115.306209

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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