Response to Letter by Karapanayiotides

Response:

We would like to thank Dr Karapanayiotides for his comments with respect to our recently published article.1 We measured representative fibrous cap thickness by visualizing three 5-μm-thick sections from each plaque (from the bifurcation or point of maximal stenosis, and from 3 mm either side) and by using a calibrated graticule in the microscope eyepiece to record the thickness of the part which was felt to be most representative of the cap as a whole. In making this measurement we took into account all 3 sections which therefore approximated to the mean cap thickness.

We agree that reliable pathological assessment is vital and we have called for better reporting.2 The intraclass correlation coefficient for measurements of representative cap thickness between and within observers were 0.57 (P=0.004) and 0.48 (P=0.01) respectively, which are roughly in line with the reproducibility for the categorical variable (representative cap thickness <500 μm): intraobserver κ=0.57 and interobserver κ=0.51. In some cases, difficulty arose when measuring cap thickness in ruptured plaques that had fragmented during processing. Thus in vivo imaging of plaques before they rupture may, in theory at least, measure representative (mean) cap thickness more reliably than is possible on histology.3 Alternatively, the application of a modification of the standard technique for endarterectomy which allows removal of intact specimens4 may enable histological assessments to be more reproducible.

As you point out, and as we stated in the article, a limitation of our study was that it was confined to symptomatic carotid plaques. We agree that a threshold cap thickness discriminating between asymptomatic and symptomatic plaques could well be different, especially given that cap ruptures can be ‘silent’. Such a threshold may well be >500 μm, but this would need validation in prospective studies of asymptomatic patients.

We assessed cap rupture using a 4-point semiquantitative scale (no, possible, probable, or definite rupture)5 from which ‘probable’ and ‘definite’ rupture were pooled to create the binary variable rupture used in this analysis. Thus, there were 92 (18%) coded as ‘possible’ rupture and 122 (24%) plaques coded as ‘not ruptured’. Nevertheless, we cannot conclude from our data that cap rupture was not the etiology of ischemic symptoms in these patients because there are several other possible explanations, not least the time delay between symptom onset and surgery which could have allowed some ruptures to heal.6

We don’t agree that the absence of rupture in some plaques can be explained by classification of patients’ stenosis or symptomatic status. First, the degree of stenosis was measured on US Doppler by experienced vascular technicians using criteria which have been validated locally against angiography. Second, we reviewed all case notes and confirmed the nature and size of ischemic symptoms. Thus, we excluded from the study 22 patients who were operated for asymptomatic stenosis (eg, prior to coronary artery bypass grafting) although we did include 14 patients with a history suggestive of cerebral hyperperfusion (7 had plaques with probable/definite rupture) and 33 with atrial fibrillation or another potentially cardioembolic source, 22 of whom (66%) had plaques with probable/definite rupture on histology.

In answer to your question ‘Do unruptured thrombogenic caps exist?’, post mortem studies of culprit plaques in cardiac death victims have described plaque erosion (thrombus at the site of denuded endothelium) in up to 44% cases.6–8 In these plaques, the exposed intima consists predominantly of smooth muscle cells and proteoglycans with very little inflammation.7,8 With regard to symptomatic carotid plaques, Spagnoli et al found plaque erosions in 18/187 (9.6%) endarterectomy specimens.9 In contrast, we found only 5 cases of surface thrombus among the 122 nonruptured plaques (constituting 0.95% plaques overall). However, this low figure could be partly due to dislodgement of thrombus during plaque processing because the prevalence of thrombus on histology (48.5%) was lower than that seen macroscopically at the time of surgery (32.5%).

If a substantial number of strokes are caused by erosion as opposed to rupture, then this could have important implications for the incorporation of in vivo imaging parameters into risk models, because plaques which undergo endothelial denudation may be associated with more ‘stable’ looking plaques on imaging. Thus as you suggest, assessing the cap-blood interaction may be important for these patients.

Disclosures

None.

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3. Touze E, Toussaint JF, Coste J, Schmitt E, Bonneville F, Vandermaarq P, Gauvrit JY, Douvrin F, Meder JF, Mas JL, Oppenheim C. Reproducibility of critical cap thickness by visualizing three 5-μm-thick sections from each plaque (from the bifurcation or point of maximal stenosis, and from 3 mm either side) and by using a calibrated graticule in the microscope eyepiece to record the thickness of the part which was felt to be most representative of the cap as a whole. In making this measurement we took into account all 3 sections which therefore approximated to the mean cap thickness.

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