which might or might not be associated with use of acetylcysteine, it could be prudent in this specific clinical setting to avoid use of ondansetron, because other antiemetics are available.

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We declare that we have no conflicts of interest.

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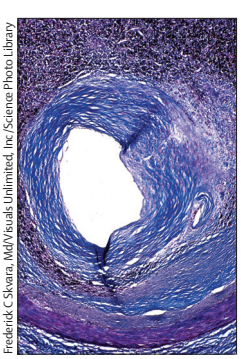
A new frontier in atherosclerotic coronary imaging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Published Online November 11, 2013 http://dx.doi.org/10.1016/S0140-6736(13)61911-X

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Ischaemic heart disease resulting from rupture of atherosclerotic plaques is a major cause of death worldwide. Precisely why a plaque ruptures remains a mystery. However, in *The Lancet*, Nikhil Joshi and colleagues' findings[1] suggest that we are close to being able to detect when rupture is about to occur.

The simple and inexpensive ^{18}F-sodium fluoride (^{18}F-NaF) PET radioisotope, used for 30 years to image bone formation, was found to signify metabolically active calcification in the aorta by Derlin and colleagues[2] and in the coronary arteries by Beheshti,[3] Dweck,[4] and Li,[5] and their colleagues. In their landmark article, Joshi and coworkers move this nascent field much farther forward.[1] They prospectively studied 40 patients with recent myocardial infarction (mean 8 days earlier) with invasive coronary angiography, CT coronary angiography, coronary calcium scoring, and cardiac gated PET-CT with ^{18}F-NaF and ^{18}F-fluorodeoxyglucose (^{18}F-FDG). Using invasive coronary angiography as the gold standard for determining the culprit plaque, the area of greatest ^{18}F-NaF uptake in the coronary arteries localised the plaque in 37 of 40 patients (maximum tissue-to-background ratio in the culprit plaque 1·66 [1·40–2·25] *vs* highest non-culprit plaque 1·24 [1·06–1·38]). By contrast, interpretation of ^{18}F-FDG PET-CT images in the same cohort was technically difficult because of the frequent overlap of myocardial ^{18}F-FDG uptake with the adjacent coronary arteries. Of the 55% of vascular territories that were interpretable by ^{18}F-FDG, only a weak correlation was seen with culprit plaque identification.

A second cohort of 40 patients with stable angina underwent the same imaging tests and an intracoronary ultrasound. 18 patients had one or more plaques with high ^{18}F-NaF uptake, defined as at least 25% greater than a proximal reference lesion. Intracoronary ultrasound identified that microcalcification, necrotic core size, and positive remodelling correlated strongly with plaques of high ^{18}F-NaF activity.

Histological correlation was assessed in a third cohort of nine patients who underwent carotid endarterectomy at a mean of 17 days after clinical symptoms. Ex-vivo PET-CT was done on the removed carotid atherosclerotic tissue. Macroscopic plaque rupture was present in each patient, all localised to areas of high ^{18}F-NaF uptake. Plaques with increased ^{18}F-NaF uptake had substantially larger necrotic cores, more cell death and macrophage infiltration, and, as measured by alkaline phosphatase and osteocalcin staining, more active calcification than those that did not.

With the strong in-vivo correlates of coronary plaque rupture seen on intracoronary ultrasound in patients with stable angina, and histological confirmation of

plaque rupture in atherosclerotic carotid tissue with high ^{18}F-NaF activity, the authors can indeed state that of 40 patients with recent myocardial infarction (37 men, three women), plaque rupture can be detected non-invasively.

Now that we can detect plaque rupture, should we? Although the radioisotope ^{18}F-NaF and PET-CT equipment are readily available in the developed world, much research needs to be done before the technique can become a viable clinical option. Just because a plaque at risk for rupture can be identified does not mean that we know what to do with this information. Prospective trials are needed to establish the frequency with which high ^{18}F-NaF plaques rupture, and the timing of rupture. Also, does plaque rupture result in events or simply the rupture and healing cycle believed to result in a stepwise increase in plaque stenosis? If such trials are positive, what will we do with the information? Of Joshi and colleagues' 40 patients with stable angina, nearly all were on antiplatelet agents and 36 were taking statins. Despite this therapy, 18 patients had at least one plaque with high ^{18}F-NaF uptake. However, the ability to assess and potentially quantitatively measure plaque at high risk of rupture as a continuous variable (by maximum standard uptake value) creates a new world of opportunity for the investigation of pharmacological and device therapy.

The technique holds greater promise in populations with myocardial infarction and acute coronary syndrome than in more stable patients. Earlier work by Joshi and colleagues, for example, found a strong correlation between patients with high NaF plaques and those with the more easily and inexpensively obtained total Agatston coronary calcium score.[4]

The technique also creates the opportunity to better assess the commonly accepted belief that most myocardial infarctions are caused by rupture of previously non-obstructive plaques. The underpinnings of this theory are derived from coronary angiography that is done distant from the index myocardial infarction.[6,7] Narula and colleagues[8] and others have questioned this assumption. The predictive value for increasing non-fatal myocardial infarction and cardiac death consistently seen in studies of increasing ischaemia, as assessed by myocardial perfusion imaging,[9] and worsening obstructive disease by coronary CT[10] and invasive angiography, are also inconsistent with this assumption.

Questions to be answered include: how best to use information derived from an assessment of inflammation by ^{18}F-FDG and active calcification by ^{18}F-NaF. In large vessels without adjacent areas of intense ^{18}F-FDG activity, ^{18}F-FDG assessment is much less handicapped by overlapping structures compared with the coronary arteries. How do Joshi and colleagues' findings apply to women, in whom plaque erosion is a much more common mechanism of myocardial infarction than in men? How do the findings apply to patients with diabetes? Does coronary artery bypass graft biology differ with respect to ^{18}F-NaF activity? Do high ^{18}F-NaF plaques in the carotid and other cerebrovascular vessels predict stroke and transient ischaemic attack? Joshi and colleagues and earlier pioneers have identified a new and hopefully fruitful frontier in nuclear cardiology and atherosclerotic coronary imaging.

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We declare that we have no conflicts of interest.

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