A new frontier in atherosclerotic coronary imaging

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A new frontier in atherosclerotic coronary imaging

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 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 and in the coronary arteries by Beheshti, Prescott, and their colleagues. In their landmark article, Joshi and coworkers move this nascent field much farther forward. They prospectively studied 40 patients with recent myocardial infarction (mean 8 days earlier) with invasive coronary angiography as the gold standard for determining the culprit plaque, the area of greatest $^{18}$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. 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 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 activity.

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 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.

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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 possible,
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.

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.
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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