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## In Vivo Imaging of Atherosclerosis by Multimodality MR, CT, and PET

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### **MR Imaging**

Conventional X-Ray angiography is an excellent tool to determine the degree and extent of luminal narrowing but it cannot detect early lesions development when luminal area is maintained by positive vascular remodelling. This is an important limitation of angiography in that high-grade coronary stenoses are more likely to produce stable ischemia, but lesions with positive remodelling are often the lesions that cause myocardial infarction or sudden death. MR imaging allows for three dimensional evaluation of vascular structures and outstanding depiction of various components of the atherosclerotic plaque, including lipid, fibrous tissue, calcium and thrombus formation.(1-3) Combining MRI with cellular and molecular targeting may provide important data on the biological activity of potentially vulnerable lesions (i.e., cap thickness, lipid content, presence of activated macrophages, micro-vessels density, tissues factors, etc.) MRI has been used to determine plaque size and composition in aortas and carotid arteries. In vivo coronary artery plaque imaging is much more challenging. Preliminary studies in a pig model showed that the difficulties of coronary wall imaging result from a combination of cardiac and respiratory motion artefacts, non-linear course, small size and location.(4) Human in vivo data have been published but future studies are still needed to further explore these advanced imaging techniques.(5) The role of MRI for assessment of plaque morphology has been demonstrated in several investigations: discrimination between medial and adventitial layers(6), between collagenous cap, lipid core and calcifications(1), determination of the presence of necrotic core and recent haemorrhage.(7, 8) MRI has been used also to diagnose and follow the development of in vivo atherosclerotic lesions either in animals(9) or humans.(10,11) An extensive area of MRI research has been the use of non-invasive MRI techniques for molecular and targeted contrast imaging. Conventional gadolinium-containing contrast agent can improve detection of plaque (12,13) or identify plaque with increased vascularity.(13) Currently the dynamic phase of gadolinium agents are being used to identify parameters associated with plaque neovascularization. (14,15) Kinetic modeling of the contrast agent dynamics is performed in order to obtain information related to atherosclerotic plaque inflammation (transfer constant  $k_{trans}$ ), fractional blood volume (vp), time to peak, and mean transit time. It is hoped that one or more of these parameters may correlate with the neovessel density (that is used to assess the neovascularization). Preliminary studies indicate that vp obtained in human carotid

plaques may correlate with vessel density and neovascularization. (14,15). However, for other fibrous tissue no significant correlations between vp and neovessel density have been observed. Further studies are therefore required to evaluate the potential of dynamic contrast enhanced MRI for the evaluation of plaque neovasculature.

Specific gadolinium based agents (Gadofluorine M) can enhance plaque characterization. (16) Ultra-small particles of iron oxide are present in 75% of the aorta vulnerable plaques but only 7% of the stable plaques (17) and are a marker of macrophage rich plaques.(18) Many specific contrast agents have been or are tested with different targets (19,20): thrombus (21), HDL-like nanoparticles (22,23), immunomicelles scavenger receptor specific (24), etc.

### **CT Imaging**

Primary requisites for the assessment of atherosclerotic calcified and noncalcified plaques are similar to the requirements for a high-quality computed tomography angiography (CTA) of the arteries, especially the coronary arteries, i.e., achieving both high spatial and high temporal resolution at the same time. Compared to low pressure arterial systems, such as the pulmonary arteries where calcifications are absent and the injection rate can be increased to visualize the smallest arterial branches, in coronary arteries the opacification must not exceed about 300 Hounsfield Units (HU) for a reliable depiction and judgment of calcifications. Optimization of the vessel contrast-to-noise ratio is also mandatory for sufficient visualization of noncalcified plaques. Methods to enhance the contrast-to-noise ratio in the vessel wall include either the use of a test bolus setting or a bolus tracking. Because non-enhanced blood and noncalcified plaques have a similar attenuation on CT (50 to 70 HU), these types of lesions can be detected only after the administration of contrast media. Therefore, vessel enhancement significantly above the CT values of noncalcified plaques (150 HU) must be achieved to allow for reliable detection of noncalcified plaques. With this vessel enhancement, calcified coronary lesions remain detectable because their attenuation is significantly higher. CT has become an established method for non-invasive and highly sensitive detection of coronary artery calcifications. It has the potential to identify early, noncalcified plaques in vivo even in the coronary arteries. MDCT sensitivity for detection of calcified plaques is high, 94 to 95%, but it drops to 53 to 78% for the detection of exclusively noncalcified plaques.(25,26) Even though some authors reported a high diagnostic accuracy for detection of vulnerable lesions when compared to intra-vascular ultrasonography(27), others reported difficulties in differentiating between fibrous-rich and lipid-rich plaques either in vivo in animals(28) or under ex vivo conditions.(29) More recently, using a 64-MDCT system, Leber et al. showed an overall sensitivity and specificity to detect non-significant coronary plaques of 84% and 91% respectively (30) and encouraging results to detect different types of coronary plaques in the proximal coronary system.(31) These different studies determine soft plaques (14 to 51 HU), intermediate plaques (71 to 116 HU) and calcified plaques (391 to 715 HU).(26,28,32) Acute intra-vascular thrombi can also be detected in vivo; the appearance of the irregular thrombus is typical with low attenuation numbers in the range of 20-30 HU. The precise characterization of plaque with CT is still not accessible with current techniques. More over, the quantification of

wall thickness is also limited.(31) New development of CT specific contrast agents for vessel wall imaging could greatly enhance the use of this imaging modality.

### **PET Imaging**

By providing a metabolic image of macrophage activity, F18-Fluorodeoxyglucose (FDG) positron emission tomography (PET) can image atherosclerotic plaque inflammation in patients and in animal models of disease, with a strong correlation between FDG uptake and plaque macrophage content.(33-35) In addition, autoradiography has confirmed that the FDG signal originates primarily from activated macrophages within the lipid core and fibrous cap of the plaque.(33) A very recent paper also suggested that activated endothelial cells were also capable of taking up FDG.(36) This has led to the suggestion that FDG-PET might have a role in identifying 'high risk' plaques and monitoring their response to therapy with drugs aimed at plaque stabilization and regression. With the advent of combined PET/CT scanners, both image co-registration and PET data attenuation correction have become simpler.

In humans, oncologists and radiologists performing PET scans for cancer workup have for years been aware of FDG accumulation in the large arteries. (37) It has been demonstrated that the degree of accumulation of FDG relates to the burden of atherosclerotic risk factors.

The first prospective study to use PET to image human atherosclerosis was published in 2002.(33) A group of 8 patients who had experienced a recent TIA and in whom there was angiographic evidence of internal carotid artery stenosis were imaged, and it was shown that recently symptomatic plaques took up significantly more FDG than those from the contralateral asymptomatic side.

More recently, other groups around the world have replicated and extended these findings.(38) Dunphy performed the first study to examine the relationship between FDG uptake and calcification as determined by CT. He noted a disparity between CT positive and PET positive plaques, suggesting that FDG uptake is an early part of the plaque lifecycle, while calcification occurs later. However, these findings are not inconsistent with current understanding of plaque cell biology which would predict that calcification is a consequence of cell death induced by inflammation. Tawakol was able to use the PET technique to prospectively classify carotid plaques into clinically relevant groups, showing different degrees of FDG uptake among plaques between plaques with <5%, 5-10% and >10% macrophage content. (39)

In order to reduce radiation dose, a group in Cambridge, UK (40), used MRI instead of CT to anatomically co-register PET images. Additionally they demonstrated that FDG uptake in symptomatic patients with posterior circulation transient ischaemic attacks could be identified using this technique. MRI also has the advantage of being able to image the wall of the artery with high resolution without the need for nephrotoxic contrast. Combined PET and MRI scanners are currently in advanced stages of development, although for the next 10 years PET/CT combinations will likely be much more commonly used.

The first atherosclerosis intervention study using PET has been published this month. In a population of oncology patients, Tahara et al (41) randomly allocated half of a group of 43 patients to either statin therapy or placebo. Using FDG PET to visualize and quantify plaque inflammation, they demonstrated a significant reduction in FDG signal amongst the statin treated group, over as short a time period of three months. This result opens the door for PET to be used in the assessment of other plaque-stabilizing therapies. Secondly, there is potential for a change in FDG uptake within a plaque to be used as a surrogate clinical marker, potentially slashing the cost of large multicenter trials of novel drugs.

A major hurdle still to be overcome is the use of FDG PET imaging to detect inflammation in the coronary arteries. Their small size, motion and proximity to the myocardium (which can avidly accumulate FDG) make this goal unlikely to be achieved in the near future. However, there are attempts being made using respiratory and cardiac gating, along with a high-fat diet prior to imaging to suppress myocardial FDG uptake. A more likely scenario is that an alternative ligand will be developed that is both taken up by plaque macrophages and not by myocardial cells. Such compounds are currently in late stage animal trials.

In conclusion, we believe currently that use of multimodality imaging (MR, PET, and CT) for the study of inflammation of vessel wall may be useful in assessment of plaque vulnerability.

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