REVIEW ARTICLE

Exploring the nature of atheroma and cardiovascular inflammation *in vivo* using positron emission tomography (PET)

J R BUSCOMBE, MD, FRCP

Department of Nuclear Medicine, Cambridge University Hospitals, Cambridge, UK

Address correspondence to: Dr John R Buscombe
E-mail: *john.buscombe@addenbrookes.nhs.uk*; *jrb.wjnm@googlemail.com*

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ABSTRACT

Positron emission tomography (PET) has become widely established in oncology. Subsequently, a whole new "toolbox" of tracers have become available to look at different aspects of cancer cell function and dysfunction, including cell protein production, DNA synthesis, hypoxia and angiogenesis. In the past 5 years, these tools have been used increasingly to look at the other great killer of the developed world: cardiovascular disease. For example, inflammation of the unstable plaque can be imaged with 18-fludeoxyglucose (^{18}F-FDG), and this uptake can be quantified to show the effect that statins have in reducing inflammation and explains how these drugs can reduce the risk of stroke. ^{18}F-FDG has also become established in diagnosing and monitoring large-vessel vasculitis and has now entered routine practice. Other agents such as gallium-68 (^{68}Ga) octreotide have been shown to identify vascular inflammation possibly more specifically than ^{18}F-FDG. Hypoxia within the plaque can be imaged with ^{18}F-fluoromisonidazole and resulting angiogenesis with ^{18}F-RGD peptides. Active calcification such as that found in unstable atheromatous plaques can be imaged with ^{18}F-NaF. PET imaging enables us to understand the mechanisms by which cardiovascular disease, including atheroma, leads to morbidity and death and thus increases the chance of finding new and effective treatments.

Positron emission tomography (PET) has become established in the staging and restaging of many common cancers and in many ways can be considered to be routine. The most commonly used radiopharmaceutical for PET imaging is 18-fludeoxyglucose (^{18}F-FDG), but it is a non-specific agent and relies on the fact that cancer cells have a higher uptake of glucose than do normal tissue. There is also increased uptake of ^{18}F-FDG in other cell types including both lymphocytes and macrophages. Therefore, when reading an ^{18}F-FDG PET study, care must be taken not to assume that focal uptake of ^{18}F-FDG is a site of cancer when it could be owing, for example, to inflammation such as can be seen in atheroma in a major artery. The use of fusion imaging with PET-CT allows for better localization and should ensure correct localization (Figure 1). There has been increasing use of ^{18}F-FDG imaging in inflammation, and recently published European and North American guidelines have recommended that ^{18}F-FDG PET can be used in cardiovascular inflammation.[1]

In oncology, the non-specific nature of ^{18}F-FDG has led to the development of a toolbox of different PET radiopharmaceuticals to look at a range of different aspects of cancer cell function and metabolism, such as carbon-11 (^{11}C) methionine to look at amino acid metabolism, ^{18}F-fluorolevothymidine to look at DNA synthesis in cancer cells and ^{18}F-fluoromisonidazole (FMISO) to look at hypoxia.[2–5] Over the next 5–10 years, a similar toolbox may be applied to the imaging of the cardiovascular system (Figure 2), which may well move from the laboratory into more routine clinical practice; therefore, the clinician who is responsible for the provision of PET services will need to know how these techniques can be used.

VASCULITIS

Although not atherosclerotic in origin, vasculitis does represent inflammatory disease in the major blood vessels and can lead to strokes and possibly myocardial infarction. In the UK, ^{18}F-FDG imaging has been approved for routine assessment of large-vessel vasculitis.[6] This acceptance has been evidence based on research over the past 10 years. This evidence includes a series of 26 patients with a prospective diagnosis of giant-cell arteritis, which demonstrated a good correlation between the activity of ^{18}F-FDG

Figure 1. Coronal CT (upper left image), 18-fludeoxyglucose (^{18}F-FDG) (upper right image), positron emission tomography-CT-fused image (lower left image) and maximal intensity projection (lower right image) of focal ^{18}F-FDG uptake on the right side of the neck, which localizes to atheroma in the internal carotid artery. FOV, field of view.
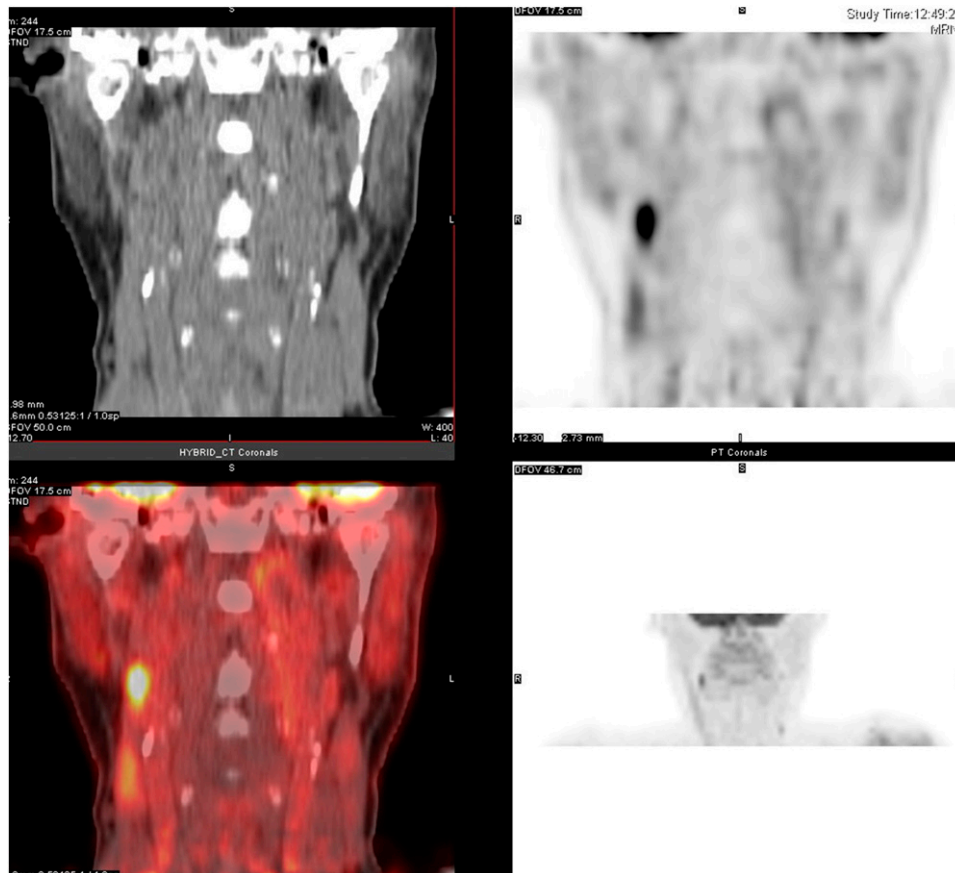
in the major vessel walls and inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein (CRP) as well as wall thickness on CT.[7] The authors also noted that the disease was much more extensive than previously recognized.

Figure 2. Diagram of the positron emission tomography agents that can be used to image factors in the atheromatous plaque. ^{18}F-FDG, 18-fludeoxyglucose; FMISO, fluoromisonidazole; VEGF, vascular epidermal growth factor.
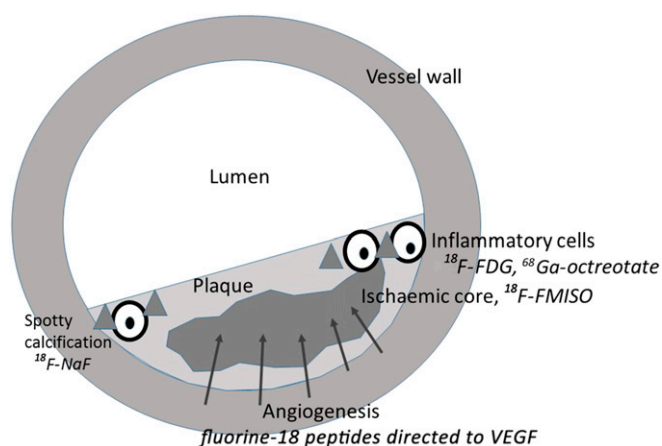

Not only were the carotid and the head and neck vessels involved but also the arch of the aorta, and the axillary and subclavian arteries. Also, this technique may yet replace the traditional temporal artery biopsy in establishing the diagnosis of giant-cell arteritis. In some patients, the inflammation can extend down to the abdominal aorta as far as the iliac arteries (Figure 3). In a prospective study of 16 patients with suspected giant-cell arteritis, it was shown that ^{18}F-FDG PET-CT identified sites of inflammation but also that the uptake of ^{18}F-FDG calculated as the mean, maximum standardized uptake value (SUV_{max}) dropped from 3.38 to 2.32 after 6 weeks of steroid treatment.[8] ^{18}F-FDG PET-CT for the diagnosis and management of vasculitis is now considered routine and is reimbursed in many countries. A systemic review published in 2011 looked at six studies using ^{18}F-FDG and determined that ^{18}F-FDG had a sensitivity of 80% and specificity of 89% for giant-cell arteritis.[9]

INFLAMMATION IN ATHEROSCLEROSIS

When reporting routine oncological ^{18}F-FDG PET, it is not unusual to identify focal ^{18}F-FDG activity in a major vessel quite unlike that seen in vasculitis. This uptake has been found to be owing to inflammation in atherosclerosis. In our understanding of atheroma, there are two types of plaque. The stable plaque has a smooth surface and is not immediately dangerous. The unstable and inflamed atheroma is thrombogenic

Figure 3. Sagittal whole-body fluorine-18 fluorodeoxyglucose (^{18}F-FDG) images showing increased uptake of ^{18}F-FDG throughout the thoracic aorta in a patient with giant-cell arteritis. [Note: the left-hand panel is the CT scan, the central panel is the positron emission tomography (PET) image and the right-hand panel is the fused PET-CT image.]
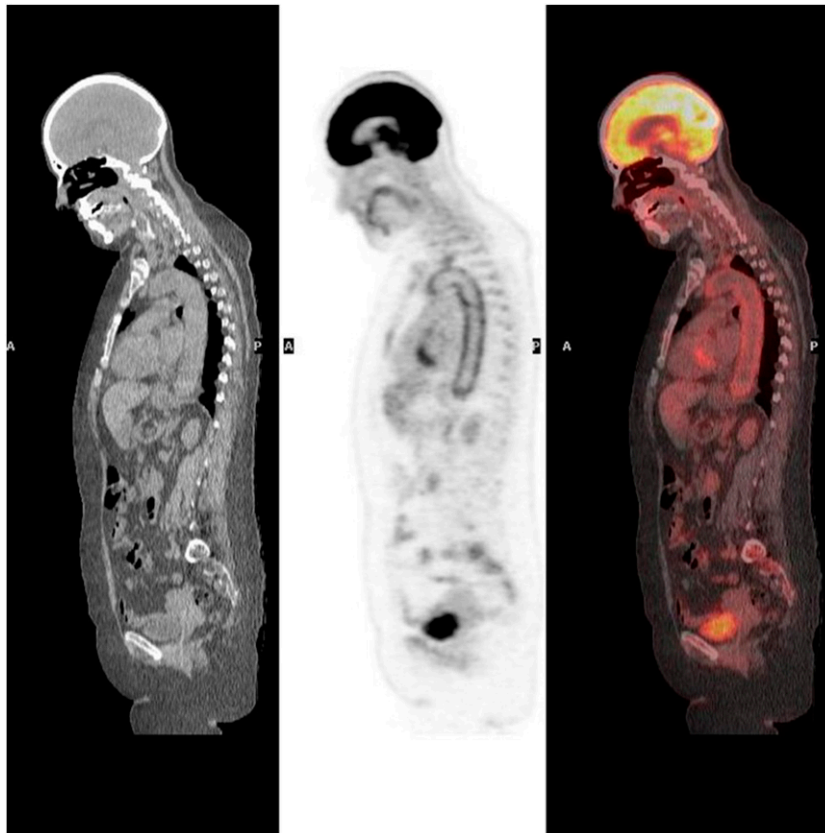
and, if sited in a carotid artery, could result in a thrombotic cerebrovascular accident, one of the main causes of death and, often more distressing, significant disability in the developing world.[10]

Although presently imaged with ultrasound and functional MR, PET imaging may provide a unique insight into the mechanisms underlying atheroma. The hope is that, by imaging of these atheromatous plaques with ^{18}F-FDG, it may be possible to identify sites of active inflammation, and this would in itself be predictive of future thrombotic effects. Initially, PET machines had a resolution of about 0.9 cm, so initial work tended to concentrate on major blood vessels such as the aorta and the femoral and carotid arteries. There is indeed a good correlation with other measures of inflammation in atheroma, including plaque thickness and suspicious looking plaque on contrast CT. Interestingly, there was little correlation between the sites of ^{18}F-FDG uptake and calcification often taken as a sign of a fragile plaque. In a prospective study of 21 patients due to undergo carotid endarterectomy, the uptake of ^{18}F-FDG was correlated with CD-68 as an expression of macrophage activity. This study showed that the SUV_{max} for ^{18}F-FDG in the affected arteries was 2.4, significantly higher than the contralateral artery (SUV_{max}, 2.2), and showed a good correlation with the expression of CD-68 ($r = 0.55$) and thus helps to underline the inflammatory nature of atheroma.[11]

In a further study looking at the reproducibility of the technique, ^{18}F-FDG uptake in femoral artery atheroma was assessed using paired scans 2 weeks apart. There was no significant difference in uptake measured using the SUV_{max} at the same site.[12] This was important as it identified that ^{18}F-FDG PET was a reproducible technique that will enable paired studies to be performed with an intervention.[13] This would mean that any change in the standardized uptake value would be owing to the meaningful change in ^{18}F-FDG uptake, which in the context of atheroma will be owing to a reduction in inflammation. This has been tested in carotid artery atheroma, where patients with inflammatory atheroma in the carotid arteries were treated either by a low cholesterol (Chol) diet or the Chol-lowering drug simvastatin. It was found that, in those patients treated with simvastatin, there was a significant reduction in the uptake of ^{18}F-FDG, with a mean drop in SUV_{max} of 0.2, which was not only significant but also correlated well with a drop in high-density lipoprotein Chol (HDL-Chol). There was no change in the SUV_{max} or HDL-Chol when a low Chol diet was given.[14] This study has recently been confirmed in a study that initially showed that arterial wall activity of ^{18}F-FDG was significantly greater in those patients with familial hypercholesterolaemia.[15] In patients with familial hypercholesterolaemia, those 12 patients who underwent lipoprotein aphaeresis not only showed a significant reduction in plasma Chol but on repeat ^{18}F-FDG imaging the median SUV_{max} of the vessel wall activity fell from 2.05

to 1.91 ($p < 0.02$). This may be owing to the fact that Chol itself is inflammogenic and may explain, in part, the claims that long-term statins reduce cardiovascular deaths.[16]

It would be ideal, if it was possible, to use a more specific anti-inflammatory agent other than ^{18}F-FDG, and these have been the basis of the use of gallium-68 (^{68}Ga). Several agents have been suggested in pre-clinical studies, including ^{68}Ga-citrate, ^{68}Ga-octreotate and ^{68}Ga-labelled antiselectin E peptides.[17–19] Translation into human studies has been slow owing to a limited number of those trained to use this product and to regulatory issues in some countries. In addition, the short half-life of gallium (68 min) means that most sites would need their own generator to be able to undertake meaningful studies. However, there has been 1 observational study of 70 patient images with ^{68}Ga-octreotate, imaged because they had a neuroendocrine tumour. There was significantly greater uptake in the coronary arteries with calcified plaques than in those without calcified plaques.[20]

METABOLIC IMAGING OF AORTIC ANEURYSM

Inflammation in aortic aneurysm may be a poor prognostic factor and is associated with focally increased uptake of ^{18}F-FDG.[21] In three patients with increased ^{18}F-FDG uptake, there was an increase in the presence of lymphocytes, macrophages and matrix metalloproteinase-9 within the atheroma, all markers of aneurysm rupture risk. In a further study of 18 patients, 8 of whom had aortic aneurysm, the uptake of ^{18}F-FDG was compared with various known genetic risk factors.[22] There was a marked correlation between the uptake of ^{18}F-FDG in the aortic wall of the aneurysm and CRP; a sign of general inflammation and increased local gene expression of collagenase and matrix metalloproteinase both identified as risk factors for rupture. However, it is unclear how useful ^{18}F-FDG imaging will be as in a review of 40 patients considered at risk by CT no patient had increased aortic uptake of ^{18}F-FDG.[23] A much larger series of 300 patients, half of whom had an aortic aneurysm, failed to show an increased uptake of ^{18}F-FDG in those patients with an aneurysm.[24] Therefore, presently the published data are mixed and, until further information is available, the role of ^{18}F-FDG, in particular when it is an unexpected finding in a study performed for other indications, remains unclear.

OTHER AGENTS IN ATHEROMA

Our knowledge of cancer has opened up a whole range of new agents that can also be applied to identify different processes in atheroma. The atheromatous plaque itself is a dynamic process and involves areas of hypoxia, angiogenesis, calcification and inflammation. There are PET agents that can look at some of these processes. One of these agents is ^{18}F-FMISO, which is retained in sites of hypoxia when imaged at 30–60 min post injection.[25] There have been some early studies that indeed do suggest that ^{18}F-FMISO may be even more specific in identifying fragile atheromatous plaque than ^{18}F-FDG.[26]

A further potential agent would be ^{18}F-labelled peptides, which is used to recognize vascular epidermal growth factor or its associated cell wall peptide alpha v beta 3 integrin. It is well known that in tumours, hypoxia results in the release of hypoxic factors which induce angiogenesis; therefore, a similar mechanism can occur in the atherosclerotic plaque that is also hypoxic. In a recent pilot study, ^{18}F-labelled galacto-RGD (arginine-glycine-aspartic acid) peptide directed against alpha v beta 3 integrin has been investigated in 10 patients before carotid endarterectomy.[27] This study showed good localization in stenotic carotid artery that correlated with alpha v beta 3 integrin expression in the excised arterial wall.

Alternative targets have been investigated using retrospective studies of patients imaged for a different indication but who may have atherosclerosis. One idea has been to look at lipid metabolism using ^{11}C-choline or ^{18}F-fluoroethylcholine (^{18}F-FEC). In two retrospective studies, ^{11}C-choline and ^{18}F-FEC PET imaging has been performed in males with prostate cancer. There was no correlation between atheroma found on CT and ^{11}C-choline uptake. However, as atheroma was defined by the presence of calcification on the CT component, these studies were suboptimal in their methodology.[28,29] There appeared to be better correlation between the uptake of ^{11}C-acetate and calcification in the aorta of males imaged for cancer, but there was a poor correlation between the intensity of that uptake and known risk factors except for age. At present, therefore, although imaging fatty acid metabolism may be useful, it needs confirmation by a well-designed prospective trial with pathological correlation.

CALCIFICATION

Calcification has been recognized as a marker of atheroma, and cardiac CT with calcium scoring has become established in assessment of coronary arteries.[30] It is not uncommon in elderly patients to see focal calcification in the wall of major peripheral as well as coronary arteries. However, the macroscopic calcification that is seen on CT may not in itself be a good predictor of future events.[31] The process of calcification is thought to start as microcalcification in sites of ischaemia and cell death, which eventually builds up to produce the recognizable calcification seen on CT. This process of micro-calcification can be tracked using a simple radiopharmaceutical ^{18}F-NaF. The radioactive fluoride has a high affinity for calcified tissue and thus has increased accumulation in sites of calcification. There has been an observation that the distribution of ^{18}F-NaF does not align exactly with calcification seen on CT, and the proposed mechanism is that ^{18}F-NaF is deposited at sites of new calcium being laid down in sites of active calcification, which is adjacent to but not at the site of the macrocalcification as seen on CT.[32]

IMAGING THE CORONARY ARTERIES WITH SODIUM FLUORIDE

Recent advances in PET imaging have resulted in improvements in both spatial and temporal resolution. Modern time-of-flight PET scanners are able to identify events 400 ps apart. This enables time-of-flight reconstruction reducing usable system resolution of PET scanners closer to 5 mm.[33] Also, the use of cardiac gating combined with this increased temporal resolution removed the blurring caused by movement of the heart; therefore now it is possible to look at the coronary arteries (Figure 4).

Figure 4. The ^{18}F-NaF image (right-hand side) shows increased uptake (arrows) at the site of a calcified coronary artery seen on the CT (left-hand side). FOV, field of view.
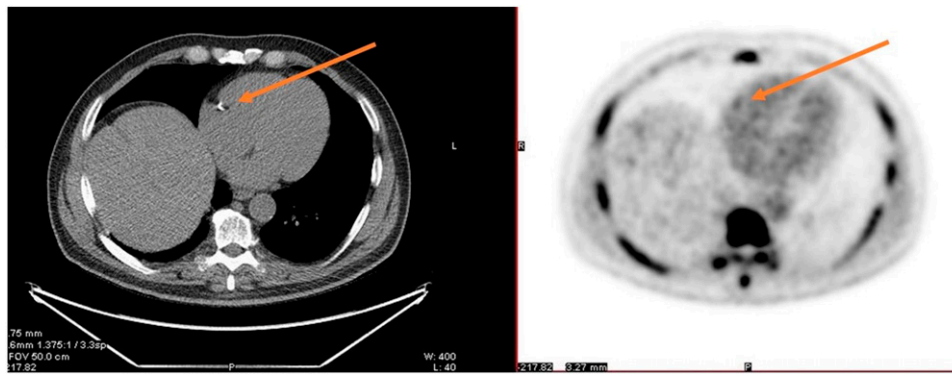
In a recent two-centre prospective trial, 80 patients were studied, 40 with a history of myocardial infarction and 40 with a history of unstable angina.[34] Each patient underwent a gated ^{18}F-FDG scan and an ^{18}F-NaF-gated scan of the heart. Then, the uptake of each tracer was compared with the culprit atheromatous plaque and the other plaques seen on angiography. Whilst there was no significant difference between the ^{18}F-FDG uptake between the culprit and non-culprit plaques, there was significantly greater uptake of ^{18}F-NaF in the culprit plaque than in the non-culprit plaque. It was also noted that, as had been seen in the carotid arteries, the uptake of ^{18}F-NaF was not at the sites of calcification seen on CT but in the adjacent tissues, which the authors felt signified that the ^{18}F-NaF uptake was identifying not sites of established calcium deposition but new sites of calcium being laid down in the sites where the plaque is most vulnerable.

CONCLUSIONS

PET techniques are beginning to show their worth in investigating cardiovascular disease. Initial work with ^{18}F-FDG has become used clinically in identifying and monitoring the treatment of large-vessel vasculitis and is also being used to identify inflammation in atheroma. Newer work has started to use the same techniques as those developed in molecular imaging in cancer by investigating different aspects of cardiovascular disease. Active calcification of coronary arteries can be identified by ^{18}F-NaF, and there is growing evidence that this methodology may find a routine clinical role.

With advances being made in the application of PET in cardiovascular disease, it will not be too long before these techniques will complement other radiological techniques used in investigating these common diseases.

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