ROLE OF PET/CT IN ASSESSMENT OF AORTA

By
Khaled El-Saban, MD, PhD
Professor of Medical Imaging
Faculty of Medicine – Taif University
The aorta is an integral part of the cardiovascular system and should not be considered as just a conduit for blood supply from the heart to the limbs and major organs.

A range of important pathologies affect the aorta and are responsible for a high level of morbidity and mortality in affected patients. Many of these conditions are seen in the adult congenital population, especially as advances in diagnosis and treatment mean these patients are surviving well into adulthood. As we gain a greater understanding of these disorders, especially the underlying genetics and pathophysiology, it becomes clear that the aorta is a highly complex part of the vascular tree.

As such, the aorta requires increasingly sophisticated imaging techniques for the diagnosis, treatment and follow-up of these patients. The advantages and disadvantages of the various imaging techniques available to clinicians will be discussed in the context of both acute and chronic aortic pathology.
**WHY PET/CT**

- PET/CT combines in a single session:
  - The sensitivity granted by PET for detection of molecular targets within the picomolar range, with
  - An underlying submillimetric resolution inherent to CT, that can precisely localize the PET findings.
- In this last decade, there have been new insights regarding the pathophysiology of atherosclerosis, particularly about plaque rupture and vascular remodeling.
- This has increased the interest for research on PET/CT in vascular diseases as a potential new diagnostic tool, since some PET molecular targets could identify diseases before the manifestation of gross anatomic features.
endothelial cells in early atherosclerosis begin to express molecules on their luminal surface in response to the presence of lipid in the vessel wall. These molecules are of the selectin (P- and E-) and adhesion classes.
proinflammatory cytokines including interleukin-1, monocyte chemotactic protein-1, and tumor necrosis factor-

enzymes capable of directly digesting the fibrous cap of the plaque, including several members of the matrix metalloproteinase (MMP) family

Once inside the vessel wall, lipid (mainly as low density lipoprotein) is targeted for oxidation and ingestion by inflammatory cells.

Recruitment of these cells, predominantly monocytes and T cells, is facilitated as they become slowed and bound by the expressed endothelial adhesion molecules.

Macrophages attempt to clear subendothelial lipid from the vessel wall, but in so doing they set up an inflammatory cycle.

Fatty-Streak Formation in Atherosclerosis
Plaque macrophages have a high rate of apoptosis and along with the accumulated lipid they constitute the “lipid core” of the plaque.

A balance is established between the proinflammatory actions of macrophages & infiltrating lymphocytes & the protective layer of smooth muscle cells separating the lipid core from the vessel lumen.
Where the degree of inflammation is sufficient, the fibrous cap can rupture, exposing the thrombogenic lipid core to the bloodstream. This may cause a local arterial thrombosis from which clinical events such as myocardial infarction can result.
**Types of Plaques seen by MDCT**

**Non-calcified plaque was defined as**
- Any discernible structure that could be assigned to the coronary artery wall, with a computed tomography (CT) attenuation below the contrast-enhanced coronary lumen but above the surrounding connective tissue/epicardial fat in at least two independent planes.

**Calcified atherosclerotic plaque**
- Any structure with a CT attenuation of 130 HU that could be visualized separately from the contrast-enhanced coronary lumen (either because it was “embedded” within non-calcified plaque or because its density was above the contrast-enhanced lumen).
Remodeling index (RI) was defined as:

The ratio between the area including both plaque and vessel lumen at the site of maximal luminal narrowing and the mean of the proximal and distal reference site.
<table>
<thead>
<tr>
<th>Type</th>
<th>Histological classification</th>
<th>Gross classification</th>
<th>Lesion</th>
<th>MSCT detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Isolated macrophage foam cells</td>
<td>Fatty dot, fatty streak</td>
<td>Early lesion, minimal lesion</td>
<td>No</td>
</tr>
<tr>
<td>II</td>
<td>Multiple foam cell layers</td>
<td>Fatty dot, fatty streak</td>
<td>Early lesion, minimal lesion</td>
<td>No</td>
</tr>
<tr>
<td>III</td>
<td>Preatheroma, intermediate lesion</td>
<td>Visually assessed</td>
<td>Chronological annotation</td>
<td>No</td>
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<tr>
<td>IV</td>
<td>Atheroma</td>
<td>Fibrolipid plaque</td>
<td>Advanced</td>
<td>Yes</td>
</tr>
<tr>
<td>V</td>
<td>Fibroatheroma</td>
<td>Fibrous plaque, plaque</td>
<td>Advanced</td>
<td>Yes</td>
</tr>
<tr>
<td>VI</td>
<td>Fissured, ulcerated, hemorrhagic, thrombotic lesion</td>
<td>Complicated lesion</td>
<td>Advanced</td>
<td>Yes</td>
</tr>
<tr>
<td>VII</td>
<td>Calcific lesion</td>
<td>Calcified lesion</td>
<td>Advanced</td>
<td>Yes</td>
</tr>
<tr>
<td>VIII</td>
<td>Fibrotic lesion</td>
<td>Visually assessed</td>
<td>Advanced</td>
<td>Yes</td>
</tr>
</tbody>
</table>
A unique example of an inflammatory condition is the one caused by the atherosclerotic plaque formation that is associated with an abundance of macrophages known by its avidity to 18F-FDG. The degree of uptake is usually less than the uptake within the neoplastic tissues. However, there is clearly an overlap between the 2 conditions and, in some cases, the uptake could even exceed the neoplastic uptake.
Aorta imaging with PET/CT. The left image is a noncontrast coronal CT image showing calcification of the abdominal aorta (group of 3 green arrows). The center and right images are coregistered PET and fused PET/CT images, respectively, demonstrating significant FDG uptake within the ascending aorta (single arrow) but relatively less FDG uptake in the calcified abdominal aorta. The green cross is in the inferior vena cava, where there is low FDG uptake.
Techniques for imaging the unstable plaque. This scheme illustrates morphological and biological tools for visualizing vulnerable plaques. Modalities with clinical applications are given in bold.
Illustration of the relative spatial resolution of common imaging techniques (top), along with their sensitivity values (bottom).
<table>
<thead>
<tr>
<th>Technique</th>
<th>Specificity</th>
<th>Sensitivity</th>
<th>Spatial Res</th>
<th>Temperature Res</th>
<th>Penetration</th>
<th>Clinical use</th>
<th>Specific features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorescence I</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>(+)</td>
<td>Experimental</td>
</tr>
<tr>
<td>Nuclear I</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>Radiation</td>
</tr>
<tr>
<td>MRI</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>No radiation</td>
</tr>
<tr>
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<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>Radiation</td>
</tr>
<tr>
<td>VH-IVUS</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>Invasive</td>
</tr>
<tr>
<td>OCT</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>Invasive, flushing</td>
</tr>
<tr>
<td>OFDI</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>Invasive, no flushing</td>
</tr>
<tr>
<td>Angioscopy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>(+)</td>
<td>(+)</td>
<td>Invasive</td>
</tr>
<tr>
<td>Thermography</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>(+)</td>
<td>Invasive</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging; CT, computed tomography; VH-IVUS, virtual histology-intravascular ultrasound; OCT, optical coherence tomography; OFDI, optical frequency domain imaging; temp, temporal; res, resolution.
Lipoproteins
- methylated and oxidized lipoproteins, and antibodies recognizing oxidized low-density lipoprotein

Markers of inflammation:
- upregulated integrin expression, endothelin receptors, IgG, chemotactant peptide expression, macrophage metabolism (18F-FDG), macrophage function, and extradomain B of fibronectin

Markers of cell death
- (e.g., especially of macrophages and smooth muscle cells, which can be identified with annexin V)

Antibodies
- recognizing a change in the smooth muscle phenotype
Antibody **Z2D3**, is a chimeric antibody generated against homogenized human atherosclerotic plaques, capable to identifies an antigen expressed exclusively by the pSMCs in the atherosclerotic lesions.

Gamma imaging studies with Z2D3 in experimental models of atherosclerosis have demonstrated **Z2D3** uptake in intimal lesions with proliferating SMCs.
Targeting Proliferating Smooth Muscle Cells in Experimental Atherosclerotic Lesions, Rabbit Aorta
Noninvasive localization of human atherosclerotic lesions with indium 111–labeled monoclonal Z2D3 antibody specific for proliferating smooth muscle cells

Ignasi Carrió, MD, Pier Luigi Pieri, MD, Jagat Narula, MD, Lourdes Prat, MD, Pietro Riva, MD, Luciano Pedrini, MD, Enzo Pretolani, MD, Guillermo Caruso, MD, Graciella Sarti, MD, Montserrat Estorch, MD, Lluís Berná, MD, Vicens Rambau, MD, Xavier Mataías-Gulu, MD, Chris Pak, PhD, Charles Ditlow, PhD, Francis Chen, PhD, and Ban An Khaw, PhD
$^{99m}$Tc-AP4A Imaging for pSMC in Atherosclerotic Lesions

Injection

3 Hours

Ex-Vivo

Elmaleh, Narula 2001
OXIDIZED LDL IMAGING
RADIOLABELED MDA2,
AN OXIDATION-SPECIFIC,
MONOCLONAL ANTIBODY

Rationale
Oxidized-LDL are present only in the atherosclerotic lesions but not in the normal arteries and play a crucial role in the pathogenesis and adverse consequences of the atherosclerotic lesions.

Tsimikas et al. JNC 1999
OXIDIZED LDL IMAGING
RADIOLABELED MDA2, AN OXIDATION-SPECIFIC, MONOCLONAL ANTIBODY

Tc99m-MDA2 In Vivo imaging  Ex Vivo (Sudan IV)  Control Rabbit
Experimental Rabbit Atherosclerotic Lesions
Tsimikas et al. JNC 1999
111In-Coproporphyrin Imaging for Experimental Atherosclerotic Lesions

Injection 3 Hours

Ex-Vivo

Control Atherosclerotic

C A

Jain, Narula JACC 2000
Vascular Inflammation Imaging with 18F FDG PET/CT: When to Image?

To address a need for harmonization of scan parameters of the ideal circulation time of 18F-FDG, we scanned patients with atherosclerotic abdominal aortic aneurysms. They performed PET/CT at 45, 60, 120, and 180 min after an injection of 18F-FDG.

They investigated whether there were 18F-FDG uptake differences with time in the aortic wall and lumen of the aneurysms to determine the optimal time to image vascular inflammation using 18F-FDG PET/CT.

Fused axial PET/CT of ROIs applied to aortic aneurysmal wall and lumen at mid-point of dynamic acquisitions at 45 (A), 60 (B), 120 (C), and 180 min (D) after injection of 18F-FDG.
There was no significant advantage in imaging at 3 h over 1 h after 18F-FDG injection.

Therefore, the FDG uptake in the aortic wall suggested increased glucose metabolism due to pathological processes (Mainly inflammatory).

The higher accumulation demonstrated the distribution of inflammatory cells, and probably correlated with the grade of inflammatory activities.

Meller et al. suggested that FDG-PET was more reliable than MRI in monitoring disease activity of aortitis during immunosuppressive therapy.
Aorta imaging with PET/CT. The left image is a noncontrast coronal CT image showing calcification of the abdominal aorta (group of 3 green arrows). The center and right images are coregistered PET and fused PET/CT images, respectively, demonstrating significant FDG uptake within the ascending aorta (single arrow) but relatively less FDG uptake in the calcified abdominal aorta. The green cross is in the inferior vena cava, where there is low FDG uptake.
FDG PET imaging showed that the presence of inflammation in one arterial territory is highly predictive of inflammation in others. This finding suggests a form of systemic arterial activation.

Supporting this theory of systemic activation, it has been found that the degree of arterial FDG uptake was associated with blood levels of several systemic inflammatory biomarkers, including those from the MMP family, and strong trends among both the interleukin group and CRP, but not with LDL.

One particular advantage of FDG PET atheroma imaging over measurement of circulating biomarkers is the ability to pinpoint a particular arterial segment as being inflamed, allowing it to be targeted for treatment.
a, b: FDG-PET images demonstrate abnormal FDG accumulation in the aortic arch. Moderate diffuse uptake is seen in the stomach (arrowhead). No other abnormal FDG uptake is seen. c, d: CT images show a dilated thoracic aorta with wall thickening. FDG-PET demonstrates intense uptake corresponding to the aneurysmal wall. (c, contrast-enhanced CT; d, FDG-PET axial views corresponding to the CT images.)
ASSESSMENT OF ARTERIAL ATHEROSCLEROSIS AND CALCIFICATION
Evaluation of $^{18}$F-FDG Uptake and Arterial Wall Calcifications Using $^{18}$F-FDG PET/CT
PET/CT image of aorta before (top) and during (bottom) antiatherosclerosis therapy. Note reduction in FDG uptake in the aortic wall.
AORTIC DISSECTION (AD)

- Onset of dissection
- Extension of dissection
- Progression of dissection

Aortic dissection
Acute aortic dissection (AD) is a potentially life-threatening disease and the tenth leading cause of death in Western societies. After myocardial infarction and before pulmonary embolism, AD represents the second most frequent cause of acute chest pain (I). The incidence of AD is about 3 in 100,000/y. Mortality rates range from 0.5 to 4 in 100,000 in national registers. However, the incidence of AD in necropsy studies is distinctively higher at 1%–2% (I), suggesting a high number of asymptomatic, overlooked, and therefore unknown chronic ADs.
Why TO image???

- Patients with stable dissection may be harmed by the risk of prophylactic and potentially complicated surgery. Thus, differentiation of acute and acute secondary progressive dissections from stable chronic dissections would be of high clinical relevance.

- However, even advanced imaging modalities, including CT and transesophageal echocardiography, fail in the differentiation of acute and chronic dissection. Also, laboratory parameters such as fibrinogen and D-dimers are unspecific and not always effective in determining the age of the AD.

- Therefore, direct proof or exclusion of acute or stable chronic AD by a new imaging modality would be helpful in clinically unclear cases for answering specific clinical problems and for risk stratification of AD.
The diagnosis of an AD was made in the case of an intimal dissection membrane separating the true and false aortic lumens.

The diagnostic criteria of an intramural hematoma included semicircular or circular aortic wall thickening without intimal disruption exceeding 5 mm.

**Metabolic Definitions**

- **Blood Pool Activity**
  - [SUVmean blood pool]

- **Aortic Wall Activity**
  - SUVmax

  A ROI corresponding to the highest 18F-FDG uptake in the dissection membrane or the adjacent vessel wall

**Morphologic Definitions**

- The diagnosis of an AD was made in the case of an intimal dissection membrane separating the true and false aortic lumens.

- The diagnostic criteria of an intramural hematoma included semicircular or circular aortic wall thickening without intimal disruption exceeding 5 mm.

\[ \text{SUV Ratio} = \frac{\text{Aortic SUVmax}}{\text{SUVmean blood pool}} \]

\[ N < 1.8 \]
Images of 37-y-old man with acute type B dissection of aorta: sagittal (A) and coronal (C) PET/CT images and the corresponding sagittal (B) and coronal (D) nonfused CT images.
The combined anatomic and metabolic information of 18FFDG PET/CT allowed an exact localization of enhanced 18F-FDG uptake in the aortic wall and dissection membrane.

It has been found that acute dissection of the aortic wall leads to elevated metabolic activity in fresh lacerated segments of the aortic wall (due to accumulation of glycolytic active cells such as macrophages and activated myofibrinocytes in the vessel wall), whereas stable chronic AD did not show increased 18F-FDG uptake. In contrast to chronic stable AD, patients with acute intramural hematoma and secondary progressive chronic AD showed also elevated glucose metabolism in the aortic vessel wall.

Therefore, increased 18F-FDG uptake in the aortic wall seems to correlate with acute injury and its repair, and 18F-FDG PET/CT may contribute to differentiation of acute and chronic AD in clinically unclear cases.
Images of 65-y-old woman with acute intramural hematoma: coronal (A) and sagittal (D) PET images, coronal (B) and sagittal (E) CT images, and coronal (C) and axial (F) PET/CT images
Images of 65-y-old man with chronic, stable dissection of aorta: coronal PET (A), fused PET/CT (B), and CT (C) images. No specific 18F-FDG uptake is detected.
• Integrated systems that combine an imaging modality with high spatial resolution (MRI or CT) with one with high sensitivity (PET or SPECT) should help to overcome limitations in aortic diseases assessment.

• Finally, molecular imaging has already spurred the development of platforms that can transport contrast moieties to specific biological targets in atherosclerotic plaque. In the future, these platforms could also simultaneously permit delivery of therapeutic agents to plaques with minimal systemic toxicity.