Magnetic Resonance Imaging and Positron Emission Tomography Approaches to Imaging Vascular and Cardiac Inflammation

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Inflammation plays a significant role in a wide range of cardiovascular diseases (CVDs). The numerous implications of inflammation in all steps of CVDs, including initiation, progression and complications, have prompted the emergence of noninvasive imaging modalities as diagnostic, prognostic and monitoring tools. In this review, we first synthesize the existing evidence on the role of inflammation in vascular and cardiac diseases, in order to identify the main targets used in noninvasive imaging. We chose to focus on positron emission tomographic (PET) and magnetic resonance imaging (MRI) studies, which offer the greatest potential of translation and clinical application. We detail the main preclinical and clinical studies in the following CVDs: coronary and vascular atherosclerosis, abdominal aortic aneurysms, myocardial infarction, myocarditis, and acute heart transplant rejection. We highlight the potential complementary roles of these imaging modalities, which are currently being studied in the emerging technology of PET/MRI. Finally, we provide a perspective on innovations and future applications of noninvasive imaging of cardiovascular inflammation. (Circ J 2016; 80: 1269–1277)

Key Words: Cardiovascular diseases; Inflammation; Magnetic resonance; Noninvasive imaging; Positron emission tomography

Cardiovascular diseases (CVDs), such as ischemic heart disease and stroke, are the leading causes of death worldwide. Inflammation, both acute and chronic, has emerged as a key underlying pathology in a wide range of CVDs, contributing to initiation, progression, and healing, as well as clinical complications. The implications of inflammation have been studied extensively in coronary and vascular atherosclerosis. Figure 1A schematically represents the implication of inflammatory actors in the pathophysiology of CVDs. Monocyte-derived macrophages play a central role in the initiation of plaque formation, its progression through phagocytosis of oxidized lipids, secretion of proteases such as matrix metalloproteinases (MMPs), and stimulation of smooth muscle cell (SMC) proliferation, as well as in the onset of plaque rupture. Inflammation is also thought to contribute to neo-vessel formation and intraplaque hemorrhage. Abdominal aortic aneurysm (AAA) formation and rupture are characterized by marked elastin degradation and reduced medial SMC cellularity in the presence of transmural inflammation, plus adventitial angiogenesis. Secretion of MMPs by macrophages also plays a strong role in remodeling of the media and in the risk of AAA rupture (Figure 1B).

Inflammation plays not only a major role in these common vascular diseases, but also in the pathophysiology of multiple myocardial diseases. Myocarditis and cardiac sarcoidosis (Figure 1C) are indeed still often under-diagnosed as the cause of unexplained cardiomyopathies. In addition, the level of regional inflammation after myocardial infarction (MI) plays a strong role in long-term evolution towards heart failure, as excessive or prolonged inflammation has been shown to promote adverse left ventricular (LV) remodeling. Lastly, acute cellular inflammation is the mechanism of cardiac transplant rejection (Figure 1D).

Although significant progress has been made in the treatment of CVDs, prevention is still suboptimal. Indeed, the current strategy, which consists of risk factor screening and monitoring for evidence of symptoms (eg, angina) or abnormal lumen size (eg, AAA) appears insufficient to predict future plaque or aneurysm ruptures. Compared with conventional methods, new noninvasive approaches targeting inflammation have the potential to improve the early detection of CVDs, enable quantification of disease activity to predict risk of complications, guide therapeutic interventions, and monitor treatment success.

In this review, we focus on 2 modalities for imaging cardiovascular inflammation: magnetic resonance imaging (MRI) and positron emission tomography (PET). These technologies demonstrate the greatest potential for clinical translation and...
and early enhancement with gadolinium on T1-weighted imaging (T1 WI), as evidence of increased vascular permeability. New quantitative approaches to measure changes in T2 and T1, including T2- and T1-mapping, have been developed to better characterize these tissue changes associated with inflammation.

Cellular Hypermetabolism
PET using the glucose analog 18F-fluorodeoxyglucose (18F-FDG-PET) enables detection of hypermetabolic cells (eg, macrophages). For myocardial diseases, the use of 18F-FDG-PET to detect inflammation is challenged by the physiological uptake of glucose by myocardial cells. Several diets to favor myocardial fatty-acid over glucose uptake have been developed to try to overcome this limitation, such as high-fat low-carbohydrate diet followed by 6–18 h of fasting before PET scanning.

Inflammatory Targets, Techniques and Tracers
We first summarize the main imaging techniques and molecular imaging tracers according to their inflammatory targets (Table 1). Although the contribution and type of inflammation vary according to the CVD considered, some shared general pathways can be individualized and targeted, which are presented in Figure 2, together with examples of imaging techniques.

Vascular Permeability and Edema
The acute inflammatory response begins with vasodilation and endothelial hyperpermeability. MRI can detect these changes through T2-weighted imaging (T2 WI), as indicative of edema, and the recent advent of combined PET/MRI scanners for clinical use offers further synergies for imaging inflammation in CVDs.

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Figure 1. Inflammation and angiogenesis in (A) atherosclerosis, (B) aortic aneurysm, (C) cardiac sarcoidosis and (D) acute heart rejection. MMP, matrix metalloproteinases; SMC, smooth muscle cell.
Phagocytosis
The phagocytic property of inflammatory cells, such as monocytes, macrophages and neutrophils, can be used for imaging. Superparamagnetic iron oxide (SPIO)-labeled cells can be detected as low signal on T2*-weighted sequences with a high sensitivity for inflammation. Iron-based nanoparticle tracers have been preclinically tested in murine models of carotid inflammation, such as engineered human ferritin protein cages encapsulating a magnetite nanoparticle and FeCo/graphitic-carbon nanocrystals. Another technique targeting phagocytes is 19Fluorine MRI (19F-MRI) utilizing perfluorocarbon-containing nanoparticles. As there is no significant background 19F signal in animals or humans, 19F-MRI displays high signal-to-noise ratio and high specificity, which is promising for future clinical use.

Cellular Apoptosis and Necrosis
Advanced inflammation leads to cellular apoptosis and necrosis in tissues, which can be visualized by late gadolinium enhancement (LGE) on T1 WI. However, LGE cannot differentiate active inflammation from advanced fibrosis after burned-out inflammation. Further tissue characterization using

Table 1. MRI and PET Imaging Techniques and Tracers for Imaging of Inflammation and Angiogenesis in Cardiovascular Diseases

<table>
<thead>
<tr>
<th>Target</th>
<th>Disease</th>
<th>Pre-clinical</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>Early gadolinium enhancement (T1WI)</td>
<td>Edema</td>
<td>Clinical</td>
<td>Disease activity sensitive</td>
</tr>
<tr>
<td>MRI</td>
<td>T2-weighted blood black imaging</td>
<td>Edema</td>
<td>Clinical</td>
<td>Disease activity sensitive</td>
</tr>
<tr>
<td>MRI</td>
<td>T1/T2/ECV mapping</td>
<td>Diffuse edema</td>
<td>Clinical</td>
<td>Contrast free (T1/T2 mapping) Sensitive for diffuse or mild change</td>
</tr>
<tr>
<td>MRI</td>
<td>SPIO/USPIO</td>
<td>Phagocytosis</td>
<td>Preclinical</td>
<td>High sensitivity and specificity to active inflammation</td>
</tr>
<tr>
<td>MRI</td>
<td>SPIO/USPIO</td>
<td>Myocardial infarction</td>
<td>Clinical</td>
<td>Monitor response to treatment</td>
</tr>
<tr>
<td>MRI</td>
<td>SPIO/USPIO</td>
<td>Myocarditis</td>
<td>Acute transplant rejection</td>
<td>Ferumoxytol approved by FDA</td>
</tr>
<tr>
<td>MRI</td>
<td>19F-MRI</td>
<td>Phagocytosis</td>
<td>Preclinical</td>
<td>Sensitive and specific to active inflammation</td>
</tr>
<tr>
<td>MRI</td>
<td>19F-MRI</td>
<td>Myocardial infarction</td>
<td>Clinical</td>
<td>Quantitative (no background signal)</td>
</tr>
<tr>
<td>MRI</td>
<td>P947</td>
<td>Matrix remodeling (MMP)</td>
<td>Preclinical</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>DCE-MRI (T1WI)</td>
<td>Angiogenesis</td>
<td>Clinical</td>
<td>High reproducibility</td>
</tr>
<tr>
<td>PET</td>
<td>18F-FDG</td>
<td>Hypermetabolism</td>
<td>Preclinical</td>
<td>High sensitivity</td>
</tr>
<tr>
<td>PET</td>
<td>18F-FDG</td>
<td>Hypoxia</td>
<td>Clinical</td>
<td>Availability</td>
</tr>
<tr>
<td>PET</td>
<td>18F-FDG</td>
<td>Macrophages (αvβ3 integrin)</td>
<td>Clinical</td>
<td>More specific than 18F-FDG</td>
</tr>
<tr>
<td>PET</td>
<td>18F-Na</td>
<td>Microcalcifications</td>
<td>Preclinical</td>
<td></td>
</tr>
</tbody>
</table>

DCE-MRI, dynamic contrast-enhanced MRI; ECV, extracellular volume; FDA, US Food & Drug Administration; FDG, fluorodeoxyglucose; MMP, matrix metalloproteinases; MRI, magnetic resonance imaging; PET, positron emission tomography; SPIO, superparamagnetic iron oxide; T1WI, T1 weighted imaging; T2WI, T2-weighted imaging; USPIO, ultrasmall SPIO.
parametric mapping techniques can help distinguish acute from chronic changes. Apoptosis-targeted MRI and PET imaging agents have also been developed, primarily using annexin, which binds to membrane phosphatidylserine externalized in early apoptosis. Additional Effects of Inflammation

**Angiogenesis** Neo-angiogenesis is implicated in rapid plaque growth, risk of plaque rupture secondary to intraplaque hemorrhage, as well as the risk of AAA rupture. Neovessels can be visualized by dynamic contrast-enhanced MRI (DCE-MRI), in which the transfer constant can be considered to reflect microvessel density and permeability. Vascular endothelial growth factor receptors expressed on macrophages, activated endothelial cells or SMC can be targeted. The cell-surface glycoprotein receptor, integrin αvβ3, plays a key role in cell-cell and cell-matrix interactions. Its expression is upregulated in angiogenic vascular endothelial cells and highly expressed in macrophages infiltrating atherosclerotic plaques. Arg-Gly-Asp (RGD) is a short amino acid sequence binder of the αvβ3 integrin; several RGD-based agents for MRI and PET have been developed, including 18F-FPPRGD2.

**Proteases** Because of the various implications of proteases produced by macrophages in atherosclerosis and aneurysms, activity-based probe tracers have been developed and tested preclinically, targeting MMPs (eg, P947) or cathepsins (eg, ABP BMV101).

**Fibrosis** T1 mapping has the potential to provide quantitative assessment of more diffuse myocardial fibrosis. Extracellular volume (ECV) mapping derived from native and post-contrast T1 mapping can detect expanded ECV in diffuse fibrosis.

**Microcalcification** Inflammatory cytokines can induce osteogenic transdifferentiation of SMC in atherosclerotic plaques. Microcalcifications, below the level usually detectable by conventional computed tomography, are seen in the earlier phase of plaques and have been linked to plaque rupture, presumably caused by stress-induced microfractures. 18F-NaF PET can be used for microcalcification imaging and shows promising results in coronary atherosclerosis.
Imaging of Cardiovascular Inflammation

Preclinical and Clinical Studies

Atherosclerosis

DCE-MRI has been linked to the macrophage content of carotid plaque, as well as neovascularization. MRI enables characterization of additional plaque features associated with vulnerability, such as intraplaque hemorrhage, presence of lipid-rich necrotic core, ulceration, and cap rupture. Sensitivity of MRI for inflammation could be improved by the use of more targeted cellular/molecular contrast agents. For example, ultrasmall SPIO (USPIO)-based MRI has been used clinically to predict disease progression, monitor disease activity and show treatment effects, such as in the ATHEROMA study showing a decrease in USPIO uptake by carotid plaque with high-dose atorvastatin.

PET/MRI

Table 2. Advantages and Disadvantages of PET, MRI and PET/MRI of Cardiovascular Inflammation

<table>
<thead>
<tr>
<th>Advantages</th>
<th>PET</th>
<th>MRI</th>
<th>PET/MRI</th>
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<tr>
<td>• High biologic sensitivity</td>
<td>• High soft-tissue contrast for myocardial and vascular wall characterization</td>
<td>• Combination of tracers and/or techniques from both modalities, particularly soft-tissue characterization by MRI with biological activity by PET</td>
<td></td>
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<tr>
<td>• Availability of existing clinical scanners</td>
<td>• Gold standard for left ventricular function assessment, volumes, mass and ejection fraction</td>
<td>• Use of MRI motion correction to enhance PET</td>
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<tr>
<td>• Ongoing development of new tracers</td>
<td>• Assessment of multiple aspects of the inflammatory process: edema, molecular imaging, necrosis, fibrosis</td>
<td>• Radiation and expense</td>
<td></td>
</tr>
<tr>
<td>Disadvantages</td>
<td>• Radiation exposure</td>
<td>• Relatively contraindicated for patients with pacemakers or implanted devices</td>
<td>• Challenges of synchronizing PET and MRI, plus combining motion and attenuation correction</td>
</tr>
<tr>
<td>• Low spatial resolution</td>
<td>• Complex, multi-parametric imaging sequences</td>
<td>• Need for more experienced personnel, complex workflow</td>
<td></td>
</tr>
<tr>
<td>• Expensive</td>
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</table>

Abbreviations as in Table 1.

Figure 3. Nonstenotic plaque of the left carotid artery imaged with 18F-FDG PET/MRI in a patient with cryptogenic stroke. Presence of a NASCET 40% stenosis of the left internal carotid artery (ICA) ipsilateral to the territory of stroke on 3D maximum intensity reconstruction of the carotid arteries obtained from the time-of-flight (TOF) MR angiography acquisition (A). On the fused coronal images of PET and TOF MR acquisitions (B), 18F-FDG uptake was intense in the vascular wall of the left carotid artery (white arrow), but was also increased in the right carotid artery (white arrowhead). A large nonstenotic atherosclerotic plaque can be seen on the axial views of TOF acquisition (C) at the origin of the left ICA (white arrow), whereas only a small plaque is present in the right carotid artery (white arrowhead). On the fused axial images of PET and TOF MR angiography acquisitions (D), high 18F-FDG uptake can be detected in the vascular walls of both carotid arteries. FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography. (Reproduced with permission from Hyafil F, et al.)
These findings were strengthened by several additional clinical studies that followed.\textsuperscript{55,56} 18F-FDG uptake in thoracic and AAAs has also been shown to correlate with higher levels of wall stress,\textsuperscript{57} local inflammatory cell infiltration, rarefaction of SMC, increased MMP activity and circulating C-reactive protein concentration.\textsuperscript{55,58} The ability of FDG-PET to monitor response to therapy was tested in a preliminary clinical study, showing no effect of statin therapy on 18F-FDG AAA uptake.\textsuperscript{56}

On the other hand, omega 3 polyunsaturated fatty acids have the potential to prevent AAA development through inhibition of aortic and macrophage-mediated inflammation.\textsuperscript{59} For $\alpha_{v}\beta_{3}$-targeted imaging, the feasibility of 18F-FPPRGD2 imaging has been demonstrated in murine AAAs,\textsuperscript{49,50} and a clinical pilot study has also been recently approved in our institution for patients with AAA.

AAAs
Fewer studies have used molecular MRI tracers in AAAs, and mostly in animal models. The gadolinium-based MRI contrast agent with affinity to MMPs, P947, has been studied in rat models of AAA but not in clinical cases.\textsuperscript{30,52} In addition, although USPIO accumulation in AAA colocalized with macrophage infiltration, nonspecific uptake of the tracer by thrombus could not be excluded; however, the atherosclerotic growth rate was higher in the patients with a specific pattern of discrete mural accumulation of USPIO distinct from per luminal uptake.\textsuperscript{53}

The first clinical study using 18F-FDG-PET for AAA in a cohort of 26 patients was published in 2002, showing the association between the uptake of 18F-FDG within the aneurysm wall and both the rate of expansion and risk of rupture.\textsuperscript{54} These findings were strengthened by several additional clinical studies that followed.\textsuperscript{55,56} 18F-FDG uptake in thoracic and AAAs has also been shown to correlate with higher levels of wall stress,\textsuperscript{57} local inflammatory cell infiltration, rarefaction of SMC, increased MMP activity and circulating C-reactive protein concentration.\textsuperscript{55,58} The ability of FDG-PET to monitor response to therapy was tested in a preliminary clinical study, showing no effect of statin therapy on 18F-FDG AAA uptake.\textsuperscript{56}

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MI
After acute MI (AMI), a sequence of inflammatory cell infiltration occurs, starting with neutrophils, and M1 and M2 macrophages.\textsuperscript{60} Native T1 mapping using MRI can detect myocardial edema after AMI. Increased T1 values reflect greater edema, suggestive of more severe cellular injury, and thus reduced likelihood of long-term improvement in myocardial function.\textsuperscript{61,62} USPIOs have been used in a clinical pilot study to evaluate myocardial inflammation in patients with recent AMI\textsuperscript{63} and some evidence in mice suggests 19F-MRI could offer more sensitivity than LGE in detecting inflammation following AMI.\textsuperscript{20,64}
Myocarditis and Cardiac Sarcoidosis

Noninvasive imaging represents a valuable alternative to endomyocardial biopsy in the diagnosis of myocarditis and cardiac sarcoidosis. Because of the patchy distribution of lesions, biopsy sensitivity is approximately 40% in myocarditis and as low as 20% in sarcoidosis. 65 MRI is able to visualize histological changes caused by inflammation even in relatively small lesions and can identify the optimal area to biopsy. 66 The current MRI diagnostic criteria for myocarditis recommends combining T2 WI and LGE, demonstrating a good diagnostic accuracy of 78%. 67 LGE is also important as a predictor of mortality. 68 On the other hand, LGE has less sensitivity for diffuse myocardial pathologies such as pan-inflammation or diffuse fibrosis, and reversible myocardial injury. 69 Combining native T1 mapping and ECV mapping, or ECV mapping and LGE, may be superior to the combination of T2 WI and LGE. 70,71 SPIOs have been used successfully for myocarditis detection in rodents, showing a better sensitivity for milder myocardial inflammation than conventional MRI sequences. 72

To date, 18F-FDG-PET appears to be the most reliable nuclear imaging method of detecting cardiac sarcoidosis, demonstrating the characteristic patchy and focal lesions with a sensitivity of 79%–100% and a specificity of 38%–100%. 73,74 123I-radioiodinated 15-(p-iodophenyl)-3(R, S)-methylpentadecanoic acid and 201thallium dual-tracer mismatch appears promising for cardiac sarcoidosis diagnosis, particularly when added to FDG-PET/CT. 75 Moreover, 18F-FDG uptake is predictive of adverse outcomes in sarcoidosis, such as cardiac death, conduction block and ventricular arrhythmia. 76

Acute Transplant Rejection

Noninvasive imaging can be useful for monitoring the cellular infiltration that occurs in case of acute cardiac transplant rejection. Because the sensitivity of current T2 WI and LGE is insufficient for detecting acute cellular rejection, several MRI tracers have been tested, mostly in animal models. USPIO and micrometer-sized paramagnetic iron oxide imaging agents have demonstrated homogeneous spatial distribution of macrophage infiltration in a rodent model of severe transplant rejection. 77 Similarly, 19F-MRI has been successfully used to detect early rejection with high specificity and spatial resolution in a murine model of acute rejection. 78

PET/MRI: The Future of Imaging Inflammation

Combining the capabilities of both PET and MRI (Table 2), using a combined PET/MRI scanner, may provide a more complete assessment of cardiovascular inflammation than MRI or PET (or PET/CT) alone. Characterization of atherosclerosis as well as inflammatory cardiomyopathies (eg, sarcoidosis) are major current fields of PET/MRI application.

PET/MRI can help better characterize both structural composition and biologic activity of atherosclerotic plaques. This synergy is demonstrated in the case of MRI showing a nonstenotic carotid plaque and PET detecting the presence of inflammation, which is associated with a cryptogenic stroke in the same territory, thus informing the etiology (Figure 3). 79 Calcagno et al 80 have recently used both DCE-MRI and 18F-FDG-PET/CT for imaging carotid atherosclerosis in 40 patients with coronary artery disease or at equivalent high risk. They report a significant although weak inverse relationship between inflammation, measured as 18F-FDG uptake by PET, and plaque perfusion by DCE-MRI, suggesting an interesting complementary role of the 2 techniques. The main challenge remaining for PET/MRI of small vessels such as coronary arteries comes from the need for respiratory and cardiac motion correction, high resolution to detect small lesions, and high signal-to-noise ratio. Notably, the ability of MRI to provide multidimensional motion correction can potentially enhance PET detection of coronary plaque tracer uptake. 81

In patients with cardiac sarcoidosis, diagnostic accuracy can be improved by the high sensitivity of 18F-FDG-PET combined with the high spatial resolution of MRI, which enables the precise localization of hot spots on PET imaging. 82 In addition, hybrid PET/MRI imaging not only improves the assessment of the extension of the disease, but also can help assess the disease stage and might be helpful for therapy guidance. Although the early stages are characterized by active inflammation (increased 18F-FDG uptake), reduced or absent uptake is usually found in the late stages. Thus, scarred fibrotic tissue (demonstrating LGE on MRI) can be differentiated from active inflammation (high 18F-FDG uptake), as shown in Figure 4. 83

Conclusions

Noninvasive molecular imaging of cardiovascular inflammation by PET and PET has been developed to improve early detection of CVDs, prediction of complications, risk stratification, and monitoring of response under treatment, as well as providing new targets for therapies. Combining these modalities with new PET/MRI scanners may allow synergies that provide more sensitivity and accuracy for vascular and myocardial inflammation detection.

Overall, multimodality imaging strategies from disease staging to therapeutic response offer motivation for further development of MRI and PET of vascular and myocardial inflammation to improve the care of patients with and at risk of CVDs.

Disclosures

M.V.M. has received cardiac MRI research support from GE Healthcare. He is now on partial leave of absence from Stanford and an employee at Vertly Life Sciences. M.A. received a research fellowship from the Federation Francaise de Cardiologie. T.S. received a research fellowship from the Manpei Suzuki Diabetes Foundation. No other authors have any potential conflicts of interest relative to the study.

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