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Molecular imaging of coronary inflammation

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ABSTRACT

Coronary inflammation is related to atherosclerotic disease and, less frequently, systemic vasculitis. Regardless of the etiology, coronary inflammation is associated with adverse cardiac events. Molecular imaging with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET/CT) allows in vivo assessment of coronary inflammation and evaluation of response to therapy. The aim of this review is to give an update on the recent development of FDG-PET/CT, discuss the potential roles of coronary inflammation imaging, review the limitations of FDG-PET/CT imaging, and give an overview of the new tracers available for PET/CT plaque imaging.

Atherosclerotic heart disease

Cardiovascular diseases remain a major cause of morbidity and mortality despite the remarkable medical advances of the past decades, and coronary heart disease (CHD) continues to be the leading cause of cardiovascular events [1]. In the United States alone, it is estimated that on average, a person will have a myocardial infarction every 40 s [1]. Considering the alarming prevalence of diabetes and obesity in younger individuals, improvement of prevention, diagnostic tools, and treatment of CHD remains essential. Moreover, with the development of more expensive and targeted therapies, individualized assessment of risks and response to specific pharmacological therapies will become indispensable [2]. In that context, development and validation of novel non-invasive imaging tools allowing evaluation of the underlying pathophysiologic processes, precise diagnosis, and evaluation of therapeutic response of CHD is of critical importance.

Clinical risk assessment has traditionally been based on severity and extent of coronary stenoses determined by invasive coronary angiography and more recently by computed tomography coronary angiography, which can also add prognostic information about plaque morphology. Molecular imaging may add physiological data about disease biology and enhance our existing anatomy-based risk prediction.

Atherosclerosis, inflammation, and the role of macrophages

The central role of inflammation in atherogenesis is well established and our understanding of the complex interactions between lipids, inflammation, and CHD progression has evolved considerably. Inflammation has been linked to all steps of atherosclerosis, from plaque formation to plaque rupture (Fig. 1). Endothelial dysfunction, which is associated with well-known CHD risk factors such as aging, smoking, hypertension, dyslipidemia, and diabetes, is one of the earliest steps in atherosclerosis formation [3]. The impaired vasodilatory function observed in endothelial cell dysfunction favors a pro-inflammatory milieu that stimulates expression of adhesion molecules on the endothelial cell surface [3]. Endothelial inflammation and expression of these adhesion molecules promote recruitment and infiltration of inflammatory cells such as monocytes and increase endothelial permeability, resulting in accumulation of lipoprotein and inflammatory cells in the artery intima [4]. Secretion of cytokines by recruited inflammatory cells and oxidation of lipoproteins perpetuate the vascular inflammation.

Recruited monocytes eventually differentiate into macrophages in the intima, promoted by colony-stimulating factor 1 and presence of low-density lipoprotein [5]. Macrophages play a central role in atherosclerotic lesion progression by secreting matrix metalloproteinases and tissue factor, which are involved in plaque rupture and clot formation [6]. Consequently, macrophage density is associated with a higher risk of plaque rupture [7]. In

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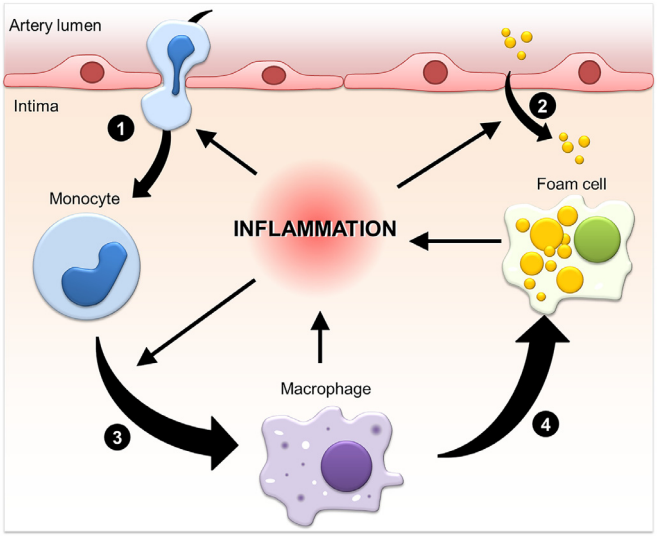

Fig. 1. Schematic representation of the central role of inflammation in the pathophysiology of atherosclerosis. Key roles of inflammation include: (1) Recruitment and infiltration of monocytes from the artery lumen into the intima. (2) Increased endothelial permeability resulting in accumulation of lipoproteins in the intima. (3) Inflammation favors differentiation of monocytes into M1 macrophages. (4) Macrophages evolve into foam cells, which contribute to the inflammatory milieu.

the intima, monocytes can differentiate into various phenotypes of macrophages, including M1 and M2. The M1 macrophages express high levels of scavenger receptors allowing internalization of modified lipoproteins and are also involved in secretion of pro-inflammatory molecules [5]. Lipoprotein-loaded macrophages, or foam cells, eventually die due to high intracellular levels of oxidized lipids, further contributing to the inflammation.

Vulnerable plaque

Acute coronary events in CHD can be attributed to plaque rupture or plaque erosion. Classically, plaque rupture has been associated with ST elevation myocardial infarction (STEMI) while plaque erosion is associated with Non-STEMI [8]. Plaques that tend to rupture, the so-called thin-capped fibroatheroma (TCFA), are characterized by a thin fibrous cap, high lipid content, high degree of inflammation, and abundant macrophage content. Conversely, plaques that tend to erode are typically lipid poor, have a thick fibrous cap, low degree of inflammation, and low macrophage content. TCFA are often considered 'vulnerable plaques', meaning that they are susceptible to rupture, and can potentially lead to acute coronary syndrome. Tremendous efforts and resources have been invested over the last two decades in order to identify such vulnerable plaques, with the hope of providing novel risk stratification information allowing to improved patient management.

Non-atherosclerotic coronary inflammation

Coronary inflammation is related to atherosclerotic disease in the vast majority of cases. Nonetheless, other entities such as systemic vasculitis can cause coronary inflammation that often leads to life-threatening consequences. Systemic vasculitis can be due to a heterogeneous group of relatively rare diseases characterized by inflammation and necrosis of the blood vessels. These diseases can affect virtually all cardiac tissue, including the coronary arteries. Vasculitis may accelerate atherosclerosis but can also cause other forms of vascular complications such as coronary stenosis, coronary aneurysms, and intracoronary thrombosis [9]. Effectively all forms of primary and secondary vasculitis can cause coronary arteritis with a variable incidence ranging from anecdotal case reports in giant cell arteritis [10] to over 50% in polyarteritis nodosa [11] (Table 1). The true prevalence of coronary arteritis is likely underestimated due to inability to obtain biopsy samples, lack of non-invasive diagnostic tools, lack of clinical recognition, and misdiagnosis as atherosclerotic coronary disease. In spite of this diagnostic difficulty, identification of patients with coronary arteritis is critical to optimize therapy and reduce risks of coronary complications. Given that molecular imaging provides accurate evaluation of large-vessel vasculitis [12], it represents a promising yet understudied tool to assess coronary arteritis.

Molecular imaging of coronary inflammation

Positron emission tomography combined with computed tomography (PET/CT) imaging has emerged as a valuable non-invasive modality for the diagnosis of cancer, infection, and inflammation. ^{18}F-fluorodeoxyglucose (FDG) is by far the most utilized PET tracer and has been proven useful in a wide range of clinical scenarios. In cardiovascular diseases, PET/CT imaging with FDG has the advantage of being very sensitive for detection of detect inflammation and allows evaluation of treatment response [13]. For this reason, the role of FDG PET/CT in cardiovascular disease is rapidly expanding and is now routinely used to detect cardiac inflammation as a marker of sarcoidosis and post infarction as

Table 1
Vasculitis and associated risk of coronary involvement.

	Typical age of onset (years)	Commonly affected arteries	Coronary arteritis frequency
Small and medium sized arteritis			
Kawasaki disease	0.5–5	Coronary arteries Muscular arteries	~25%
Polyarteritis nodosa	< 40	Small vessels of the lungs, kidneys, skin, and peripheral nervous system	~50%
Medium and large sized arteritis			
Takayasu's arteritis	< 50	Aorta and its main branches Pulmonary arteries Coronary arteries	15–25%
Giant cell arteritis	> 50	Temporal arteries Aorta	Very rare
Connective tissue disease			
Systemic lupus erythematosus	30–50	Arteries of the skin, liver, lungs, gastrointestinal tract, kidneys, and nervous system	Rare
Rheumatoid arthritis	40–60	Arteries of the skin, peripheral nerve system, eyes Coronary arteries	~20%

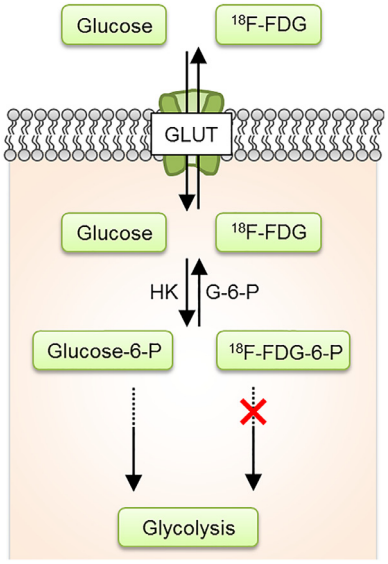

Fig. 2. Mechanism of FDG uptake and retention. G-6-P, glucose-6-phosphatase; GLUT, glucose transport protein; FDG, fluorodeoxyglucose; HK, hexokinase.

well as infection of valves and implanted devices. Indeed, in addition to the detection of vascular and myocardial inflammation, FDG PET/CT imaging was shown to enable assessment disease activity and monitoring response to therapy in different inflammatory disorders such as sarcoidosis, vasculitis, and atherosclerosis [14,15]. For example, FDG PET/CT is used to demonstrate in vivo the effectiveness of lipid lowering and anti-inflammatory therapies in atherosclerosis [16]. Because uptake of FDG PET/CT imaging is proportional to the macrophage content and does not rely on chronic and irreversible morphological changes, it has the unique ability of detecting variation of disease activity in response to interventions.

Mechanism of FDG uptake in inflammation

FDG, a glucose analogue labeled with the positron emitting isotope Fluorine-18, enters the cell through the membrane via the glucose transporter protein (GLUT) and is phosphorylated by glucose-6-phosphatase (Fig. 2). Once phosphorylated, the tracer does not undergo further metabolism through the glycolysis pathway as would glucose and is trapped in the cell [14]. Cellular uptake of FDG is proportional to glycolytic activity and can be promoted by upregulation of GLUT, increased hexokinase activity, and reduced glucose-6-phosphatase activity. FDG has been shown to accumulate in a broad range of inflammatory disorders, before any morphological changes can be appreciated on anatomical imaging modalities such as CT and MRI [17]. In inflammation, FDG accumulates mostly in macrophages due to their high glycolytic activity and high density in inflamed areas (Fig. 3) [18]. In atherosclerotic disease, FDG accumulates in macrophages and in foam cells in which uptake is correlated with early foam cell formation and increased hexokinase activity [19]. Hypoxia further increases glycolysis and FDG uptake by macrophage within the plaques [20,21].

Significance of FDG uptake

Several animal and human studies demonstrated increased FDG plaque uptake in various models of atherosclerosis. Intensity of FDG uptake in atherosclerosis is associated with macrophage plaque content, systemic inflammation biomarkers, as well as different vascular risk factors such as age, male gender, diabetes, and Framingham risk scores [22,23]. On the other hand, FDG uptake does not correlate with vessel wall thickness, plaque thickness, or plaque smooth muscle cells [23]. FDG accumulation is seen early in the disease and can precede calcium deposition [24].

In patients imaged for cancer diagnosis and staging, FDG uptake in the major arteries was a strong and independent predictor of future cardiovascular events [25]. More specifically, the prognostic value of FDG was independent of arterial calcium burden [25]. In another retrospective study, increased FDG uptake indicating inflammation in the proximal coronary arteries, carotid bifurcation, and thoracic aorta preceded and rarely overlapped with calcification suggesting that inflammation and calcification identify different stages of atherosclerosis [26]. In patients with recent ACS, FDG uptake was increased in the culprit coronary lesions, the ascending aorta, and left main coronary artery, emphasizing the importance of local and systemic inflammation in acute coronary syndromes (ACS) [27]. Interestingly, lesions that are associated with symptoms have higher FDG accumulation compared to asymptomatic lesions [28].

Vascular inflammation imaging with FDG PET/CT has been shown to be very reproducible, allowing comparison of multiple FDG-PET/CT scans and assessment of evolution of inflammation over time (Fig. 4) [29]. Several studies have demonstrated that a reduction in arterial FDG uptake intensity can be observed in response to therapy [30]. Conversely, increased FDG uptake correlates with disease progression [31]. Furthermore, changes over 6 months can predict longer term progression of the disease [32]. For these reasons, FDG imaging is now used to assess drug response in various clinical indications and clinical trials.

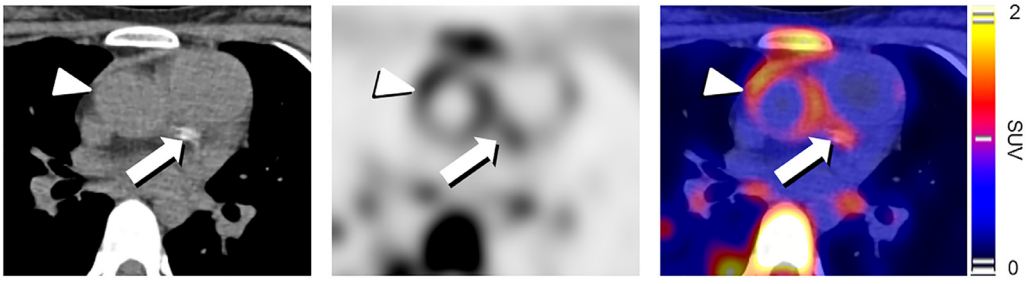

Fig. 3. Selected CT (left), FDG PET (middle), and fused (right) transaxial images of a FDG-PET/CT study performed in a 26 y-o female with history of Takayasu arteritis with aortic and coronary involvement and stenting of the left main artery 1 year prior to the study. The study was performed following a myocardial suppression protocol including prolonged fasting, high-lipid low-carbohydrate diet, and intravenous heparin injection. Increased uptake in seen in the ascending aorta (arrowheads) as well as in the left main artery (arrow), corresponding to the stent. Uptake in the ascending aorta is compatible with aortitis. Subsequent angiography showed a 50% intra-stent stenosis extending in the circumflex artery.

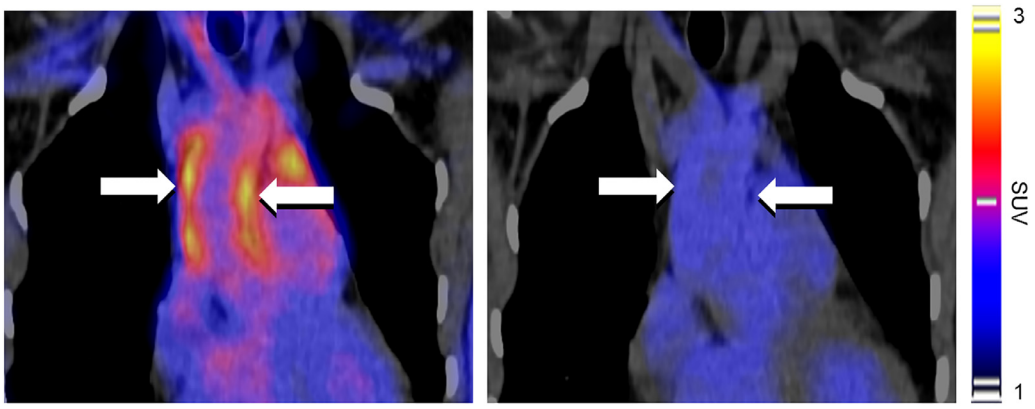

Fig. 4. Fused FDG-PET/CT coronal images (left) of the patient with Takayasu arteritis presented in Fig. 3 demonstrate increased FDG uptake in the aortic wall (arrows), compatible with aortitis. A follow up study (right) performed 10 months later after corticosteroid therapy shows complete resolution of the inflammation (arrows).

Potential roles of coronary inflammation imaging

In the past few years, the importance and clinical relevance of vulnerable plaque identification has been debated [33,34]. As demonstrated by the PROSPECT trial, the risk of ACS or sudden cardiac death associated to vulnerable plaque is very low [35]. Although STEMI are more frequently caused by plaque rupture, the vast majority of TCFA will never rupture, and most plaque ruptures are not causing ACS. In fact, an individual can have several TCFA lesions in multiple vessels at the same time. It has been suggested that current therapies, including statins and modification of risk factors, have created a shift from plaque rupture to plaque erosion, with corresponding shift from STEMI to Non-STEMI presentations [33]. Thus, presence of a vulnerable plaque might not be the main factor predicting undesirable outcomes. Plaque burden, rather than the presence of vulnerable plaque, may be a better predictor of ACS and should instead be targeted [34]. Based on this information, identification of a single vulnerable plaque is likely not the best approach for detection of high risk patients. With the recognition that vulnerable plaque presence might not provide independent prognostic information, the objective of identifying a single TCFA non-invasively to tailor therapy and prevent ACS has lost some appeal [33,34]. Inability to show benefit of lesion-based treatment compared to medical therapy in patients with stable CHD, regardless of the stenosis severity, further supports the fact that global inflammation and plaque burden are better predictors rather than single lesion characteristics [36]. Nonetheless, inflammation plays a central role in the pathophysiology of atherosclerosis and ACS. For example, systemic inflammatory biomarkers, including CRP, have been associated with increased risk of acute coronary events [37]. Following ACS, diffuse coronary inflammation is observed rather than inflammation in a single lesion [27]. Identification of inflammation in the coronary tree and other arteries correlate with patient outcome [27]. The identification of a marker specific for vascular inflammation is therefore of interest to improve risk stratification of patients with CHD and potentially assess therapeutic response at the coronary level and also in other vascular beds, recognizing atherosclerosis as a systemic process. Such tools could also be used as non-invasive surrogate end-points in trials evaluating the efficacy of new interventions. Because FDG PET/CT imaging allows whole-body imaging, systemic and coronary arterial inflammation can be assessed in a single study, which can provide prognostic information. A list of potential roles of FDG PET/CT imaging in atherosclerotic and non-atherosclerotic coronary disease is presented in Table 2.

Table 2
Potential roles of molecular imaging of coronary inflammation.

Potential roles for coronary inflammation imaging
Risk stratification
Identification of 'at risk' lesions
Modulation of therapy
Assessment of therapy efficacy
Surrogate end point in clinical trials

Limitations of coronary imaging with FDG PET/CT

One of the main limitations of coronary imaging with FDG is the potential physiological uptake in the adjacent myocardium. The myocardium can metabolize different substrates which include free fatty acids (FFA), glucose, pyruvate, and ketone bodies. Under normal conditions, FFA represents 60% to 90% of the energy substrates used by the myocardium and glucose accounts for the remaining 10–40% [14]. If the myocardium metabolizes glucose at time of FDG injection, there will be physiological myocardial FDG uptake which can be very intense, thereby limiting the ability to identify pathological uptake in the coronary arteries (Fig. 5). To circumvent this issue, different imaging protocols have been developed.

Myocardial uptake suppression protocol

Since myocardial substrate utilization depends mostly on FFA, glucose plasma concentrations, and insulin levels, special preparations have been described in order to minimize normal physiological myocardial uptake [13,14]. These protocols include 1) prolonged fasting of 12–16 hours, which shifts myocardial metabolism to FFA utilization, 2) a high fat, low carbohydrate diet prior to fasting, which minimizes myocardial glucose utilization; and 3) intravenous injection of unfractionated heparin, which reduces myocardial FDG uptake by increasing FFA serum concentration.

Technical factors

The relatively low spatial resolution of PET/CT systems limits the ability to evaluate smaller structures. As well, unavoidable motion due to cardiac and respiratory motion lead to 'partial volume effects', causing underestimation of the actual activity present in smaller structures such as coronary plaques. Ultimately, these limitations can limit evaluation of coronary inflammation, especially in the left circumflex and right coronary arteries [27].

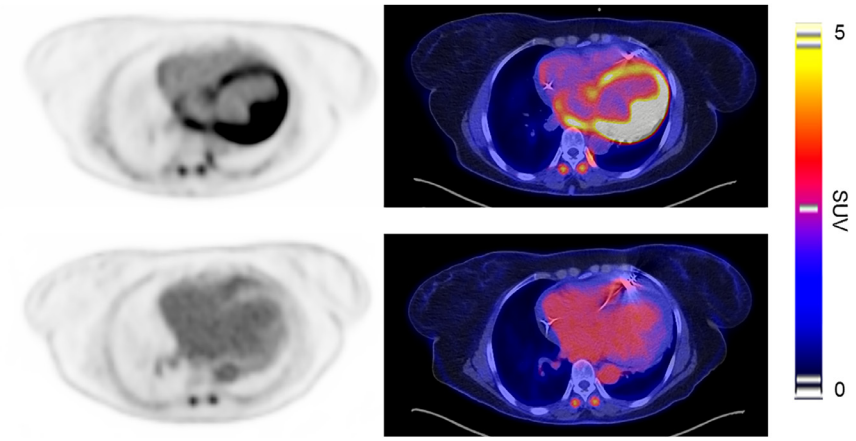

Fig. 5. PET (left) and fused (right) FDG-PET/CT images of a patient before (top) and after (bottom) adequate myocardial suppression preparation including of prolonged fasting, high-lipid low-carbohydrate diet, and intravenous heparin injection. Without optimal preparation, evaluation of coronary inflammation can be challenging, if not impossible, due to high adjacent myocardial activity.

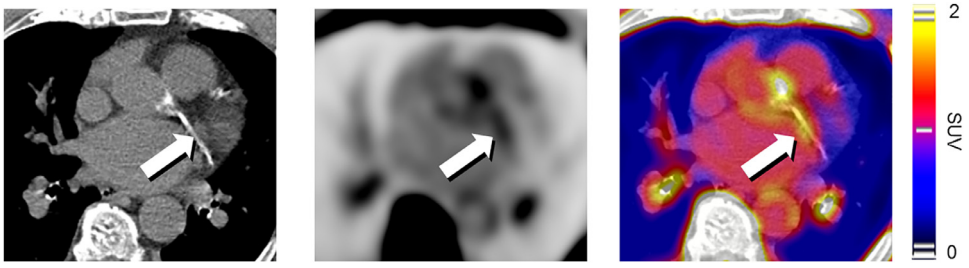

Fig. 6. Axial CT (left), PET (middle), and fused (right) images of a NaF-PET/CT study in an 88 year-old male with left ventricular hypertrophy and aortic stenosis investigated for cardiac amyloidosis. Although the study showed no evidence of cardiac amyloidosis, increased NaF uptake is seen in the left main artery (arrows), corresponding to coronary calcification seen on CT, identifying potential high risk coronary lesions.

Non-FDG tracers of plaque inflammation

Because a significant proportion of patients imaged with FDG following a suppression protocol will still present undesirable myocardial uptake [13], an ideal tracer for coronary inflammation would have no physiological myocardial uptake. Several tracers with different uptake mechanisms are currently under investigation. ^{68}Ga-DOTATATE binds to somatostatin receptor-2 over-expressed on activated macrophages and has been used for coronary inflammation imaging [38]. Imaging with ^{68}Ga-DOTATATE provided superior image quality and better discrimination between high-risk and low-risk coronary plaques compared to FDG [38]. Choline tracers are substrates of membrane synthesis with uptake associated with cell proliferation and activity and may accumulate in activated macrophages. Preliminary results showed that ^{18}F-fluorocholine accumulated in vulnerable carotid plaques [39]. Other tracers, not targeting directly macrophages and inflammation, have been used in atherosclerosis imaging. ^{18}F-sodium fluoride (NaF), a bone imaging agent that binds to hydroxyapatite, allows imaging of active microcalcification in coronary plaques (Fig. 6). In a prospective trial comparing NaF and FDG, NaF was superior to FDG with no myocardial uptake, more rapid tissue clearance and better localization of ruptured and high risk plaques [40]. In a study comparing the vascular uptake of FDG and NaF, only 6.5% of cases showed increased uptake of both FDG and NaF, suggesting that the two tracers are elucidating different process of atherosclerosis [41]. Several other tracers targeting hypoxia, angiogenesis, apoptosis, etc., have also been described and have been recently reviewed elsewhere [42]. Whether any of these promising tracers can impact patient management and outcome remains to be demonstrated.

PET/MR imaging of coronary inflammation

Systems combining PET and magnetic resonance imaging (MR) into a single scanner allow simultaneous PET and MR acquisitions. PET/MR has been shown to allow detection and follow evolution of vascular inflammation in the aorta and carotids arteries, with PET and MR providing complementary information [40]. For coronary imaging, PET/MR imaging presents several advantages over PET/CT. As stated above, the small size of the coronary artery and the motion associated with cardiac and respiration movement are major factors limiting the ability of PET/CT to evaluate the coronary arteries. MR enables tracking of respiratory and cardiac motion, allowing reduction of motion artifacts of PET coronary imaging [43]. This translates into improved PET image resolution and accuracy and enables better delineation of the coronary artery. Moreover, MR provides incremental information over PET/CT alone, including vessel wall morphology and other markers of high risk plaques such as plaque remodeling, hemorrhage, and inflammation [44]. Preliminary studies show feasibility of plaque imaging with PET/MR [43,45,46]. As of now, utilization of PET/MR imaging is hampered

by its limited availability and the complexity of the acquisition parameters compared to conventional PET/CT.

Conclusion and future directions

PET/CT molecular imaging with FDG provides unique information on the environment and pathobiology of coronary disease. FDG and other tracers allow non-invasive assessment of the different mechanisms involved in the development of coronary disease and detection of high risk plaques. Although the results of several relatively small studies demonstrating the feasibility and clinical potential of coronary inflammation imaging are encouraging, larger prospective trials evaluating the exact role of this modality in the treatment and management of patients are lacking. Completion of ongoing and proposed trials are required for this technology to move from a research tool for understanding physiology and in pharmacological trials to a clinical tool for patient risk stratification and monitoring of personalized therapies.

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