Current and Emerging Radiotracers in Molecular Cardiovascular Imaging

Running title: Radiotracers in Molecular Cardiovascular Imaging

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Abstract

Cardiovascular imaging has rapidly advanced over the past decades. Traditional imaging techniques like echocardiography, computed tomography (CT), and cardiovascular magnetic resonance (CMR) are essential for assessing the structural and functional aspects of the cardiovascular system but often fall short in providing direct insights into disease activity. This gap is increasingly being bridged by molecular nuclear imaging techniques, including positron emission tomography (PET) and single-photon emission computed tomography (SPECT), which enable the visualization of disease processes at the molecular and cellular levels. This review highlights the role of cardiovascular molecular imaging, emphasizing its current and potential applications in diagnosing and managing cardiovascular disease. With advancements in PET scanners, novel radiotracers, and sophisticated imaging software, molecular imaging is set to play an essential role in precision medicine by enhancing our understanding of disease mechanisms, accelerating the development of targeted therapies, and facilitating personalized patient care.

Key words: molecular cardiovascular imaging, novel radiotracers, PET/CT, radiotracers

Introduction

Cardiovascular imaging has evolved at an accelerated pace over the last two decades adding a range of advanced imaging modalities to our armamentarium of investigational tools. In particular, non-invasive imaging has solved many of the issues around motion correction and spatial resolution, and imaging modalities like CT and CMR are now performed as part of routine care across the world. Similar approaches can be applied to molecular nuclear imaging techniques. They too, are now being used to investigate patients in clinical practice, with a range of exciting research approaches on the horizon that might further contribute to patient care.

Traditional imaging techniques like echocardiography, CT and CMR are invaluable for assessing structural and functional aspects of the cardiovascular system, but provide limited and indirect information regarding disease activity. This diagnostic gap is bridged by molecular imaging techniques including PET and SPECT that can measure 'disease activity' as it is occurring in the body. This article will review molecular nuclear imaging in humans, outlining the most promising techniques and exploring their current and potential applications in patients with cardiovascular disease (Figure 1). The focus will be on the application of these molecular imaging techniques to study disease activity, whilst acknowledging that the vast majority of current clinical PET and SPECT imaging focuses on myocardial perfusion imaging. The latter will not be discussed further here.

Cardiovascular molecular imaging

Molecular imaging involves the visualization, characterization, and measurement of biological processes at the molecular and cellular level. This technique provides crucial insights into the cellular and molecular mechanisms underlying various cardiovascular conditions. In today's era of precision medicine, molecular imaging is anticipated to play an increasingly vital role in establishing clinical diagnoses, distinguishing between active and inactive disease states, accelerating the development of novel drug therapies, and facilitating a personalized approach where the right medication is targeted to the right patient at the right time and at the correct dose. Indeed, molecular imaging has already become an integral part of routine clinical cardiovascular practice. For example, ^{18}F-Fluorodeoxyglucose ([^{18}F]FDG) PET imaging is recommended by international guidelines for the evaluation of different cardiovascular disease stages, such as the assessment of myocardial viability, in patients with suspected endocarditis, cardiac sarcoidosis, and large vessel vasculitis [1–3]. However, with the advancements in PET scanners, image analysis software and development of novel radiopharmaceuticals, these advanced imaging techniques have the potential to play an even more significant in both clinical and research settings.

An ideal radiotracer should exhibit high specificity for its molecular target of interest (e.g., an enzyme, receptor, or transport protein) that is linked to a specific cell population or disease state with minimal uptake in other tissues. The tracer should also be stable, resisting enzymatic degradation and maintaining integrity during imaging. Other desirable qualities include fast uptake into the tissues of interest and favorable kinetics such as rapid clearance to ensure a high signal-to-noise ratio [4]. Several novel tracers display excellent imaging

properties, allowing the *in vivo* assessment of many of the key pathological processes involved in cardiovascular diseases, including inflammation, infection, calcification, fibrosis, and thrombosis. For widespread clinical adoption, these imaging tests will likely need to be clearly associated with specific changes in patient management.

Glucose metabolism / ^{18}F-Fluorodeoxyglucose ([^{18}F]FDG)

Myocardial Hibernation

One of the commonest indications for molecular imaging in clinical practice is assessment of myocardial hibernation. PET is considered the gold standard for myocardial hibernation assessments and is based on the glucose analogue [^{18}F]FDG. This tracer is transported into viable myocytes by GLUT1 and GLUT4 transporters, where it is subsequently phosphorylated to [^{18}F]FDG-6-phosphate by hexokinase [5], which cannot undergo further metabolism. The tracer is thereby trapped within viable myocardial cells. Myocardial cells exposed to repeated or chronic ischemia switch their metabolism from lipids to sugar consumption. [^{18}F]FDG is therefore particularly well suited to identify hibernating myocardium. Mismatch in perfusion-metabolism data denotes hibernating myocardium with a high likelihood of functional recovery following revascularization. The extent of perfusion-metabolism mismatch on PET is a good predictor of myocardial recovery after coronary revascularization [6]. Whilst the STICH trial questioned the role of viability imaging, an important limitation is that it did not include [^{18}F]FDG PET assessments to quantify the extent of hibernating myocardium. The PARR2 trial demonstrated significant benefits in patients where PET recommendations were adhered to and in patients without recent angiography [7]. More studies, and in specific randomized clinical trials, are now required to further test the hypothesis that [^{18}F]FDG PET viability imaging improves clinical outcomes.

Inflammation and Infection

Inflammation is a key pathological process underlying many cardiac conditions, including atherosclerosis, large vessel vasculitis, myocarditis, sarcoidosis as well as infective conditions such as endocarditis. Inflammation is therefore a key target for molecular imaging with a range of different tracers having been developed for that purpose.

^{18}F-Fluorodeoxyglucose

[^{18}F]FDG PET is also the most well-established radiotracer to image cardiovascular inflammation on the basis that activated macrophages and other inflammatory cells have higher glucose requirements than surrounding cardiovascular tissue. Whilst in viability assessments, physiological [^{18}F]FDG uptake by viable myocytes is encouraged, in studies of inflammation it should be suppressed so that signals related to inflammation can be more readily visualized.

Endocarditis

Despite advances in clinical investigations, the diagnosis of prosthetic valve endocarditis remains challenging. Echocardiography and blood cultures are inconclusive in 14-30% of episodes, especially in the early stages of disease [8]. [^{18}F]FDG PET-CT can detect the increased metabolic activity due to immune cell accumulation at sites of prosthetic valve infection [1] even in the absence of structural changes like vegetations or valve incompetence. Overall, [^{18}F]FDG PET has a sensitivity of 81-91% and a specificity of 73-95% for the detection of prosthetic valve endocarditis and provides improved diagnostic certainty and detection of extracardiac sites of infection [1]. This technique has an established clinical role in the diagnosis

of implantable device infections with a sensitivity of 89% and specificity of 86% [9] and to guide decisions regarding the need for device removal- often a complex and high-risk procedure. However, evidence for [^{18}F]FDG PET in native valve endocarditis is more limited, demonstrating lower sensitivity compared to prosthetic valve endocarditis [10]. More specific molecular imaging probes to image native valve endocarditis are currently being developed and assessed (Table S1).

Atherosclerosis and Vasculitis

[^{18}F]FDG PET imaging has been widely researched in atherosclerosis as a marker of vascular inflammation, particularly in the aorta and carotid arteries. [^{18}F]FDG uptake is associated with plaque macrophage accumulation and hypoxic plaque conditions [11]. Its ability to image vulnerable plaques in humans was first demonstrated more than 20 years ago with higher uptake of [^{18}F]FDG in patients with symptomatic carotid plaques, as opposed to the asymptomatic contralateral side and healthy arteries [12]. [^{18}F]FDG has since been validated as a surrogate marker of plaque macrophage content and hypoxia in humans by several independent studies and in different vascular beds [13]. [^{18}F]FDG PET has been used as an endpoint in trials assessing the efficacy of drugs targeting atherosclerotic inflammation in the carotid arteries and ascending thoracic aorta with the results mirroring those of large clinical endpoint studies [14]. Further work is required to assess whether [^{18}F]FDG PET imaging can improve patient risk stratification and can help direct the use of novel anti-inflammatory agents. [^{18}F]FDG PET imaging is also being increasingly used to aid the diagnosis and management of rarer aortic conditions like large vessel vasculitis and prosthetic vascular graft infections [15].

Sarcoidosis

Sarcoidosis is a multisystem granulomatous disease of unknown etiology that can affect any organ system including the heart. Cardiac involvement is characterized by focal regions of inflammation (non-caseating granulomas) that are often asymptomatic but can also lead to AV conduction disease, ventricular arrythmias, heart failure and sudden cardiac death. Indeed, cardiac sarcoidosis accounts for 13-25% of sarcoid-related deaths [16]. Accurate diagnosis of cardiac involvement is important to initiate appropriate treatment and to prevent complications due to the sarcoid disease process. The diagnosis of cardiac sarcoidosis remains challenging. Isolated cardiac sarcoidosis can occur, and echocardiography has poor sensitivity meaning it cannot be used to rule out the disease. Guidelines therefore recommend [^{18}F]FDG alongside echocardiography and CMR in the diagnostic pathway [17]. Increased myocardial [^{18}F]FDG uptake is observed in regions of active myocardial sarcoidosis and can be used to direct and monitor the use of anti-inflammatory therapies (Figure 2) [18,19]. A meta-analysis of 7 studies involving 164 patients, assessing [^{18}F]FDG PET in the diagnosis of cardiac sarcoidosis, reported 89% sensitivity and 78% specificity [20], with other studies also demonstrating the powerful prognostic information provided by this approach and its ability to track response to therapy [21]. However, robust quantitative analysis methods and specific imaging phenotypes predictive of adverse outcomes are currently lacking, and would enable better understand long-term outcomes and selection of patients who may benefit from early aggressive strategies. Investigation of more specific inflammatory tracers is also required.

Limitations of [^{18}F]FDG

Although now widely used in clinical practice, [^{18}F]FDG has important limitations as a radiotracer for cardiovascular applications. First and foremost, it is a glucose analogue that

lacks specificity, as most human cells metabolize glucose for adenosine triphosphate (ATP) synthesis. Physiologic FDG uptake therefore occurs throughout the body including the myocardium. This can hamper the interpretation of cardiac inflammation, with high-intensity physiological [^{18}F]FDG uptake obscuring any underlying inflammatory signal. Whilst physiological [^{18}F]FDG uptake can be suppressed by dietary restrictions (e.g. a 12-hour fast with avoidance of carbohydrate for 24 hours) and/or intravenous heparin administration, these measures are not always successful with diffuse or patchy myocardial [^{18}F]FDG uptake remaining, potentially causing diagnostic difficulties [22]. Second, non-infected prosthetic heart valves frequently display homogenous [^{18}F]FDG uptake in the perivalvular area on PET/CT, particularly in early stages following surgery and can demonstrate high intensity uptake when different forms of surgical glue are used as part of the operative strategy [9]. Interpretation of [^{18}F]FDG PET/CT in suspected prosthetic valve endocarditis can therefore be challenging with similar issues also arising in suspected cardiac device infections. On this basis, there is a major interest in developing more specific tracers for infection imaging.

Somatostatin receptor radiotracers

Activated inflammatory cells have abundant somatostatin receptors (SSTR) on their surface compared to normal cardiomyocytes. As such, there is very little background uptake of somatostatin receptor radiotracers like ^{68}Ga-DOTA-NaI-octreotide (DOTANOC), ^{68}Ga-DOTA-D-Phe-Tyr^{3}-octreotate (DOTATATE) and ^{68}Ga-DOTA-D-Phe-Tyr-octreotide (DOTATOC) in the heart [23]. SSTR targeted radiotracers have now been investigated in myocarditis, sarcoidosis, coronary atherosclerosis and large vessel vasculitis.

Increased [^{68}Ga]DOTATOC and [^{68}Ga]DOTATATE activity is seen in patients with acute peri/myocarditis or acute myocardial infarction, demonstrating good agreement with the pattern of injury on CMR [24]. [^{68}Ga]DOTATATE PET has also been validated as a marker of atherosclerotic inflammation, with increased [^{68}Ga]DOTATATE activity observed in culprit coronary and carotid plaques following acute myocardial infarction and stroke respectively with more favorable imaging characteristics compared to [^{18}F]FDG [25]. Similarly, higher [^{64}Cu]DOTATATE uptake is observed in symptomatic versus contralateral carotid plaques ($p<0.001$) in stroke patients, whilst aortic [^{68}Ga]DOTATATE uptake correlates with the calcific plaque burden as well as [^{18}F]FDG activity ($r=0.64$, $p<0.01$) [26]. Finally, few studies have investigated the utility of SSTR-PET-CT imaging to diagnose cardiac sarcoid, again reporting good concordance with CMR [27]. Similarly, [^{68}Ga]DOTATOC can identify active granulomatosis and help with treatment evaluation in cardiac sarcoidosis [27].

Chemokine receptors

Chemokines are involved in the recruitment of leucocytes and chemokine receptor type 4 (CXCR4) is expressed on several pro-inflammatory immune cell types, in particular macrophages and T lymphocytes [28]. Therefore, CXCR4-directed PET tracers such as [^{68}Ga]pentixafor are used to image inflammation in clinical research.

Increased CXCR4 expression and [^{68}Ga]pentixafor uptake is observed in the infarct zone in patients with acute myocardial infarction, negatively correlates with scar volume and predicts cardiac outcomes [29]. [^{68}Ga]pentixafor has also been used to detect coronary inflammation in patients with acute myocardial infarction with increased [^{68}Ga]pentixafor activity localizing to culprit lesions and outperforming the results of [^{18}F]FDG [30]. Imaging-based guidance to optimize therapeutic timing of CXCR4 inhibition resulted in improved functional outcome in

mice [31], but although very promising, clinical studies proving this concept are lacking and now required.

Recent studies have also shown the importance of chemokine receptor type 2 (CCR2) positive monocytes and macrophages as mediators of adverse remodeling in myocardial infarction, of inflammation after heart transplantation [32], and of leukocyte trafficking to the site of arterial inflammation in abdominal aortic aneurysm [33]. However, previous work on CCR2 has mainly been limited to animal models, with clinical evaluation in patients now warranted.

Mitochondrial translocator protein

Mitochondrial translocator protein (TSPO) is a key outer mitochondrial membrane protein that is expressed by activated mononuclear cells and other inflammatory cells. The abundant expression of TSPO in macrophages has been utilized to image the immune response of the heart to inflammatory conditions like myocarditis. Several PET radioligands for TSPO have been described including [^{11}C]PK11195 and [^{18}F]flutriciclamide (^{18}F-GE180). Increased [^{11}C]PK11195 activity is observed in the culprit carotid plaques of patients with recent stroke [34]. Similarly, increased [^{11}C]PK11195 uptake has also been demonstrated in patients with large vessel vasculitis, correlating with other markers of inflammation and demonstrating increased activity in symptomatic versus asymptomatic patients [35].

Despite promising results from initial studies with TSPO radiotracers, these radiotracers have some major limitations including high non-specific uptake, and wide variability in TSPO binding caused by a single nucleotide polymorphism in the TSPO gene, which leads to patients with high, mixed and low affinity binding potential [36]. Interpretation of TSPO activity therefore

requires genetic assessment for this polymorphism, greatly increasing the complexity and expenses of TSPO imaging. A new selective PET radiotracer for imaging TSPO, [^{18}F]LW223 appears to overcome this issue, although human studies are lacking [37].

Infection Specific radiopharmaceuticals

While the radiotracers discussed above are useful for detecting inflammation, there is still a need for radioligands that can distinguish between infection and sterile inflammation. Examples of novel infection specific radiotracers include [^{89}Zr]SAC55 which consists of a monoclonal antibody against *Staphylococcus aureus* labelled with Zirconium-89, [^{68}Ga]NOTA-UBI which consists of chelated ubiquicidin (an antimicrobial peptide) labelled with Gallium-68, and 2-^{18}F-fluorodeoxysorbitol which consists of sorbitol (a metabolic substrate for Gram negative bacteria) labelled with Fluorine-18 [38]. These radiotracers have shown promising results in infective conditions like prosthetic joint and lung infections, although they have not yet been tested in cardiovascular infections and their utility may depend on prior identification of the causative organism.

<u>Calcification</u>

Calcification is a key healing response to cardiovascular injury and is a common pathological feature in atherosclerosis, valvular heart disease, and peripheral vascular disease. Assessing calcification activity provides a readout for vascular injury and disease activity across multiple disease states. Nuclear molecular imaging allows assessment of calcification activity with both SPECT and PET providing complementary information to the presence of established macroscopic calcification detected by CT [39].

Bisphosphonate SPECT tracers

Transthyretin cardiac amyloidosis (ATTR-CM) is a progressive, potentially fatal, infiltrative cardiomyopathy caused by extracellular deposition of transthyretin-derived insoluble amyloid fibrils in the myocardium. ATTR-CM is more common than previously thought and treatable [40], with early diagnosis and distinction from light chain (AL) cardiac amyloidosis key to improving patient outcomes. Bisphosphonate tracers including ^{99m}technetium 3,3-diphosphono-1,2-propanodicarboxylic acid ([^{99m}Tc]DPD), and ^{99m}technetium pyrophosphate ([^{99m}Tc]PYP), ^{99m}technetium hydroxymethylene diphosphonate ([^{99m}Tc]HMDP) demonstrate increased myocardial uptake in ATTR-CM with high sensitivity and specificity [41]. The value of bone scintigraphy in the diagnosis of cardiac amyloidosis was first demonstrated in the 1980s. Subsequently the Perugini grading system was developed based on a simple 4-point visual scoring system of delayed (3 hour) planar images (Grade 0 – no cardiac uptake and normal bone uptake, Grade 1: cardiac uptake which is less intense than bone signal, Grade 2 - cardiac uptake with intensity similar or greater than bone signal; and Grade 3 - cardiac uptake greater than bone uptake with much attenuated or absent bone signal) (Figure 3) [42,43]. Gillmore et al. analyzed bone scintigraphy and biochemical investigations from 1217 patients with suspected cardiac amyloidosis and confirmed that Perugini Grade ≥2 myocardial uptake on bone scintigraphy in absence of monoclonal gammopathy was >99% sensitive and 86% specific for cardiac ATTR amyloid [44]. Several other studies have confirmed similar findings, and this combination is therefore sufficient to establish a diagnosis of ATTR-CM, without the need for endomyocardial biopsy [45]. The use of advanced SPECT/CT cameras can further increase the sensitivity of the exam.

Other PET radiopharmaceuticals that bind amyloid deposits directly include [^{11}C] Pittsburgh Compound B (PIB), [^{18}F]Florbetapir (Figure 4)[46], and [^{18}F]Florbetaben. These have demonstrated promising results in clinical research studies as recently described in the expert consensus recommendations for multimodality imaging in cardiac amyloidosis[47]. [^{18}F]Florbetapir and [^{18}F]Florbetaben were able to distinguish light chain (AL) cardiac amyloidosis from ATTR cardiac amyloid or other mimicking conditions, in clinical studies [48]. PET imaging can potentially provide incremental information in cardiac amyloid. In particular it may play a role in risk stratification of patients with cardiac amyloidosis and several studies demonstrated poorer outcomes in patients with higher [^{11}C]PIB accumulation in the myocardium [49]. Furthermore, to improve clinical outcomes, PET tracers have the potential to allow for early detection of preclinical amyloid deposits, which is lacking with current technologies. A dual-center study that examined PIB PET in a large cohort of amyloidosis patients and controls found a high prevalence of PIB uptake among amyloidosis patients without increased myocardial wall thickness, indicating the potential ability of PIB PET to detect early stages of cardiac amyloidosis [50].

With current available precursor protein-directed therapies, there is increasing interest in imaging methods to accurately evaluate and monitor treatment response. Preliminary data showed a reduction in cardiac tracer uptake versus whole body uptake on planar scintigraphy as early as 4 months after treatment initiation with the recombinant human anti-ATTR monoclonal antibody NI006 [51]. However, visual identification of changes on serial amyloid scans is extremely challenging, and more research on quantitative PET imaging with kinetic modelling methods to allow accurate monitoring of therapy and early identification of non-responders is needed [52]. The ongoing I-CARE study is investigating whether ^{18}F-Sodium

fluoride PET imaging can be used to track treatment responses in TTR cardiac amyloidosis and whether this offers incremental information to CMR approaches.

^{18}F-Sodium Fluoride

^{18}F-Sodium fluoride (Na[^{18}F]F) is an established bone PET tracer that binds to hydroxyapatite, a key crystalline component of both bone and vascular calcification. The mechanism of Na[^{18}F]F uptake in bone is well established. It diffuses via the capillary network into the bone extracellular fluid, and then exchanges with hydroxyl groups on exposed regions of hydroxyapatite crystals on the surface of the calcium deposit to form fluorapatite. The intensity of Na[^{18}F]F uptake depends on the surface area of exposed hydroxyapatite available for binding, which is much higher in regions of newly developing powdery microcalcification than in areas of established macrocalcification (the type of calcium imaged with CT) where most of the hydroxyapatite signal is internalized and not available for binding. Na[^{18}F]F PET has now been investigated across multiple different cardiovascular disease states, where it consistently provides an assessment of calcification activity and vascular injury, detecting newly developing microcalcification before it is visible on CT and predicting disease progression and clinical events (Figure 5)[53].

Coronary Na[^{18}F]F uptake as a novel marker of calcification activity was first described in 2012. Participants with increased Na[^{18}F]F activity had higher rates of prior cardiovascular events (p=0.016), angina (p=0.023) and higher Framingham risk scores (p=0.011) [54]. Subsequent studies demonstrated that intense Na[^{18}F]F uptake localizes to the culprit coronary vessel and areas of recent plaque rupture in patients with acute myocardial infarction. In patients with stable disease it localizes to plaques with multiple high risk features on intravascular

ultrasound as well as a range of other adverse plaque characteristics assessed by different techniques [55]. Doris et al confirmed that Na[^{18}F]F provides an assessment of disease activity in the coronary arteries, predicting subsequent disease progression at both the plaque and patient level. Indeed, patients without coronary Na[^{18}F]F activity at baseline did not demonstrate subsequent progression in their coronary CT calcium score whereas patients with coronary Na[^{18}F]F uptake did, despite similar baseline plaque burdens [56]. Kwiecinski and colleagues demonstrated that coronary Na[^{18}F]F uptake also predicts subsequent clinical events. In a cohort of patients with advanced established coronary artery disease, coronary Na[^{18}F]F activity emerged as the strongest predictor of fatal or non-fatal MI outperforming cardiovascular risk factors and CT assessments of luminal stenosis and atherosclerotic plaque burden [57]. More recently, results from the prospective multicenter PRE^{18}FFIR trial showed that coronary atherosclerotic plaque activity assessed with Na[^{18}F]F PET predicts spontaneous recurrent atherosclerotic events in a large cohort (n=704) of patients with established multivessel coronary artery disease [58]. Based on these findings, Na[^{18}F]F PET might be used to guide the application of more intensive lipid-lowering, anti-inflammatory or other advanced therapies in this patient cohort who are already on standard secondary prevention treatments. Nevertheless, further work is required to investigate how coronary plaque disease activity should be used in clinical practice, and how this information might ultimately improve clinical decision making. This will require randomized controlled trials investigating whether targeting of therapy using plaque activity imaging assessments improves patient outcomes in a cost-effective way.

Na[^{18}F]F uptake has also been widely investigated in heart valve disease. In aortic stenosis, intense Na[^{18}F]F uptake is observed within the valve, identifying where new macrocalcific

deposits will develop on CT as well as predicting subsequent disease progression as assessed by CT calcium scoring and echocardiography [59]. Whilst the clinical use of Na[^{18}F]F is likely to be limited by CT calcium scoring, which provides similar predictive and prognostic information, Na[^{18}F]F is used increasingly in the research arena, in particular to investigate the factors associated with calcification activity in aortic stenosis and as an endpoint in clinical trials of novel therapies aiming to slow valve calcification.

Similar findings have been observed in patients with mitral annular calcification [60] and bioprosthetic valve degeneration. Marked Na[^{18}F]F uptake is seen in explanted degenerated bioprosthetic valve tissue and this correlated with valve degeneration on histology. In a prospective clinical cohort study of patients with surgically implanted bioprosthetic aortic valves, increased Na[^{18}F]F PET uptake occurred in 34% of patients who did not have any clinical or echocardiographic suspicion of bioprosthetic valve degeneration. Baseline Na[^{18}F]F PET went on to provide the most powerful prediction of subsequent valve deterioration, outperforming all other known predictive markers [61]. These findings were subsequently confirmed in patients with TAVI valves [62], providing further support to Na[^{18}F]F as an early marker of bioprosthetic valve degeneration. Further studies are required to evaluate how best to employ this novel technique in routine clinical practice and how it might be used to complement the current strategy of echocardiographic surveillance. Other conditions where Na[^{18}F]F PET has demonstrated exciting early results and where further research is ongoing include abdominal aortic aneurysmal disease, peripheral vascular disease and carotid atherosclerosis [53].

Fibrosis

Fibrosis is a fundamental pathological process in cardiovascular disease and appears to be the common final pathway of injury in the myocardium, underlying almost every form of heart muscle disease. It plays a crucial role in cardiac remodeling that leads to heart failure, as well as ventricular dysrhythmia. Myocardial fibrosis takes two predominant forms: replacement and interstitial fibrosis. Replacement fibrosis is focal and non-reversible, often occurring as a result of myocyte necrosis, for example following myocardial infarction. Interstitial fibrosis is diffuse and potentially reversible, characterizing conditions such as hypertension and valvular heart disease. Activated fibroblasts are the most prominent cells involved in myocardial fibrosis. Activation of fibroblasts occurs in response to myocardial injury under the influence of several pathways including the renin-angiotensin-aldosterone-system (RAAS), transforming growth factor-beta and interleukin-11 [63].

Radiotracers targeting fibroblast activation protein (FAP)

Fibroblast activation protein (FAP) is a cell surface proteinase that is almost exclusively expressed on activated fibroblasts, with no expression on myocytes, inflammatory cells or quiescent fibroblasts [64]. FAP is an excellent imaging target to inform about fibroblast activation. Recently, fibroblast activation protein-specific inhibitors (FAPI) have been developed and radiolabeled with either Gallium-68 or Fluorine-18 aluminium fluoride ([^{68}Ga]-FAPI AlF[^{18}]F-FAPI). These PET tracers are highly specific for FAP, becoming internalized within the cell after receptor binding and demonstrating very low levels of leakage thereafter. Combined with rapid renal clearance, [^{68}Ga]-FAPI and Al[^{18}F]F-FAPI have emerged as highly specific tracers for fibroblast activation across a range of different organ systems, demonstrating high intensity signal in regions of activated fibroblasts and very low background uptake as well as low radiation doses [65].

In the cardiovascular system, the first case report described increased myocardial [^{68}Ga]-FAPI uptake in a patient with treated pancreatic adenocarcinoma and chemotherapy associated cardiotoxicity. Subsequent case reports have demonstrated increased myocardial [^{68}Ga]-FAPI uptake in patients with dilated cardiomyopathy, hypertensive heart disease, chemotherapy cardiotoxicity and radiation heart disease [66]. Recently, a retrospective study described cardiac [^{68}Ga]-FAPI uptake in 229 oncology patients, undergoing PET-CT to evaluate metastatic cancer. Increased myocardial [^{68}Ga]-FAPI uptake was associated with cardiovascular risk factors including diabetes mellitus (odds ratio 2.9, p=0.04), and with previous platinum-based chemotherapy (OR: 3.0, p=0.03). [^{68}Ga]-FAPI uptake was also higher in patients with reduced versus preserved ejection fraction [67]. Several studies have now described intense [^{68}Ga]-FAPI uptake in patients following acute myocardial infarction with the PET signal extending beyond the infarct zone towards the infarct border zone, and predictive of the evolution of ventricular dysfunction [68]. A recent study demonstrated increased [^{68}Ga]-FAPI uptake in patients with hypertrophic cardiomyopathy and that this was association with cardiovascular events [66]. In patients with aortic stenosis planned for valve replacement, [^{68}Ga]-FAPI uptake was heterogeneous among individuals, but significantly higher than in matched controls, and correlated with left ventricular dysfunction [69]. Whilst early in its development, there is considerable excitement about the investigation of activated fibroblasts with [^{68}Ga]-FAPI and [^{18}F]F-FAPI across a range of cardiomyopathic conditions (Figure 6), which parallels the progression and understanding of cardiac fibrosis and allows for development of novel targeted antifibrotic therapies. Indeed, not only molecular imaging with [^{68}Ga]-FAPI, but also experimental approaches for treatment of cardiac fibrosis by chimeric antigen receptor T cells targeted against FAP has seen rapid development [70], with recent introduction of a

nanoparticle-based approach for transient in vivo FAP chimeric antigen receptor T-cell production to address the temporal dynamics and avoid long-term effects of fibrosis [71].

Although [^{68}Ga]-FAPI PET is a promising tool for evaluating cardiovascular fibrosis, there are still gaps in knowledge and studies needing filling. Large-population and multicenter studies are warranted to evaluate the role of [^{68}Ga]-FAPI PET imaging in early detection and risk stratification of various cardiovascular diseases. A promising future research perspectives on [^{68}Ga]-FAPI PET imaging could be response to therapy and prediction of the evolution of LV function, as there are merely a few related small-volume studies to date. The relationship between [^{68}Ga]-FAPI PET imaging and other imaging modalities should be investigated to better understand advantages and possible applications of [^{68}Ga]-FAPI PET imaging. Moreover, given the current application of FAP inhibitors in cancer treatments [72], FAPI-PET imaging opens the door to new theranostic approaches to cardiovascular diseases.

A range of tracers targeting alternative pathways involved in tissue fibrosis have been investigated, but most work in this area is preclinical, and translation to humans is not as extensive when compared with FAPI tracers [73].

Thrombosis

Arterial and venous thrombosis plays an important role in various cardiovascular conditions like myocardial infarction, stroke, transient ischemic attacks, deep vein thrombosis and pulmonary embolism. Arterial thrombosis results from clot formation in the setting of atherosclerotic plaque rupture, leading to platelet aggregation, thrombus formation, vessel occlusion and possible myocardial infarction or ischemic stroke. The glycoprotein IIb/IIIa

receptor is integral to acute thrombus formation, with expression falling as the thrombus matures [74]. It is an attractive target for both therapeutic modulation and the molecular imaging of acute thrombus formation.

Early ex-vivo and in-vivo data have demonstrated that [^{18}F]GP1 is highly sensitive to the formation of acute arterial and venous thrombus in humans (Figure 7). Kim et al performed [^{18}F]GP1 PET-CT in patients (n=20) with either suspected lower limb deep vein thrombosis or acute pulmonary embolism demonstrating excellent image quality, signal to noise and diagnostic accuracy [75]. Similarly, Chae and colleagues demonstrated the ability of [^{18}F]GP1 to diagnose acute arterial thrombosis in 10 patients across multiple sites in the body including the abdominal aorta (n=7), internal carotid artery (n=1), superficial femoral artery (n=1) and popliteal artery (n=1) [76]. Furthermore, [^{18}F]GP1 uptake is higher in the presence of thrombus associated with bioprosthetic valves compared to normal native aortic valves and it [^{18}F]GP1 uptake regresses with anticoagulation [77]. Its role has also been reported in acute myocardial infarction [78]. Other clinical studies are underway exploring the efficacy of [^{18}F]GP1 PET-CT in detecting a range of pathological conditions including left ventricular thrombus. Tantalizingly, a recent case report demonstrated that [^{18}F]GP1 was able to identify acute thrombus in both the circumflex coronary artery and the left atrial appendage, leading to a change in clinical diagnosis from type 1 to a type 2 myocardial infarction [79]. As demonstrated by the above, [^{18}F]GP1 PET-CT imaging can be a promising tool in different cardiovascular conditions, however, limited number and volumes of studies are available to date, and its potential role in clinical practice needs to be identified in future research.

Alternatively, Izquierdo-Garcia and colleagues [80] demonstrated the feasibility to detect (sub)acute left atrial appendage thrombus using combined PET/CMR of the fibrin-binding radiotracer [^{64}Cu]FBP8 with good accuracy. This first-in-human study is promising but further validation in larger prospective clinical trials is warranted.

Cardiac Innervation Imaging

Increased myocardial sympathetic activity is a prominent feature of heart failure and is associated with progressive cardiac remodeling, decline in left ventricular function and worsening symptoms. Alterations in myocardial sympathetic activity also play an important role in the generation of ventricular arrhythmias and sudden cardiac death.

[^{123}I]- Meta-iodobenzylguanide ([^{123}I]-MIBG)

Cardiac SPECT with ([^{123}I]-MIBG) is the most commonly employed method to assess cardiac sympathetic innervation [81]. [^{123}I]-MIBG is a guanethidine analogue whose uptake at the post ganglionic presynaptic nerve ending is mediated by noradrenaline uptake and storage mechanisms. Chronic high sympathetic cardiac activity results in reduced presynaptic noradrenaline uptake as an adaptative mechanism. The intensity of [^{123}I]-MIBG uptake in the heart (quantified as a heart-to-mediastinum ratio) is thus inversely correlated with the degree of sympathetic activation. In patients with ischemic heart disease, measuring the heart-to-mediastinum ratio on [^{123}I]-MIBG scintigraphy helps identify patients at high risk for developing heart failure, whilst in patients with established heart failure, irrespective of the etiology, reduced cardiac uptake is associated with poor survival and a higher incidence of cardiac arrhythmias [82]. Indeed, in a study 90 patients with chronic heart failure (New York Heart Association – NYHA II to IV, ejection fraction <45%) the [^{123}I]-MIBG heart-to-mediastinal

ratio emerged as the best predictor of survival [83]. This powerful prognostic information has been confirmed in several other reports, including a study of 414 patients with known or suspected cardiac disease, where [^{123}I]-MIBG scintigraphy again emerged as the most powerful predictor of cardiac death [84].

Carbon-11 Metahydroxyephedrine ([^{11}C]mHED)

([^{11}C]mHED) is a norepinephrine analogue and the most commonly used PET radiotracer in cardiac sympathetic imaging. [^{11}C]mHED was developed based on metaraminol, a synthetic false transmitter analogue of norepinephrine, that accumulates in nerve terminals like norepinephrine. It is released by nerve stimulation but has only weak post-synaptic effects. Like MIBG, [^{11}C]mHED shares the same neuronal uptake mechanism as norepinephrine and is resistant to enzymatic degradation, making it a good radioligand to assess the integrity of the presynaptic sympathetic nerve terminal [85]. High myocardium [^{11}C]mHED uptake (79 ±31%) denotes an intact cardiac sympathetic nervous system, whereas reduced uptake is observed in diseased states like heart failure [86]. Vesalainen et al. demonstrated that global myocardial [^{11}C]mHED uptake was 30% lower in patients with chronic heart failure compared to healthy controls [87]. [^{11}C]mHED also provides prognostic information. In the "Prediction of Arrhythmic Events with Positron Emission Tomography" (PAREPET) trial, 204 patients with ischemic cardiomyopathy (left ventricular ejection fraction ≤35%) were imaged with [^{11}C]mHED PET. The risk of sudden cardiac death was higher in patients with lower [^{11}C]mHED uptake [88]. Further studies are needed, in particular studies investigating whether its prognostic power might be used to guide the implantation of implantable cardioverter-defibrillators for primary prevention.

Challenges and Opportunities

Advances in hybrid imaging technologies like PET-CT and PET-MRI alongside improved motion correction and image analysis techniques make the non-invasive assessment of cardiovascular disease activity a clinical reality. Hybrid imaging combines the strengths of two powerful imaging modalities, allowing for the assessment of disease activity together with detailed anatomical information and tissue characterization. Nuclear cardiology has nowadays a large armamentarium of tools to prevent, detect and correct for motion, including techniques addressing heart contractions, tidal breading, and patient repositioning; and new algorithms to further improve overall quality of the imaging study are under development. Recent technical advances have led to new possibilities for accurate image quantification and quantification of radiotracer kinetics, allowing for better evaluation of disease activity, and treatment response monitoring [89]. Whilst the lack of specific radiotracers was previously an important barrier, we now have an array of tracers allowing us to measure inflammation, infection, activated fibroblasts, calcification activity, myocardial sympathetic activity and thrombus formation as they are occurring in the body, potentially heralding a new era of cardiovascular imaging. However, it is important to acknowledge that not all molecular imaging targets hold the same clinical value. For example, the proximity of the imaging target to the therapeutic target and the differences between hot spot and cold spot imaging in therapy guidance are critical factors that influence the clinical impact of specific tracers. Some targets may have more immediate clinical relevance, particularly in guiding therapeutic decisions, while others might offer broader insights into disease processes. Although a detailed exploration of these variations is beyond the scope of this review, it is crucial to consider these factors in future research and clinical applications. A range of other

tracers targeting yet more pathological processes are currently under development or are being tested in preclinical studies (Table S1) but are beyond the scope of this review article.

Despite its numerous benefits, molecular imaging remains expensive and not readily available at all centers. The increasing use of PET to assess patients with cancer is gradually addressing both of these issues but further collaborative work is required to make molecular imaging more accessible and equitable for patients. Future clinical studies will need to demonstrate the clinical utility and cost effectiveness of molecular imaging to justify its increased clinical use. These will need to be matched by improved education of cardiologists and imaging specialists as well as patients and allied health professionals.

Future Directions

Precision-based medicine, defined as tailored therapy based on an individual's underlying disease biology, now underpins research and clinical aspirations within many medical specialties. With further evolution of the field, molecular imaging has the potential to deliver precision-based cardiovascular medicine by identifying the active processes driving disease in a particular patient, identifying the presence or absence of a therapeutic target before initiation of therapy, and measuring efficacy of treatment by repeated imaging. Theranostic application, or the coupling of imaging agent to the therapy, is already entering clinical practice best exemplified by cardiac sarcoidosis and amyloidosis but with major potential to revolutionize the application of molecular imaging in a wider range of cardiovascular conditions. In addition, molecular assessments of disease activity are increasingly used as

endpoint in clinical trials of novel therapies, providing rapid readouts that might accelerate the development of new treatments.

The future of molecular cardiovascular imaging will likely see a significant contribution from artificial intelligence and machine learning platforms. Artificial intelligence may help improve molecular cardiovascular imaging in various methods and domains: e.g., reconstruction, denoising, partial volume correction, motion compensation, image registration, reconstruction and segmentation, and automated quantification[90]. Machine learning algorithms can efficiently connect information from multiple complex data sets and are well suited to hybrid imaging where information from PET can be combined with the rich information provided by CT and MRI [90]. Moreover, newer total body PET camera systems and newer technologies like cardiofreeze will be able to offer higher sensitivity and better signal to noise ratio.

Conclusion

Advances in molecular imaging and radiotracer discovery now allow the assessment of disease activity across a range of cardiovascular conditions, complementing the structural and functional information provided by traditional imaging techniques. We currently have an array of radiotracers that inform about each of the major processes driving cardiovascular disease including inflammation, calcification, fibrosis, thrombosis, myocardial metabolism, and sympathetic innervation, and molecular imaging is nowadays an integral part of the clinical workup of patients with acute myocardial infarction, cardiac amyloidosis, endocarditis, and sarcoidosis. Cardiovascular molecular imaging is likely to play a pivotal role

in improving our understanding of disease mechanisms, developing and screening novel therapeutics as well as playing an increasing role for patient management in a wider range of cardiovascular conditions.

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DECLARATIONS

No relevant conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

SUPPLEMENTAL MATERIAL

Table S1

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FIGURE LEGENDS

Figure 1

Established radiotracers for clinical use targeting key pathological processes underpinning cardiovascular diseases, including inflammation, fibrosis, amyloid deposits, calcification, innervation, and thrombosis.

^{68}Ga = ^{68}Gallium, ^{18}F = ^{18}Fluorine, FDG = fluorodeoxyglucose, GP1 = glycoprotein 1, ^{125}I = ^{125}Iodine, MIBG = metaiodobenzylguanidine, FAPI = fibroblast activation protein-specific inhibitors, PIB = Pittsburgh Compound B, [^{99m}Tc] = ^{99m}technetium, DPD = 3,3-diphosphono-1,2-propanodicarboxylic acid, PYP = pyrophosphate, HMDP = hydroxymethylene diphosphonate.

Figure 2

PET/MR imaging in Cardiac Sarcoidosis. (Reprinted from Dweck et al, doi: 10.1016/j.jcmg.2017.02.021.)

MR and PET images from 4 patients with active cardiac sarcoidosis in whom characteristic patterns of myocardial late gadolinium enhancement (left column) co-localize with increased ^{18}F-FDG uptake (fused images, right column)[19].

MR = magnetic resonance, PET = positron emission tomography, ^{18}F-FDG = ^{18}Fluorine Fluorodeoxyglucose.

Figure 3

Examples of a whole-body anterior ^{99}mtechnetium 3,3-diphosphono-1,2-propanodicarboxylic acid ([^{99}mTc]DPD) scintigraphy (a) and single photon emission computerized tomography-CT (b) showing abnormal uptake in a patient with cardiac

transthyretin type amyloidosis consistent with Perugini grade 2. (Reprinted from Martinez-Naharro et al. Copyright © 2018, Elsevier. The article is available under the Creative Commons CC-BY-NC-ND license)[43].

Figure 4

Cardiac [^{18}F]Florbetapir uptake in patients with and without cardiac amyloidosis.

(A) [^{18}F]Florbetapir cardiac positron emission tomography/computed tomography images demonstrating identifiable myocardial uptake in a patient with cardiac amyloidosis confirmed by technetium PYP (mean myocardial SUB 3.3), (B) a patient with light chain MGUS and potential for having cardiac light chain amyloidosis (mean myocardial SUB 2.7), and (C) control patient with negative tenosynovial biopsy for amyloidosis at time of carpal tunnel release surgery (mean myocardial SUB 2.0) (Reprinted from Sperry et al. Copyright © 2021, Frontiers Media SA. The article is available under the Creative Commons CC-BY-NC-ND license)[46].

Figure 5

[^{18}F]NaF uptake in different disease states. A, Patient with recent myocardial infarction, (B) patient with recent transient ischemic attack and uptake in the culprit carotid artery, (C) patient with abdominal aortic aneurysm, (D) patient with mild aortic valve stenosis and corresponding [^{18}F]NaF uptake in areas of leaflet calcification, (E) patient with aortic valve degeneration and corresponding ^{18}F-NaF uptake, and (F) patient with erectile dysfunction and high penile uptake (reprinted from Tzolos et al. Copyright ©2020, Wolters Kluwer Health. The article is available under the Creative Commons CC-BY-NC-ND license)[53].

^{18}F-NaF = ^{18}Fluorine Sodium Fluoride.

Figure 6

Data demonstrating increased [^{68}Ga]FAPI activity in different cardiovascular diseases

(A) Patient with acute anterior myocardial infarction and increased myocardial [^{68}Ga]FAPI uptake in the anterior, anteroseptal and apical region. (B) Patient with acute inferior myocardial infarction demonstrating myocardial [^{68}Ga]FAPI uptake in the inferior wall. (C) Patient with acute posterior and chronic apical myocardial infarction with increased myocardial [^{68}Ga]FAPI uptake present in the posterior wall, but not in the apical region. (D) patient with chronic inferior myocardial infarction with no evidence of myocardial [^{68}Ga]FAPI uptake. (E) Patient with acute anterior myocardial infarction demonstrating rapid myocardial [^{68}Ga]FAPI uptake in the infarct zone. (F) Patient with aortic stenosis demonstrating increased [^{68}Ga]FAPI uptake in both the aortic valve leaflets and in the myocardium. (G) Globally increased myocardial [^{68}Ga]FAPI uptake in patient with chemotherapy induced cardiotoxicity (Data from University of Edinburgh).

[^{68}Ga]FAPI = [^{68}Gallium] fibroblast activation protein-specific inhibitors.

Figure 7

Data demonstrating increased [^{18}F]GP1 uptake in (A) patient with left ventricular thrombus following heart infarct with tracer uptake overlying the thrombus on CT, and (B) in a patient with acute inferior myocardial infarction with high thrombus burden in the right coronary artery detected on angiography and clear [^{18}F]GP1 uptake overlying the area of thrombus on CT. Note that there is almost no background myocardial uptake resulting in high signal to noise ratio (Data from University of Edinburgh).

[^{18}F]GP1 = [^{18}Fluorine]Glycoprotein 1.