

## Cardiac hybrid imaging: novel tracers for novel targets

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**ABSTRACT** Non-invasive cardiac imaging has explored enormous advances in the last few decades. In particular, hybrid imaging represents the fusion of information from multiple imaging modalities, allowing to provide a more comprehensive dataset compared to traditional imaging techniques in patients with cardiovascular diseases. The complementary anatomical, functional and molecular information provided by hybrid systems are able to simplify the evaluation procedure of various pathologies in a routine clinical setting. The diagnostic capability of hybrid imaging modalities can be further enhanced by introducing novel and specific imaging biomarkers. The aim of this review is to cover the most recent advancements in radiotracers development for SPECT/CT, PET/CT, and PET/MRI for cardiovascular diseases.

During the last decades, the emergence of new technologies able to integrate dual imaging modalities into hybrid systems and to combine the acquisition of different data sets (e.g., positron emission tomography (PET)/computed tomography (CT)) has dramatically improved the management of oncologic patients compared to stand-alone CT and PET images.<sup>[1]</sup> Moreover, hybrid imaging techniques in cardiovascular field combining either single-photon emission computed tomography (SPECT) or PET with CT may simultaneously capture morphological abnormalities and related pathophysiological processes.<sup>[2]</sup> Therefore, hybrid systems are able to provide a more comprehensive dataset compared to traditional imaging techniques in patients with cardiovascular diseases.<sup>[3,4]</sup> Since 2010, when the first hybrid PET/magnetic resonance imaging (MRI) platform equipped with sequential and integrated scanners has been introduced, hybrid imaging protocols have been increasingly included in clinical practice.<sup>[5,6]</sup> Complementary information obtained from hybrid systems simplifies the evaluation procedure of various pathologies in a routine clinical setting. The diagnostic capability of hybrid imaging modalities can be further enhanced by introducing novel and specific imaging biomarkers.<sup>[7]</sup>

Conventional nuclear cardiology evaluates myocardial perfusion, viability, function, and scar in order to assess the severity of the disease after an initial injury.<sup>[4]</sup> The development of new molecular-targeted imaging probes offers the potential to deepen our understanding of the physiology and the underlying molecular physiology of various cardiovascular diseases, enabling imaging at an earlier stage of the disease. This allows a timely intervention, an improved patient risk stratification, therapeutic guidance, optimized diagnostic accuracy, and ultimately improves prognosis.<sup>[8,9]</sup> This paper will review the most recent advancements in radiotracer development for SPECT/CT, PET/CT, and PET/MRI to evaluate the main pathophysiological processes of cardiomyopathies.

### INFLAMMATION TRACERS

Inflammation plays a pivotal role in the pathogenesis of cardiovascular diseases. After an ischemic damage, cardiomyocyte death determines the release of inflammatory factors, which is generally followed by leukocyte infiltration and tissue remodeling.<sup>[10]</sup> Non-ischemic cardiac diseases are characterized by diffuse myocardial inflammation

too. The presence of inflammation in atherosclerosis of coronary arteries is an important factor to predict future adverse cardiac events.<sup>[11]</sup> Molecular imaging could enable a non-invasive tissue characterisation and represent an added value in diagnosis, prognosis and probably even in therapy because of the emerging of precise molecular therapies which binds to specific elements of inflammation.<sup>[12]</sup> For these reasons, many radiotracers have been explored for the evaluation of cardiovascular inflammation. Even if the majority of medical experience relies on <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG), novel molecular radioligands have been developed to study specific cellular components of the inflammatory response.<sup>[9,13,14]</sup>

### <sup>68</sup>Ga-DOTA-ECL1i for Chemokine Receptor CCR2

<sup>68</sup>Ga-DOTA-ECL1i (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid)-(extracellular loop 1 inverso) is a peptide-based PET tracer able to bind an allosteric position within the CCR2 (C-C chemokine receptor type 2) protein which is typically expressed in activated monocytes and macrophages. Furthermore, ECL1i-CCR2 binding is selectively increased in the presence of a CCR2 ligand.<sup>[15,16]</sup> <sup>68</sup>Ga-DOTA-ECL1 has been recently shown to track the recruitment, accumulation, and resolution of CCR2<sup>+</sup> monocytes and macrophages in the injured myocardium in a mouse model, proving its potential to imaging inflammation<sup>[16]</sup> in to the infarct and peri-infarct area. In mouse models, <sup>68</sup>Ga-DOTA-ECL1i also showed its predictive value in monitoring left ventricular function and the extent of infarction and its ability to recognize human CCR2<sup>+</sup> monocytes and macrophages within tissue specimens obtained from patients who either experienced a myocardial infarction (MI) or were diagnosed with chronic ischemic cardiomyopathy. This makes <sup>68</sup>Ga-DOTA-ECL1i a promising candidate to image the injured myocardium in humans.<sup>[16]</sup> The short half-life and rapid clearance with low liver retention are the main advantages of <sup>68</sup>Ga-DOTA-ECL1i. Furthermore, commercially available <sup>68</sup>Ge/<sup>68</sup>Ga generators enable in-situ multiple-dose preparations and serial imaging.<sup>[16]</sup> When used in combination with MRI or CT, <sup>68</sup>Ga-DOTA-ECL1i PET could provide new insights into the pathophysiology of inflammation in myocardial injuries

and identify patients that would benefit from immunomodulatory therapy.<sup>[16]</sup> One of the major drawbacks associated with <sup>68</sup>Ga-DOTA-ECL1i lie in its ability to recognize other immune cells that express CCR2 (e.g., cardiac dendritic cells), which may compromise its diagnostic efficacy.<sup>[17]</sup> Despite its potential, further studies on the use of <sup>68</sup>Ga-DOTA-ECL1i in humans are required for its clinical translation.

## ATHEROSCLEROSIS TRACERS

### <sup>68</sup>Ga-Pentixafor for Cytokine Receptor CXCR4

<sup>68</sup>Ga-pentixafor is a radiotracer for PET that exhibits high affinity and selectivity for C-X-C chemokine receptor type 4 (CXCR4), which is a protein involved in biological trafficking processes and have an essential role in the signaling of inflammatory cells.<sup>[18,19]</sup> Due to its overexpression on membranes of cells involved in the inflammatory process, such as macrophages, some groups hypothesized that <sup>68</sup>Ga-pentixafor might find a role in the detection of inflammatory cells with PET, and so to non-invasively evaluate atherosclerosis plaques. Hyafil, *et al.*<sup>[19]</sup> revealed that CXCR4 expression grade in atherosclerotic plaques could be evaluated with <sup>68</sup>Ga-pentixafor-PET-MRI imaging in rabbits. Subsequently, they used a small cohort of patients to confirm <sup>68</sup>Ga-pentixafor uptake in human carotid plaques. These results support a potential role of <sup>68</sup>Ga-pentixafor-PET imaging for the visualization of macrophages in atherosclerotic plaques exceeding the well-known limitations of FDG.<sup>[19]</sup> Li, *et al.*<sup>[20]</sup> evaluated CXCR4 expression in carotid atherosclerotic lesions through <sup>68</sup>Ga-Pentixafor PET/MRI in oncologic patients. The Authors demonstrated that <sup>68</sup>Ga-Pentixafor uptake was abnormally increased in eccentric carotid atherosclerosis showing its potential to non-invasively evaluate atherosclerotic lesions by combining morphological plaque characterisation via MRI and quantifying the inflammatory activity measuring CXCR4 expression via PET.<sup>[20]</sup> For imaging atherosclerosis, compared to <sup>18</sup>F-FDG, radiolabeled pentixafor binds exclusively to CXCR4 expressed on the cell membrane, generating high signal intensity in atherosclerosis plaques to be detectable with PET. Furthermore, consider-



ing that CXCR4 is expressed only in the spleen, adrenal glands, and bone marrow, it generates a low background signal adjacent to the arterial wall. It does not require the patient to fast, as is the case for  $^{18}\text{F}$ -FDG. Moreover, it can be easily radiolabeled with the generator nuclide  $^{68}\text{Ga}$  and does not require an on-site cyclotron.<sup>[19]</sup> However, the value of  $^{68}\text{Ga}$ -pentixafor PET imaging for atherosclerosis cannot be assessed yet because of the small number of patients examined.

### $^{68}\text{Ga}$ -DOTATATE SST2-binding for Imaging Atherosclerotic Inflammation

$^{68}\text{Ga}$ -DOTATATE (1,4,7,10-tetraazacyclododecane- $\text{N,N',N'',N''}'$ -tetraacetic acid-D-Phe1, Tyr3-octreotate) is widely used for molecular imaging of neuroendocrine tumors where somatostatin receptor, mainly somatostatin receptor-2 (SST2), are generally overexpressed.<sup>[21,22]</sup> It also binds to SST2 expressed exclusively by proinflammatory M1 macrophages in atherosclerosis. Tarkin, *et al.*<sup>[23]</sup> validate  $^{68}\text{Ga}$ -DOTATATE as a marker for atherosclerotic inflammation. They showed it can differentiate culprit from non-culprit lesions, both on coronary and carotid arteries, in groups of patients with previous acute coronary syndrome and cerebrovascular accident, respectively. Although atherosclerosis plaque inflammation and consequently the risk of plaque rupture can be estimated using  $^{18}\text{F}$ -FDG, it does not show a good cell specificity, and above all, coronary imaging is not assessable because of the myocardial background. It becomes clear that  $^{68}\text{Ga}$ -DOTATATE has superior coronary imaging, excellent macrophage specificity, and it is capable of discriminating high-risk versus low-risk plaques.<sup>[23]</sup> However, it produces many image artefacts due to cardiorespiratory motion that are accentuated by the high positron energy of  $^{68}\text{Ga}$ . To now, a very low number of patients have been imaged with  $^{68}\text{Ga}$ -DOTATATE for atherosclerosis inflammation, so further researches are needed to explore the utility of  $^{68}\text{Ga}$ -DOTATATE PET imaging in inflammatory cardiovascular diseases.<sup>[23]</sup>

### $^{18}\text{F}$ -NaF

$^{18}\text{F}$ -NaF has been used for long as bone tracer to detect conditions associated with high bone turnover and new bone formation.<sup>[24,25]</sup> Its uptake mechanism

in bones is well known.  $^{18}\text{F}$ -NaF diffuses via the capillary system into the bone extracellular liquid, and then it exchanges with hydroxyl groups on exposed regions of hydroxyapatite crystals on the bone surface to form fluorapatite.<sup>[26]</sup> The intensity of the PET signal depends mainly on the bone blood flow and the surface area of exposed hydroxyapatite.<sup>[26]</sup> More recently, the use of  $^{18}\text{F}$ -NaF has been explored for cardiovascular imaging applications. As for bone tissue,  $^{18}\text{F}$ -NaF binds to calcified tissue within the heart. Here, the blood flow is generally constant, making the uptake of  $^{18}\text{F}$ -NaF dependent only on the surface area of hydroxyapatite.<sup>[24,26,27]</sup> Furthermore,  $^{18}\text{F}$ -NaF also demonstrates very low uptake in the myocardium, which is a crucial feature to enable good visualization of regions of increased  $^{18}\text{F}$ -NaF uptake in areas of active calcification in the heart.<sup>[28]</sup> Dweck, *et al.*<sup>[29]</sup> were the first to study the feasibility of using  $^{18}\text{F}$ -NaF PET-TC to assess coronary artery plaque biology. Their study showed how  $^{18}\text{F}$ -NaF uptake could discriminate between patients with active and inactive coronary calcification exploiting the spatial resolution of PET/CT that allows localization of the  $^{18}\text{F}$ -NaF signal to specific coronary territories and plaques, offering the possibility of identifying vulnerable or culprit plaque. This information is of critical relevance, correlating with higher rates of anginal symptoms, prior major adverse cardiovascular events, and cardiovascular risk factor scores observed in active disease patients.<sup>[29]</sup>  $^{18}\text{F}$ -NaF PET in combination with either computed tomography or magnetic resonance can also be used to evaluate calcification and microcalcification activity to investigate a wide range of cardiovascular diseases, both valvular conditions such as aortic stenosis, mitral annular calcification and bioprosthetic valve disease, as well as vascular conditions, including abdominal aortic aneurysm disease, carotid atherosclerosis, peripheral vascular disease, and erectile dysfunction.<sup>[30]</sup>  $^{18}\text{F}$ -NaF PET represents a marker of calcification activity across a range of cardiovascular diseases and could be helpful in the prediction of disease progression and clinical events. Anyway, further work is required to demonstrate this imaging technique's incremental clinical utility and justify its relatively



high costs.  $^{18}\text{F}$ -NaF has also been investigated to study cardiac amyloidosis, but this will be discussed in the following sections.

## FIBROSIS TRACERS

Myocardial fibrosis represents the last stage of cardiovascular diseases and exhibits cardiac fibroblast activation, which releases fibrillary collagen and remodels the extracellular matrix. An ischemic injury triggers reparative fibrosis, which initiates scar formation to stabilize the infarcted area.<sup>[31]</sup> Many different inputs trigger fibrosis as myocyte death, a mechanical stimulus such as pressure or volume overload, or neurohormonal activation.<sup>[32]</sup> Also, the prolonged duration of the pathological processes supports progressive fibrogenesis over time.<sup>[33]</sup> Echocardiography and MRI are two primary imaging modalities to non-invasively characterize fibrosis by estimating ventricle stiffness and filling and characterizing tissue differences.<sup>[34,35]</sup> Unfortunately, they only target the late stages of the disease when the process is irreversible. Therefore, new biomarkers of fibroblast activation at the early stages of the disease are needed. Activated myofibroblasts highly release fibroblast activation protein (FAP) in response to ischemic and non-ischemic injury.<sup>[12]</sup> Thanks to these features, FAP-targeted cardiac imaging has gained increasing attention.

### $^{68}\text{Ga}$ -FAPi for Fibroblasts Activation

Radiolabeled FAP inhibitors (FAPi) for non-invasive imaging of FAP expression<sup>[36,37]</sup> recently led to  $^{68}\text{Ga}$ -FAPi development. FAPi binds to the FAP, a serine protease expressed explicitly by activated fibroblasts during wound healing.<sup>[38]</sup> A high level of FAP in myofibroblasts has been reported in infarcted rat hearts and human hearts<sup>[39]</sup> and more generally in different fibrotic processes like liver cirrhosis and fibrosis.<sup>[40]</sup> Varasteh, *et al.*<sup>[41]</sup> non-invasively image activated fibroblasts using PET/CT and PET/MRI with  $^{68}\text{Ga}$ -FAPi to investigate ventricular remodeling after MI in rats. The Authors also evaluate the grade of fibroblast activation at different time points from MI. Furthermore, while MRI late gadolinium enhancement identifies just the presence of fibrous tissue at its final stage, through  $^{68}\text{Ga}$ -FAPi, evaluating and monitoring fibroblast activa-

tion and formation is possible. This is theoretically feasible for all cardiologic conditions associated with fibroblast activation.<sup>[41,42]</sup> Some authors studied cardiac FAPi uptake in cancer patients, trying to assess localized and generalized myocardial injury in oncologic patients. They imaged fibroblast activity via  $^{68}\text{Ga}$ -FAPi PET, demonstrating that it is well correlated with coronary atherosclerosis, MI, age, and especially left ventricular ejection fraction, thus highlighting the potential of this technique to better understand cardiac remodeling.<sup>[43]</sup> For the reasons above,  $^{68}\text{Ga}$ -FAPi is a promising radiotracer to study and monitor tissue alterations such as fibrosis formation and remodeling that generally led to heart failure, the last stage of any cardiac physiopathological processes, including chemo- or radiation therapy toxicity.<sup>[44]</sup> Early detection of myocardial remodeling and fibrosis may be critical to prevent the development of heart failure and to guide therapy. Compared to FDG,  $^{68}\text{Ga}$ -FAPi presents a more specific signal with a very low background in organs adjacent to the heart, low nanomolar affinity, an almost complete internalization and rapid clearance.<sup>[36]</sup> However, these studies cannot demonstrate that FAPi accumulation is specific for FAP expression or myofibroblast activation because there is no histopathological validation. Further research is needed to link myocardial  $^{68}\text{Ga}$ -FAPi uptake to myocardial fibroblast activation and to risk-stratify patients for progression of left ventricular remodeling and heart failure.

## INNERVATION TRACERS

The sympathetic nervous system is the main control system of heart rate and contractility. It has a high sensitivity to ischemia which can determine cardiac dysinnervation, generating a substrate of ventricular arrhythmia and sudden cardiac arrest.<sup>[45,46]</sup> Imaging of the cardiac sympathetic nervous system has been pursued over the last decades, but with poor impact on clinical routine. Newer radiotracers with better labelling and kinetics and binding new targets such as angiotensin II type 1 and cannabinoid type 1 receptors have been proposed.<sup>[47,48]</sup>

### $^{11}\text{C}$ -KR31173 for AT<sub>1</sub>R and $^{11}\text{C}$ -OMAR for CB<sub>1</sub>-R

$^{11}\text{C}$ -KR31173 is a selective AT<sub>1</sub>R antagonist ra-





diolabeled with  $^{11}\text{C}$  for PET imaging to non-invasively visualize AT1R upregulation in different cardiac pathophysiological processes.<sup>[48]</sup> At the heart level, renin-angiotensin system activation determines inflammation, fibrosis and apoptosis through AT1R,<sup>[49]</sup> and its disproportionate activation may contribute to tissue remodeling.<sup>[48,50]</sup>  $^{11}\text{C}$ -OMAR is a radioligand that selectively bind to CB1-R that is already used for PET in patients with schizophrenia.<sup>[51]</sup> Fukushima, *et al.*<sup>[52]</sup> explored the feasibility of imaging cardiac AT1R, using PET/CT in combination with using  $^{11}\text{C}$ -KR31173. They first experimented the radiotracer on healthy farm pigs and after induced MI. Then the group evaluate this biomarker in four healthy men, both baseline and under AT1R blocking; their first-in-man application was safe and showed detectable and specific myocardial  $^{11}\text{C}$ -KR31173 retention.<sup>[52]</sup> Recent studies have demonstrated the capability of  $^{11}\text{C}$ -OMAR or  $^{11}\text{C}$ -KR31173 and PET/CT to image and quantify myocardial CB1-R and/or AT1-R expression, respectively. As told before, these receptors seem to play a role in influencing ventricular remodeling process in heart failure.<sup>[53]</sup> After MI, they could evaluate the grade of upregulation and predict the risk for subsequent heart failure. Imaging myocardial AT1R could be convenient also in other condition as left ventricular hypertrophy and hypertension. And finally, molecular imaging could facilitate and improve targeted therapy, adapting drug dosage on the basis of myocardial CB1-R and/or AT1-R expressions as determined with PET/CT.<sup>[48,53]</sup> However,  $^{11}\text{C}$ -KR31173 uptake signal cannot differentiate between myofibroblasts and cardiomyocytes, so the precise contributions of these cell lines to signal formation in the infarcted areas remain to be explored.<sup>[48,54]</sup>  $^{11}\text{C}$ -OMAR lipophilicity determines high background in adjacent organ and could compromise myocardial analysis. This limitation calls for the development of less lipophilic CB1-R radiotracer ligand.<sup>[55]</sup> Further evaluation of the feasibility and practicability of this PET imaging approach in different forms of heart failure development is warranted.

### $^{11}\text{C}$ -meta-hydroxyephedrine

$^{11}\text{C}$ -meta-hydroxyephedrine is an ephedrine analogue radiotracer that binds to sympathetic nerve terminals with a similar metabolic profile to nore-

pinephrine. It is transported to the pre-synapsis via the uptake-1 mechanism and is resistant to MAO and COMT metabolism. Its retention in the myocardium mainly reflects a continuing release and reuptake, which allows the quantification of retention fraction in myocardial tissue.<sup>[56]</sup> Harms, *et al.*<sup>[57]</sup> have explored the possibility of measuring myocardial blood flow and myocardial innervation via single PET scan using 15O-water and  $^{11}\text{C}$ -meta-hydroxyephedrine to eventually assess myocardial perfusion-innervation mismatches that represent the substrate of ventricular arrhythmias and consequently of sudden cardiac arrest.<sup>[46]</sup> Furthermore, Werner, *et al.*<sup>[58]</sup> used  $^{11}\text{C}$ -HED PET imaging to estimate the effects of ageing on cardiac innervation in rats. They observed a dose-dependent reduction of cardiac  $^{11}\text{C}$ -HED uptake at different ages points, underlying potential correlation between age and damage to sympathetic innervation.<sup>[58]</sup> Another group<sup>[59]</sup> evaluated sympathetic abnormalities in Brugada syndrome through  $^{11}\text{C}$ -HED PET, finding out an increased presynaptic norepinephrine recycling with average adrenoceptor density, suggesting the hypothesis of autonomic dysfunction in Brugada syndrome. Through PET  $^{11}\text{C}$ -HED, Schafers, *et al.*<sup>[60]</sup> observed that both myocardial catecholamine reuptake and beta-adrenoceptor density were abnormally reduced in idiopathic right ventricular output tachyarrhythmia suggesting a new pathophysiological process. Also, in long QT patients, PET imaging studies have shown a heterogeneous and decreased cardiac retention of  $^{11}\text{C}$ -HED at left ventricular walls. They stated that the number of heterogeneous sectors could play a role in stratifying the severity of the disease.<sup>[61]</sup> All these studies represent a step toward understanding the pathophysiology of these diseases. In this setting,  $^{11}\text{C}$ -HED PET imaging could play a role in establishing the diagnosis, risk stratification and therapeutic strategies. However, because it needs an on-site cyclotron and  $^{11}\text{C}$  has a very short half-life, the use in clinical routine is challenging, and further studies are needed.

### LMI1195

Heart failure represents the last stage of many cardiac diseases, and it is associated with many molecular abnormalities, among which increased nore-



pinephrine release and impaired cardiac neuronal norepinephrine transporter (NET) function play a fundamental role.<sup>[62]</sup> False radiolabeled neurotransmitters such as <sup>11</sup>C-HED and <sup>123</sup>I-meta-iodobenzylguanidine (MIBG) are substrates for the NET and are currently used for cardiac imaging of the sympathetic neuronal function.<sup>[63]</sup> LMI1195 (*N*-[3-Bromo-4-(3- [18F]fluoro-propoxy)-benzyl]-guanidine) is a new radiolabeled tracer that was designed like <sup>123</sup>I-MIBG as a benzylguanidine-based false neurotransmitter for the NET but labelled with <sup>18</sup>F. Yu, *et al.*<sup>[64]</sup> studied LMI1195 as a novel <sup>18</sup>F imaging agent for a better evaluation of the cardiac sympathetic neuronal function by PET imaging *in vitro* and *in vivo* in animals compared to MIBG and <sup>11</sup>C-HED. They found out that LMI1195 grants a better resolution and good attenuation correction than <sup>123</sup>I-MIBG. Also, MIBG liver accumulation is high and can interfere with cardiac visibility, while LMI1195 has an optimal background activity. Many of these advantages are also seen with the NET substrates labelled with <sup>11</sup>C, but a longer half-life of LMI1195 could grant a wider clinical application.<sup>[64]</sup> Sinusas, *et al.*<sup>[65]</sup> designed the first study to evaluate the feasibility of using LMI1195 for PET imaging in humans, establishing the normal quantitative regional myocardial uptake of LMI1195. So, LMI1195 provides a potentially quantitative approach for evaluating both regional denervation and the heterogeneity of innervation, features that could be predictive of sudden cardiac death. In this study, LMI1195 was well tolerated by patients with a radiation dose comparable to that of other commonly used PET radiotracers.<sup>[65]</sup> However, to define the true advantage of LMI1195 imaging over currently used radiotracers, additional comparison studies are required.

## MITOCHONDRIAL MEMBRANE POTENTIAL ( $\Delta\Psi_m$ ) TRACERS

Mitochondria are responsible for the production of approximately 90% of cellular adenosine triphosphate (ATP) through oxidative phosphorylation.<sup>[66]</sup> The electron transport chain (ETC) of the mitochondrion converts supplied nutrients into energy; in this context, the mitochondrial membrane potential ( $\Delta\Psi_m$ ) is needed for the conversion of adenosine diphosphate (ADP) to ATP. The  $\Delta\Psi_m$  is typically

about  $-140$  mV and can vary among different cells types.<sup>[67]</sup> In healthy conditions, the  $\Delta\Psi_m$  is within the physiological range and a small amount of reactive oxygen species (ROS) is generated. In pathological mitochondrial dysfunction, a change in the  $\Delta\Psi_m$  results in the overproduction of ROS, which lowers the amount of ATP produced, and pathological conditions.<sup>[68]</sup> Since mitochondria are the most important source of energy and ROS for the cells, mitochondrial dysfunctions are associated to several diseases, including myopathies and cardiac arrhythmias.<sup>[69-71]</sup>

## <sup>18</sup>F-TPP+ for Mitochondrial Membrane Potential

Alpert, *et al.*<sup>[72]</sup> introduced a method to perform *in vivo* imaging with PET/CT to measure and map the total membrane potential ( $\Delta\Psi_T$ ) of cells, whereby  $\Delta\Psi_T$  is defined as the sum of  $\Delta\Psi_m$  and of cellular ( $\Delta\Psi_c$ ) electric potential. A cationic lipophilic tracer, TPP<sup>+</sup>, labeled with <sup>18</sup>F was used to quantitatively map myocardial  $\Delta\Psi_T$ . The Nernst equation was used to calculate the transmembrane electric potential from the radiotracer concentration measured by PET. This method was used for the quantitative mapping of  $\Delta\Psi_T$  of myocardial swine cells.<sup>[72]</sup> In a follow-up study, Pelletier-Galarneau, *et al.*<sup>[73]</sup> imaged 13 healthy subjects using <sup>18</sup>F-triphenylphosphonium (<sup>18</sup>F-TPP+) on a PET/MR scanner and confirmed the ability of this methodology to measure  $\Delta\Psi_T$  in humans.<sup>[73]</sup> Given the role of mitochondrial dysfunction in numerous pathologies, this imaging methodology has wide applicability. The possibility to quantify the membrane potential allows a direct comparison between subjects and is particularly relevant for the study of several pathologies such as diabetes and chemotherapy-induced cardiotoxicity, which are typically associated with diffuse myocardial involvement. Furthermore, measuring  $\Delta\Psi_T$  could inform the progress of clinical trials involving the use of mitochondria-targeting therapeutics and assess the response to therapy. The method can be easily applied to image other organs and tissues and could be used for tumor characterization.<sup>[74]</sup>

## AMYLOIDOSIS TRACERS

Amyloidosis is a group of protein-folding disorders that cause organs infiltration by deposits res-



ulting from misfolded precursor protein, with characteristic histopathological features of apple-green birefringence with polarized light on Congo red staining, that lead to organ damage.<sup>[75]</sup> Cardiac amyloidosis is most commonly secondary to the accumulation of amyloid fibrils derived from immunoglobulin light chains (AL) which is often associated with extra-cardiac manifestations and multi-organ involvement. More recently, transthyretin amyloidosis (ATTR) has been identified as an important cause of cardiac amyloidosis subdivided into senile cardiac amyloidosis, due to amyloid fibrils composed of wild-type non-mutant transthyretin (ATTRwt), and hereditary forms caused by gene mutations in the transthyretin.<sup>[76]</sup> The gold standard for diagnosis of cardiac amyloidosis is endomyocardial biopsy but cardiac imaging techniques can non-invasively detect amyloid with high sensibility. Thioflavin-analogue based tracers such as <sup>18</sup>F-florbetapir, <sup>18</sup>F-florbetaben, <sup>18</sup>F-flutemetamol, and <sup>11</sup>C-labeled Pittsburg Compound-B (PiB) could enhance amyloid deposition in the heart targeting the beta-pleated motif of the amyloid fibril due to their similarity to the thioflavin structure.<sup>[77]</sup>

### <sup>11</sup>C-labeled Pittsburg Compound-B (PiB)

<sup>11</sup>C-PiB is a widely studied brain radiotracer that was designed by modifying the amyloid-binding site, thioflavin-T.<sup>[78]</sup> Antoni, *et al.*<sup>[79]</sup> first found out that there was high <sup>11</sup>C-PiB uptake values in the heart of amyloidosis patients, but no uptake was present in their control group. This finding was successively confirmed by another group in a study on patients with monoclonal gammopathy and suspected cardiac amyloidosis where <sup>11</sup>C-PiB PET/CT uptake was highlightable in the majority of the patients with positive biopsy, while it was absent in the negative ones.<sup>[80]</sup> Furthermore, Pilebro, *et al.*<sup>[81]</sup> stated that <sup>11</sup>C-PiB is a sensitive method for detecting ATTR amyloid through its greater binding affinity with fibril type B. Considering that ATTR amyloidosis generally has a late onset, it could represent a sensitive biomarker for its early diagnosis.<sup>[81]</sup> However, <sup>11</sup>C-PiB has some disadvantages: it needs an on-site cyclotron and, as told in previous section <sup>11</sup>C has a very short half-life, making challenging its use in clinical practice.<sup>[77]</sup> These data suggests that <sup>11</sup>C-PiB may be a sensitive tracer for diagnosis CA

but further studies are needed for its application in clinical routine.

### <sup>18</sup>F-Florbetapir

<sup>18</sup>F-florbetapir has a different structure from <sup>11</sup>C-PiB, since it is composed by a styrylpyridine radiolabeled with <sup>18</sup>F.<sup>[82]</sup> Some authors studied the feasibility of <sup>18</sup>F-florbetapir for imaging in CA and tried to understand if its myocardial uptake could differentiate AL from ATTR CA but without reaching any clear conclusion.<sup>[83]</sup> The same group also analyzed endomyocardial biopsy specimens with autopsy-positive AL and ATTR using <sup>18</sup>F-florbetapir and digital autoradiography, demonstrating high affinity of the tracer to myocardial amyloid fibers, particularly in those with AL amyloid, suggesting a difference in concentration of available binding sites AL and ATTR.<sup>[84]</sup> Since there are no modalities to identify multi-organ involvement in AL amyloidosis accurately, recent researches suggest that <sup>18</sup>F-florbetapir could be useful to evaluate fibril deposition in systemic AL amyloidosis, even in patients where there is no clinical appearance of organ involvement. It may also be helpful to monitor organ response to therapies.<sup>[85]</sup>

### <sup>18</sup>F-Florbetaben

Florbetaben is a stilbene derivative that shares similar structural features to PiB but radiolabeled with <sup>18</sup>F. In cardiac amyloidosis, Law, *et al.*<sup>[86]</sup> were the first to evaluate Florbetaben in cardiac amyloidosis and to understand that it does not differentiate between AL and ATTR. However they show a correlation between radiotracer retention and contractile function via an inverse curve relationship, suggesting it may play a role in monitoring the severity of disease and response to therapies.<sup>[86]</sup> More recently, another study<sup>[87]</sup> evaluated <sup>18</sup>F-florbetaben via PET/CT highlighting different retention patterns for any amyloid subtypes. At this point, data are controversial and so further studies are needed to understand if <sup>18</sup>F-florbetaben could be helpful in differentiating among CA subtypes and for establish severity of disease. Thus, PET amyloid radiotracers are promising; however, more data is needed to define their accuracy and added value in quantification and therapy monitoring in patients with cardiac amyloidosis.



## <sup>18</sup>F-NaF

As stated above, <sup>18</sup>F-NaF has been traditionally employed as a bone tracer and it is currently under investigation for cardiovascular diseases. In the context of amyloidosis, it has been postulated that ATTR fibrils have high calcium content and can interact with calcium-sensitive probes such as <sup>18</sup>F-NaF. The use of <sup>18</sup>F-NaF allows the detection of cardiac amyloidosis and treatment monitoring; furthermore, <sup>18</sup>F-NaF is more readily available than other F-labeled tracers. However, the ability of this tracer to discriminate between mutant ATTR and AL is still unclear, as highlighted by two European case reports.<sup>[88,89]</sup> More recently, the use of <sup>18</sup>F-NaF in patients with AL and ATTR CA was evaluated by using qualitative and quantitative analysis with average left ventricular standardized uptake value (SUV) and target to background ratio (TBR). The authors found that the TBR was significantly higher in patients with ATTR compared with AL patients and healthy controls.<sup>[90]</sup> However, more studies are necessary to benchmark <sup>18</sup>F-NaF against <sup>99m</sup>Tc-PYP, which is bone tracer currently used in the clinical practice.

## CONCLUSIONS

The recent advancements in radiotracers development for specific targets in cardiovascular imaging confirm that the way forward for a personalized medicine is just at beginning of the race.

## DISCLOSURES

None.

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