



Molecular Imaging of Heart Failure: An Update and Future Trends

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Molecular imaging can detect and quantify pathophysiological processes underlying heart failure, complementing evaluation of cardiac structure and function with other imaging modalities. Targeted tracers have enabled assessment of various cellular and subcellular mechanisms of heart failure aiming for improved phenotyping, risk stratification, and personalized therapy. This review outlines the current status of molecular imaging in heart failure, accompanied with discussion on novel developments. The focus is on radionuclide methods with data from clinical studies. Imaging of myocardial metabolism can identify left ventricle dysfunction caused by myocardial ischemia that may be reversible after revascularization in the presence of viable myocardium. In vivo imaging of active inflammation and amyloid deposition have an established role in the detection of cardiac sarcoidosis and transthyretin amyloidosis. Innervation imaging has well documented prognostic value in predicting heart failure progression and arrhythmias. Tracers specific for inflammation, angiogenesis and myocardial fibrotic activity are in earlier stages of development, but have demonstrated potential value in early characterization of the response to myocardial injury and prediction of cardiac function over time. Early detection of disease activity is a key for transition from medical treatment of clinically overt heart failure towards a personalized approach aimed at supporting repair and preventing progressive cardiac dysfunction. *Semin Nucl Med* 54:674-685 © 2024 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

Cardiac imaging is essential in establishing the diagnosis of heart failure, determining its mechanisms and prognosis, identifying the specific causes of cardiac dysfunction as well as planning and monitoring treatment.¹ Molecular imaging aims at the visualization, characterization, and quantification of biologic processes taking place at the cellular and subcellular levels within intact living subjects using specific probes.^{2,3} Thus, molecular imaging can provide information on pathophysiological processes underlying heart failure that complements assessment of cardiac structure and function with the use of other imaging modalities.^{2,3,4,5}

Nuclear imaging techniques, single-photon emission computed tomography (SPECT) and positron emission tomography (PET), allow for the detection of intravenously injected

radiopharmaceuticals in tissues with very high sensitivity.²⁻⁵ Molecule-targeted radiopharmaceuticals have enabled investigation of several biological processes involved in heart failure, including myocardial metabolism, innervation, inflammation, angiogenesis, amyloidosis, and fibrosis.^{3,4} Currently, molecular imaging is routinely performed for the clinical diagnosis of cardiac sarcoidosis, cardiac amyloidosis as well as device or prosthetic valve infections.^{6,7,8} However, several emerging radiotracers and applications are in earlier stages of preclinical and clinical development with potential for early detection, improved risk stratification, and guiding therapy in heart failure.^{2,3,4,5} This review provides an update on main applications of molecular imaging in heart failure together with discussion on recent developments and future trends.

Technical Aspects of Molecular Imaging

Development of new targeted tracers is central for advancing the role of molecular imaging in cardiovascular diseases.^{3,4}

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Comprehensive reviews on tracer development including tracers that are undergoing preclinical validation can be found elsewhere.^{3,4}

This review focuses on molecular imaging with SPECT and PET, because most of the clinical data on molecular imaging is based on these techniques. Both SPECT and PET scanners are often integrated with either computed tomography (CT) or magnetic resonance imaging (MRI) systems in hybrid devices. Hybrid devices and image processing techniques have facilitated fusion of nuclear images with high-resolution morphologic images of cardiac structure and function obtained with other imaging modalities.⁹ The use of state-of-the-art technology enables integration of CT and nuclear imaging with an acceptable radiation exposure to the patient.⁹

Cardiac PET is an advanced nuclear imaging technique with high-resolution, sensitivity and accurate quantification of radioactivity.¹⁰ Dynamic imaging enables measurements of radiotracer concentration and kinetics in the myocardium over time, enabling absolute quantification of several parameters, such as myocardial blood flow and oxygen consumption.^{11,12} Recent advances in PET technology include introduction of PET scanners with long axial field of view that enable large anatomical coverage (whole-body PET) and increase in system sensitivity.^{13,14} High sensitivity of scanners and techniques for motion correction facilitate detection of signals coming from small targets and advanced modeling of tracer kinetics.^{14,15,16} The availability of PET has improved due to increase in the number of PET scanners and cyclotrons needed to produce tracers, as well as new radiotracers labeled with radionuclides with physical half-life long enough to allow for distribution to sites without a cyclotron.³

Recent advances in cardiac SPECT technology include developments in detector technology (solid-state detectors and cardio centric collimators), image reconstruction algorithms and dedicated cardiac scanner systems.¹⁷ As a result, image quality and spatial resolution have improved, acquisition times have shortened, and radiation exposure to the patient has reduced due to the need for less injected radioactivity.¹⁷ Studies using ¹²³I-metaiodobenzylguanidine (¹²³I-MIBG), targeting sympathetic nerve endings, have shown initial feasibility of the evaluation of tracer kinetics in dynamic three-dimensional SPECT studies.¹⁸ Furthermore, protocols using simultaneous acquisition of multiple tracers are feasible, potentially improving accuracy of cardiac molecular imaging with SPECT.¹⁹

Myocardial Viability

Ischemic heart disease is the most common cause of heart failure.¹ In ischemic heart failure, left ventricular dysfunction may be reversible and improve after myocardial revascularization.²⁰ Myocardial perfusion imaging is an established modality for the evaluation of the presence and severity of coronary artery disease (CAD).^{1,21} Furthermore, perfusion imaging combined with metabolic imaging can detect

ischemic myocardium that is dysfunctional, but viable and has potential for recovery of contractile function upon revascularization.²⁰

Evaluation of myocardial viability is partly based on uptake of myocardial perfusion tracers that is dependent on cell viability.²⁰ Furthermore, the assessment of residual myocardial glucose uptake with ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET, can reveal viable myocardium in areas of reduced perfusion.^{20,22} A preserved or increased uptake of ¹⁸F-FDG in the presence of reduced resting myocardial perfusion, known as flow-metabolism mismatch, is a hallmark of prolonged contractile dysfunction of severely ischemic myocardium called myocardial hibernation. The presence of myocardial hibernation shown by ¹⁸F-FDG PET had sensitivity of 92% and specificity of 63% for recovery of contractile function after revascularization in a pooled analysis of 24 studies with a total of 756 patients.²²

The value of viability imaging in guiding revascularization was evaluated in a meta-analysis, including 24 single-center observational studies with a total of 573 patients with CAD and left ventricular systolic dysfunction (mean ejection fraction 33%).²³ The meta-analysis showed that the presence of myocardial viability was associated with a significant benefit from myocardial revascularization annual mortality being 16% with conservative therapy and 3.2% with myocardial revascularization.²³ A more recent observational single-center study also found a significant interaction with the extent of hibernating myocardium and survival benefit from revascularization.²⁴ However, the randomized Positron Emission Tomography and Recovery Following Revascularization (PARR-2) trial that assigned 430 heart failure patients with an ejection fraction below 35% to either management assisted by ¹⁸F-FDG PET imaging or standard care, showed only a nonsignificant trend towards reduction in cardiac events for ¹⁸F-FDG PET assisted management versus standard care.²⁵ At long-term follow-up, benefit from the ¹⁸F-FDG PET assisted management was found only in the subgroup of patients whose treatment adhered to the recommendations based on flow-metabolism mismatch.²⁶ Similarly, randomized controlled trials comparing conservative treatment and revascularization, including Surgical Treatment for Ischemic Heart Failure (STICH), Revascularization for Ischemic Ventricular Dysfunction (REVIVED-BCIS2), and Heart Failure Revascularization Trial (HEART), have found that the presence myocardial viability evaluated with various imaging modalities did not appear to interact with treatment strategies in favorably affecting outcomes in ischemic heart failure.²⁷⁻³¹

Current guidelines recommend that myocardial revascularization may be considered in patients with chronic ischemic heart failure with reduced ejection fraction after careful evaluation of the individual risk to benefit ratio.¹ Although the evidence does not support routine testing of myocardial ischemia and viability in ischemic cardiomyopathy, it remains an option to predict the response to revascularization in selected patients with CAD, in whom increased perioperative risk and the absence of typical angina make decisions on revascularization difficult (Fig. 1).^{1,31,32}

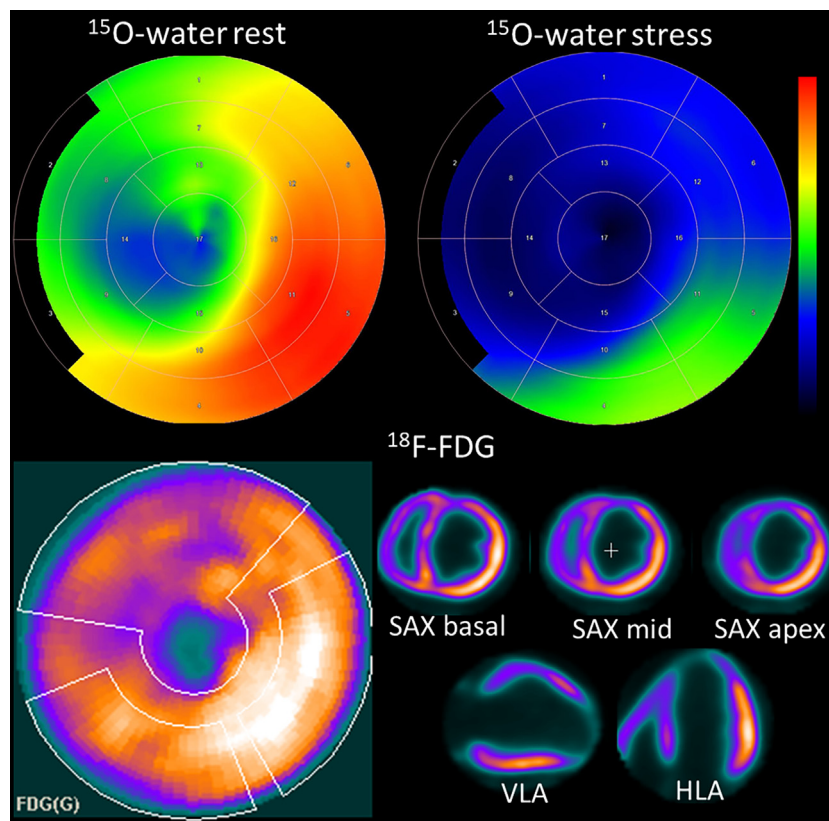


Figure 1 Evaluation of myocardial ischemia and viability in ischemic heart failure. The patient had 3-vessel obstructive coronary artery disease, severe wall motion abnormality in the territory of the left anterior descending (LAD) coronary artery, reduced left ventricular ejection fraction (35%), and high surgical risk due to comorbidities. ^{15}O -water PET showed globally reduced stress myocardial blood flow (scale is 0-3.5 mL/g/min). Resting myocardial blood flow (scale 0-1.0 mL/g/min) was also reduced in the LAD territory. ^{18}F -FDG PET showed the absence of glucose metabolism in the apex indicating scar, but partially preserved glucose metabolism elsewhere in the LAD territory indicating the presence of viable myocardium. The patient underwent successful coronary artery bypass surgery and ejection fraction was improved (45%) at follow-up. SAX, short axis; HLA, horizontal long axis; VLA, vertical long axis. Reproduced with permission from reference 5. (Color version of figure is available online.)

Advanced Metabolic Imaging

In order to analyze myocardial substrate metabolism, glucose uptake assessed with ^{18}F -FDG can be measured quantitatively and combined with PET tracers of fatty acid metabolism, such as palmitate analogue ^{18}F -fluoro-6-thiaheptadecanoic acid (^{18}F -FTHA) or carbon-11 labeled palmitate (^{11}C -palmitate),^{33,34} or a SPECT tracer β -methyl-p- ^{123}I -iodophenylpentadecanoic acid (BMIPP).³⁵ Furthermore, hyperpolarized MRI, based on amplification of the MRI signal from small molecules, has shown promise in informing about glucose metabolism by hyperpolarized [^{13}C] pyruvate.³⁶ Myocardial external efficiency describes the ability of myocardium to convert energy into external stroke work.¹² This can be evaluated noninvasively as the relation of left ventricular external work (product of mean arterial pressure and stroke volume) and myocardial oxygen uptake measured by carbon-11 labeled acetate (^{11}C -acetate) PET.^{12,37}

Studies using metabolic tracers have shown distinct alterations in myocardial substrate metabolism and myocardial external efficiency in heart failure that are related to

alterations in systemic metabolism, such as those that occur in obesity and diabetes.^{33,34} Reduced myocardial external efficiency is a typical feature of heart failure, where oxygen consumption is increased in relation to the amount of external work.³⁸⁻⁴⁰ In addition to heart failure with reduced ejection fraction, myocardial external efficiency may be reduced in the presence of preserved ejection fraction, for example in patients with hypertrophic cardiomyopathy,⁴¹ cardiac amyloidosis,⁴² and severe valvular heart disease.^{40,43} In addition to contractile function, increased afterload, activation of the sympathetic nervous system, increased wall stress, and left ventricular hypertrophy may contribute to reduced efficiency depending on etiology and stage of the disease.^{12,40,43,44}

It has been hypothesized that impaired myocardial energetics is a contributing factor to the progression of heart failure and thus, myocardial external efficiency can be a useful surrogate marker for heart failure trials.^{12,33,34,45} In a small study, impaired myocardial efficiency was a stronger predictor of survival than ejection fraction in patients with dilated cardiomyopathy.⁴⁶ Furthermore, impaired myocardial efficiency

has been associated with reduced exercise capacity and severity of heart failure symptoms.^{39,30,42} However, it remains unknown to what extent reduced myocardial external efficiency represents a cause or sequence of cardiac dysfunction. Many therapies that have been proven beneficial in heart failure, such as beta-blockers, mineralocorticoids, and cardiac resynchronization, have been shown to improve myocardial efficiency.¹² However, in a recent short term study, sacubitril/valsartan therapy had no effect on myocardial oxygen consumption or efficiency as compared to valsartan alone, despite reducing afterload, myocardial perfusion and cardiac mechanical work.⁴⁵ Studies that have addressed the effect of substrate metabolism modulation have yielded mainly discouraging results in heart failure.³⁴ For example, acute fatty acid deprivation by blocking lipolysis in patients with idiopathic dilated cardiomyopathy, in contrast to healthy controls, led to reduced stroke volume, but not oxidative metabolism so that myocardial efficiency deteriorated further.⁴⁷

Inflammatory Cardiomyopathy and Cardiac Sarcoidosis

Cardiac sarcoidosis is a granulomatous inflammatory disease with unknown etiology, which can occur in the presence or absence of systemic sarcoidosis.⁴⁸ In a majority of patients, cardiac sarcoidosis appears to be a slowly progressive cardiomyopathy.⁴⁹ However, there is controversy regarding the more aggressive forms of cardiac sarcoidosis previously also called as giant cell myocarditis.⁵⁰ Ventricular arrhythmias and sudden cardiac death are common manifestations of cardiac sarcoidosis pointing to the need of early diagnosis and risk stratification.⁵¹

Diagnosis of cardiac sarcoidosis and stratifying the risk of ventricular arrhythmias is challenging.^{48,51} Endomyocardial biopsy has low sensitivity, because of the focal nature of the disease.⁴⁸ Advanced non-invasive cardiac imaging, including cardiac MRI and ¹⁸F-FDG PET, play an important role in detecting myocardial abnormalities in suspected cardiac sarcoidosis.⁶ Cardiac MRI provides high spatial resolution for

identifying the presence and extent of myocardial damage, whereas ¹⁸F-FDG PET is a marker of active myocardial inflammation and can also reveal extra-cardiac sarcoid lesions that may be targeted for histological diagnosis.^{6,52-54}

Active inflammation in cardiac sarcoidosis can be detected as focal myocardial uptake of ¹⁸F-FDG, reflecting the high metabolic activity of immune cells, after suppression of physiological myocardial glucose metabolism. In a meta-analysis of 26 studies (1363 patients, 528 with cardiac sarcoidosis), ¹⁸F-FDG PET had overall sensitivity and specificity of 82% and 82%, respectively, for cardiac sarcoidosis.⁵⁴ However, sensitivity was higher (94%) in studies that excluded patients who were already on anti-inflammatory therapy at the time of imaging.⁵⁴ Often ¹⁸F-FDG PET is combined with myocardial perfusion imaging, because resting perfusion abnormalities commonly coexist with inflammation in cardiac sarcoidosis. The prognostic implications of PET imaging were studied in a series of 118 patients with known or suspected cardiac sarcoidosis who underwent ⁸²Rb perfusion and ¹⁸F-FDG PET imaging.⁵⁵ Abnormal ¹⁸F-FDG uptake combined with reduced perfusion predicted 2.9-times increased risk of ventricular tachycardia and death during follow-up compared with normal PET results.⁵⁵

Patient preparation to suppress physiological glucose uptake is essential for the detection of cardiac inflammation by ¹⁸F-FDG PET, since both normal myocytes and immune cells take up glucose. Measures to suppress physiological myocyte ¹⁸F-FDG uptake include prolonged fasting combined with low-carbohydrate meals and/or intravenous heparin.⁵⁶ The success of these measures is variable, and incomplete suppression of physiological myocardial ¹⁸F-FDG uptake may significantly impair diagnostic accuracy of PET and in particular, monitoring disease activity in repeated studies.^{6,56} Therefore, new tracers have been sought to improve the accuracy of PET imaging in cardiac sarcoidosis. Small clinical studies and experimental studies have demonstrated promising results with ⁶⁸Ga-DOTANOC or ⁶⁸Ga-DOTATOC targeting somatostatin receptors on immune cells,^{57,58} radiolabeled amino acid ¹¹C-methionine PET,⁵⁹ radiolabeled cell proliferation marker ¹⁸F-fluorothymidine (FLT),^{60,61} and a tracer targeting folate receptor β expressed on activated macrophages (Fig. 2).⁶²

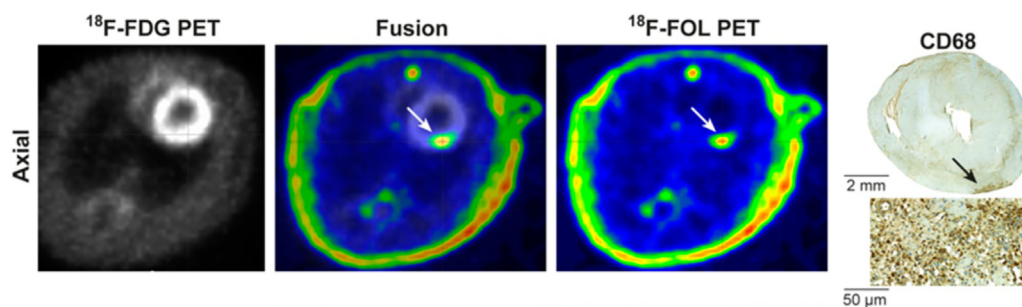


Figure 2 Folate receptor β -targeted imaging of macrophages in experimental autoimmune myocarditis. In vivo PET images with ¹⁸F-FDG and aluminum fluoride-18-labeled 1,4,7-triazacyclononane-N,N',N''-triacetic acid conjugated folate (¹⁸F-FOL) in a rat with autoimmune myocarditis. PET images show focal ¹⁸F-FOL uptake (white arrows) in the posterior left ventricle (LV) wall. Uptake is colocalized with macrophages stained with antibodies against CD68 in an inflamed myocardial lesion in the posterior wall of the LV. Uptake of ¹⁸F-FOL is low elsewhere in the LV myocardium. This research was originally published in Jahandideh et al. Folate Receptor β Targeted PET Imaging of Macrophages in Autoimmune Myocarditis. *J Nucl Med.* 2020;61:1643-1649. © SNMMI. (Color version of figure is available online.)

Cardiac Amyloidosis

Cardiac amyloidosis results from the myocardial extracellular deposition of misfolded proteins, known as amyloid fibrils, associated with left ventricular hypertrophy.⁷ Although a rare disease, recent data suggest that cardiac amyloidosis is underappreciated as an underlying mechanism of heart failure with preserved ejection fraction and left ventricular hypertrophy.⁷ The introduction of disease-modifying therapies for cardiac transthyretin amyloidosis (ATTR) that inhibit accumulation of misfolded proteins thereby preventing disease progression, has emphasized the need for an early diagnosis.^{7,63}

Bone avid SPECT radiotracers, ^{99m}Tc-pyrophosphate (PYP), ^{99m}Tc-3,3-diphosphono-1,2-propanodiacarboxylic acid (DPD), and ^{99m}Tc-hydroxymethylene diphosphonate (HMDP) as well as a PET tracer ¹⁸F-sodium fluoride bind to microcalcification associated with transthyretin fibrils.^{7,64-66} Uptake is analyzed semi-quantitatively or by visual grading, myocardial uptake of the tracer equal or higher than in the ribs (grades 2 and 3) indicating the presence of cardiac ATTR.^{64,65} A multicenter study of patients with suspected amyloid cardiomyopathy found that significant cardiac uptake of bone avid radiotracers is close to 100% sensitive for cardiac ATTR amyloidosis.⁶⁷ When light chain amyloidosis (AL) was excluded, specificity and positive predictive values were also close to 100%.⁶⁷ When cardiac amyloidosis is suggested clinically and supported by echocardiographic or cardiac MRI findings, current guidelines recommend SPECT bone scintigraphy for the diagnosis of ATTR.^{7,65}

Amyloid-targeted PET tracers are emerging in evaluation of cardiac amyloidosis. The ¹¹C-labeled Pittsburgh compound B (¹¹C-PIB),⁶⁸⁻⁷⁰ as well as the ¹⁸F-labeled alternatives florbetaben or florbetapir,^{71,72} bind to both transthyretin and light-chain amyloid and allow the detection of cardiac AL and ATTR. Amyloid-targeted PET provides quantitative measures of amyloid burden in the myocardium and other organs, potentially already in early stages of the disease.^{70,73} Semi-quantitative measures of cardiac uptake of bone avid radiotracers correlate with markers of disease severity and mortality.⁶⁵ However, quantitative measures of amyloid burden have been investigated to better stratify prognosis, assess subtle cardiac uptake possibly representing early stage of disease, and detect changes in amyloid burden in response to disease-modifying therapy.^{65,68} Small studies have found correlation between quantitative SPECT measures of PYP and DPD accumulation and surrogate markers of cardiac ATTR burden, including left ventricular mass and myocardial extracellular volume measured by cardiac MRI.^{74,75} The cardiac uptake of ¹¹C-PIB has been found to correlate with the degree of histological myocardial amyloid deposition⁷⁶ and independently predict outcome in cardiac AL amyloidosis.^{76,77}

Innervation Imaging

Radiotracers for noninvasive imaging of cardiac innervation have provided insights into pathophysiology of

myocardial disease and a noninvasive approach to risk-stratify patients with heart failure and at risk of arrhythmias.^{3,78} The most common approach to study cardiac innervation is by radiolabeled catecholamine analogues targeting presynaptic nerve terminals, including SPECT tracer ¹²³I-MIBG and PET tracer ¹¹C-metahydroxyephedrine (¹¹C-mHED).⁷⁸ In addition to ¹¹C-mHED, other ¹¹C labelled PET tracers, such as ¹¹C-epinephrine and ¹¹C-phenylephrine are available that differ from ¹¹C-mHED in their affinity to intra-neuronal vesicular storage and metabolism.^{79,80} Combination of tracers and pharmacologic challenge may provide mechanistic information about differential effects of disease on cellular catecholamine uptake, storage, and metabolism. In order to overcome limitations related to short physical half-life of ¹¹C, tracers labelled with ¹⁸F have been introduced in early clinical studies, including ¹⁸F-meta-fluorobenzylguanidine (¹⁸F-LMI1195), and ¹⁸F-fluorohydroxyphenethylguanidines.^{81,82}

In heart failure, the sympathetic nervous system is activated and there may be damage to presynaptic nerves.^{78,79} Studies have demonstrated that reduced cardiac uptake of ¹²³I-MIBG measured as myocardial activity relative to background mediastinal activity (heart-to-mediastinum H/M ratio) or myocardial washout is a marker of poor prognosis in heart failure.^{78,79} The prospective, multi-center trial AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF), which included 961 patients in New York Heart Association (NYHA) functional class II – III and ejection fraction $\leq 35\%$, showed that late H/M ratio < 1.6 was associated with an increased incidence of worsening NYHA class, life-threatening arrhythmias and cardiac death at the follow-up of 17 months.^{83,84} Incidence of cardiac death was 1% vs. 9.6% in patients with H/M ratio > 1.6 and < 1.2 , respectively. Regional heterogeneity of cardiac innervation has emerged as a risk marker for ventricular arrhythmias.⁷⁸ Studies suggest that the presence of regions of abnormal innervation with relatively preserved perfusion (innervation/perfusion mismatch), typically located adjacent to scarred regions, can represent a marker of arrhythmic susceptibility in patients with CAD.^{85,86} In the Prediction of Arrhythmic Events with Positron Emission Tomography (PAREPET) trial the extent of regional denervation assessed with quantitative ¹¹C-mHED PET was predictor of sudden cardiac arrest (arrhythmic death or intracardiac defibrillator shock) independently of ejection fraction, infarct size, symptoms, and natriuretic peptide level in CAD patients who were candidates for an implantable cardioverter defibrillator placement for primary prevention of sudden cardiac death.⁸⁷

Despite prognostic evidence of innervation imaging, in the absence of prospective evaluation of the prognostic impact of innervation imaging on clinical decision-making and patient management, it has not been incorporated in current clinical practice guidelines to risk stratify heart failure patients. Yet, it might be of value in specific patient groups, such as borderline risk for arrhythmias based on other investigations, as well as in guiding therapeutic interventions, such as catheter ablation of ventricular arrhythmias.⁷⁸

New Markers of Myocardial Injury and Fibrosis

Acute myocardial injury, such as myocardial infarction, initiates several maladaptive changes in cardiac myocytes and the extracellular matrix (ECM), which can contribute to progressive left ventricular dysfunction, adverse remodeling, and eventual failure.⁸⁸ Inflammation, fibrosis, and angiogenesis play a role in myocardial repair after acute myocardial injury. Healing of the infarcted myocardium is a tightly regulated process involving the pro-inflammatory phase (clearance of dead cells, from day 0 to day 4) and the reparative phase (resolution of inflammation, from day 4 to day 14), which results in maturation of a durable scar. However, excessive early inflammatory response and/or diffuse interstitial myocardial fibrosis are implicated in the pathogenesis of different forms of heart failure.^{88,89} New targeted tracers have been evaluated in experimental and translational clinical studies to evaluate the extent, time-course, and prognostic value of maladaptive and repair mechanisms in cardiac diseases (Fig. 3).

Myocardial inflammation following acute myocardial infarction has been studied with ¹⁸F-FDG⁹⁰ and tracers targeting chemokine receptors CXCR4^{91,92} and CCR2,^{93,94} somatostatin receptor subtype 2 (SSTR2),⁹⁵ the mitochondrial 18-kDa translocator protein TSPO,⁹⁶ amino acid methionine,⁹⁷ and other pro-inflammatory targets (Fig. 3).⁹⁸ These

studies have demonstrated increased tracer uptake in the infarcted region early after myocardial infarction, indicating the immune response to myocardial injury. While ¹⁸F-FDG and CXCR4-targeting PET tracers bind to a broad spectrum of activated inflammatory cells including monocytes, macrophages and neutrophils, it has been suggested that tracers targeting CCR2, SSTR2, and TSPO can selectively recognize pro-inflammatory monocytes and macrophages.⁹⁸ Of note, an excessive immune response, as indicated by imaging markers of early post-infarction inflammation, provides information about the risk of subsequent development of cardiac dysfunction, adverse remodeling and even patient outcome that may be incremental over standard markers of scar extent.^{90-92,95,96} Molecular imaging of the immune response to injury may even be used for guidance of targeted immunomodulatory drug intervention. In an experimental study, a CXCR4-targeted imaging signal was used to identify optimal timing and candidates for treatment with a CXCR4-blocking drug, which subsequently improved function only when PET indicated high expression of the CXCR4 target in myocardial tissue.⁹¹

As pro-inflammatory signaling is repressed, reparative mechanisms including activation of the pro-fibrotic signaling, angiogenesis, and ECM remodeling take over, which initially promote tissue repair (replacement fibrosis), but if dysregulated, may also contribute to excessive, reactive

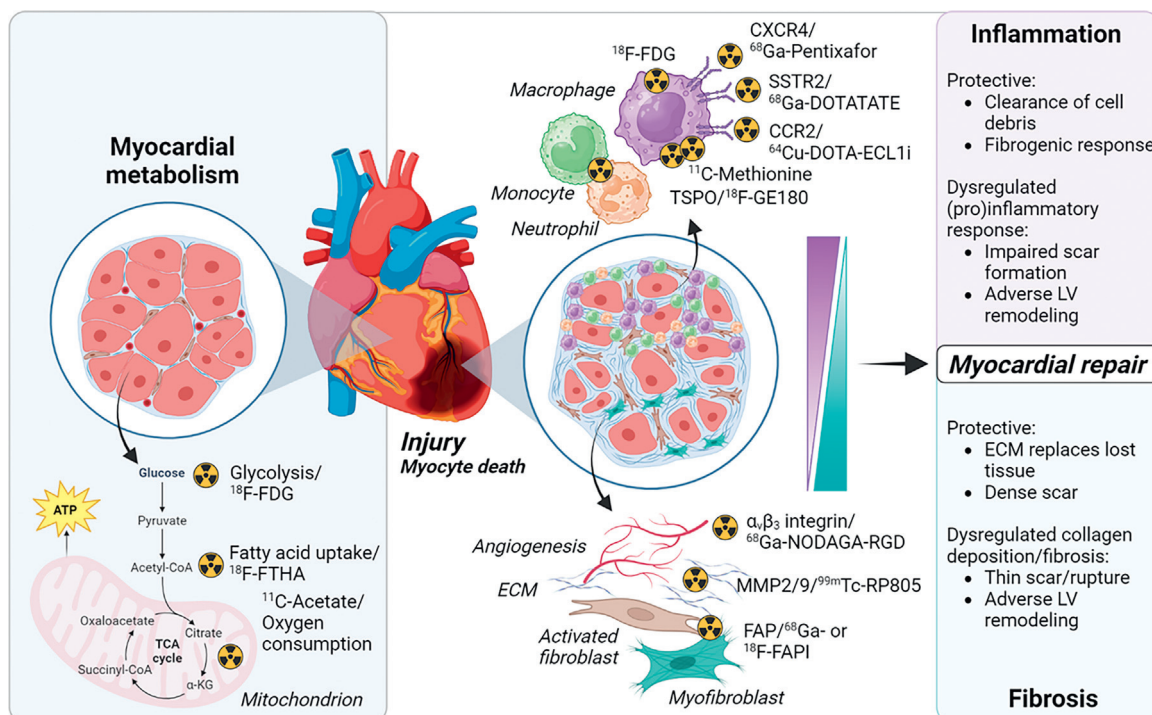


Figure 3 Schematic overview of targets and molecular imaging tracers that have been investigated for imaging of myocardial injury responses. Tracers of glucose, fatty acid and oxygen metabolism provide information of myocardial viability and metabolic responses. Tracers targeting activated immune cells (mostly macrophages) and fibrotic activity have been investigated in experimental and translational clinical studies to evaluate the extent, time-course, and prognostic value of maladaptive and repair mechanisms in cardiac diseases. CCR2, C-C motif chemokine receptor 2; CXCR4, C-X-C motif chemokine receptor 4; FAP fibroblast activation protein α ; ECM, extracellular matrix; LV, left ventricle; MMP2/9, matrix metalloproteinase 2/9; SSTR2, somatostatin receptor subtype 2; TSPO, 18 kDa mitochondrial translocator protein. (Color version of figure is available online.)

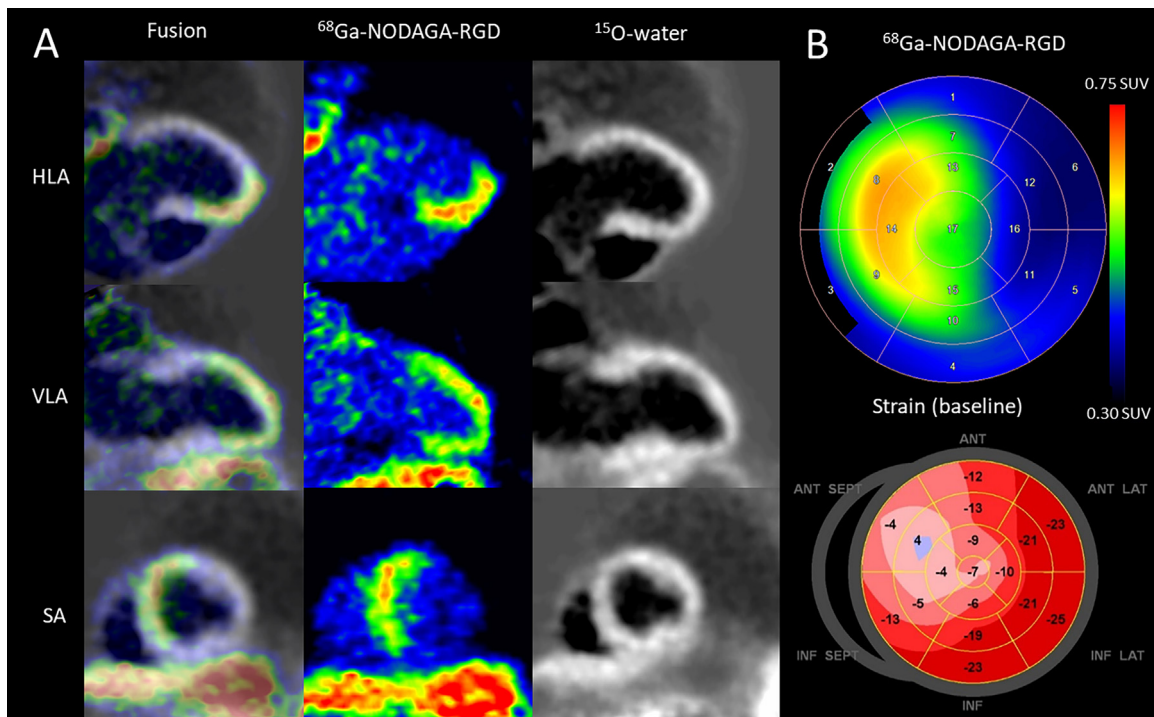


Figure 4 $\alpha_v\beta_3$ integrin -targeted imaging after acute myocardial infarction. Uptake of ^{68}Ga -NODAGA-RGD 7 days after acute occlusion of the proximal left anterior descending coronary artery. Panel A shows myocardial contours in [^{15}O] O-water images, ^{68}Ga -NODAGA-RGD uptake images, and corresponding fusion images. Panel B shows polar maps of ^{68}Ga -NODAGA-RGD uptake and longitudinal myocardial strain at the time of PET. Note the reduced longitudinal strain in the antero-septal region. HLA, horizontal long axis; SA, short axis; SUV, standardized uptake value; VLA, vertical long axis. This research was originally published in Nammias et al. Imaging of Myocardial $\alpha_v\beta_3$ Integrin Expression for Evaluation of Myocardial Injury after Acute Myocardial Infarction. *J Nucl Med* 2024;65:132-8. © SNMMI. (Color version of figure is available online.)

fibrosis implicated in adverse left ventricular remodeling.⁸⁸ The most extensively studied target in myocardial repair is a transmembrane glycoprotein receptor $\alpha_v\beta_3$ integrin. Early after acute myocardial infarction, expression of $\alpha_v\beta_3$ integrin is upregulated in proliferating vascular endothelial cells and can serve as a biomarker of angiogenesis.^{99,100} Studies in experimental models and humans have demonstrated the feasibility of using radiolabeled tracers containing the Arg-Gly-Asp (RGD) motif for the non-invasive detection of $\alpha_v\beta_3$ integrin expression after myocardial infarction (Fig. 4).¹⁰¹⁻¹⁰⁷ The uptake of RGD-based tracers is associated with neovascularization, hypoperfusion,^{102,105} myocardial injury,^{104,106} and the degree of global left ventricular dysfunction.¹⁰⁶ Furthermore, increased $\alpha_v\beta_3$ integrin expression after acute myocardial infarction predicts subsequent improvement of regional and global left ventricular function^{104,106} and the absence of adverse remodeling.^{107,108} Thus, molecular imaging of $\alpha_v\beta_3$ integrin expression may serve as a biomarker of myocardial injury responses early after myocardial infarction. However, its value as a marker of angiogenic therapies remains to be studied.

The presence, extent, and activity of fibrosis contribute to the development and progression of heart failure. Hence, reactive fibrosis has emerged as target for therapy, and thereby also for diagnostic imaging.¹⁰⁹ Current MRI methods, T1 mapping and late gadolinium enhancement, are

useful in identifying the presence and extent of myocardial fibrosis. However, novel molecular ligands, such as tracers targeting matrix metalloproteinases (MMPs),¹¹⁰ neurohormonal activation,¹¹¹ and fibroblast activation¹¹²⁻¹¹⁶ hold promise in providing information on fibroblast activation, myofibroblast transformation, and ongoing fibrotic activity (Fig. 3). Fibroblast activation protein α (FAP) is a membrane-bound serine protease specifically expressed on activated myofibroblasts, but not in resting fibroblasts. Thus, FAP serves as a marker of profibrotic activity and can be targeted by FAP inhibitor (FAPI) radiotracers for PET. In initial clinical studies, ^{68}Ga or ^{18}F labeled FAPI tracers showed strong signal early after acute myocardial infarction that exceeded the infarct zone indicating that FAP upregulation plays a role not only in replacement fibrosis in the primary injured region, but also in reactive fibrosis that may compromise non-infarcted myocardium (Fig. 5).^{112,113} Furthermore, studies utilizing hybrid PET/MRI devices, have found that the FAP signal is distinct from MRI tissue characterization and its extent correlates with contractile dysfunction at follow-up.^{113,114} Other studies have found evidence of FAP activation in non-ischemic cardiomyopathies.^{115,116} Activation of fibroblasts as well as inflammation represent early steps in the initiation of myocardial fibrosis and therefore, their imaging may provide an opportunity for an early intervention at a reversible stage before irreversible fibrosis.¹¹⁷ Of

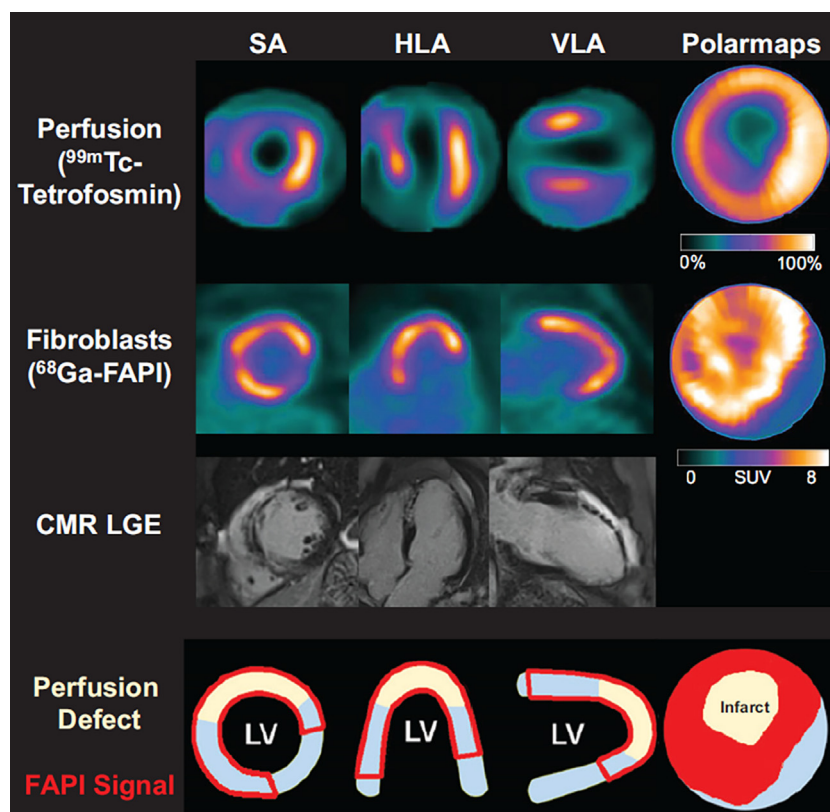


Figure 5 Myocardial perfusion images using ^{99m}Tc -tetrofosmin at rest, ^{68}Ga -FAPI PET, late gadolinium enhancement (LGE) from CMR, and schematic drawings of the left ventricle. Area of myofibroblast activation as indicated by ^{68}Ga -FAPI PET signal exceeds infarct area and LGE signal. HLA, horizontal long axis; SA, short axis; VLA, vertical long axis. This research was originally published in Diekmann et al. Cardiac Fibroblast Activation in Patients Early After Acute Myocardial Infarction: Integration with MR Tissue Characterization and Subsequent Functional Outcome. *J Nucl Med* 2022;63:1415-23. © SNMMI. (Color version of figure is available online.)

note, an experimental therapy based on targeting FAP expressing fibroblasts was able to reverse interstitial fibrosis in mouse model of heart failure.^{118,119} Such therapies may be guided by FAP-targeted PET or other imaging markers of fibrotic activity to identify optimal timing and candidates for therapy.

Multiorgan/Whole Body Imaging

The recent introduction of long axial field of view PET systems that enable simultaneous assessment of multiple organs throughout the entire human body provides new possibilities for studying systemic mechanisms, disorders or treatments and their interactions with the cardiovascular system.¹²⁰ Heart failure is associated with multiple comorbidities that involve interactions between function of the heart and other organ systems, such as the kidneys, endocrine organs, nervous system and hematopoietic organs.¹ Furthermore, medical therapy of heart failure involves modulation of such systems.¹

An example of the use of nuclear imaging in system-based cardiovascular medicine is studies that have characterized associations between inflammatory response in the

myocardium and systemic inflammatory networks, including the hematopoietic organs, kidneys and central nervous system.¹²¹ Bone marrow activation regulates hematopoietic stem cell proliferation and hence the systemic leukocyte pool, eventually contributing to accumulation of monocytes and neutrophils in acutely ischemic and the chronically failing ischemic myocardium.¹²¹ Studies have found that in response to myocardial infarction, uptake of PET tracers detecting inflammation increases in the bone marrow in parallel with inflammation in the infarcted myocardium.^{95,122} Similarly, in parallel with the detection of cardiac inflammation in response to myocardial injury, CXCR4 PET ligands and tracers targeting TSPO in immune cells have demonstrated inflammation in the kidneys¹²³ and the brain⁹⁶ in experimental models. Furthermore, a recent study found an inter-connection between stress-associated (amygdalar) activity, arterial wall inflammation, and hematopoietic activity in acute myocardial infarction by demonstrating enhanced ^{18}F -FDG uptake at baseline followed by concurrent dynamic changes over time.¹²⁴ In addition to inflammation, detection of active fibrosis for example by FAPI whole-body PET may provide opportunities to detect extracardiac injury associated with heart failure.

Summary and Future Directions

Nuclear imaging of myocardial perfusion and viability are established tools for the detection of ischemic etiology of heart failure and estimating benefit from revascularization. Advances in molecular imaging as well as other imaging modalities, emerging evidence questioning establishes approaches to diagnose and risk stratify CAD, and the emergence of targeted therapies that require imaging biomarkers for guidance with respect to identifying the right patients and timing have effects on the use of nuclear imaging in cardiac diseases. High sensitivity of nuclear imaging and development of new targeted tracers have enabled assessment of various cellular mechanisms of heart failure, such as inflammation, infiltration, innervation, metabolism, and fibrosis. Furthermore, recently introduced large field of view scanners provide improved evaluation of systemic distribution of tracers that may provide mechanistic information on systemic therapies that improve outcomes in cardiovascular diseases and heart failure, and simultaneously have beneficial effects on other organ systems.¹

Molecular imaging is used for the diagnostic evaluation of cardiac sarcoidosis and amyloidosis as underlying causes of heart failure. Innervation imaging has well documented potential to predict heart failure progression and risk of arrhythmias, but its specific role in patient management remains to be established and will depend on integration with guidance of therapies. New tracers, such as those specific for inflammation and detecting early activation of fibrotic processes have shown promise as biomarkers to assess functional outcomes after myocardial injury. Molecular imaging of early disease activity has potential to provide tools for transition from current practice of treating heart failure to a future of systems-based cardiovascular medicine aiming at prevention of heart failure and support of tissue repair. However, clinical implementation requires clear definition of the prognostic value of new imaging techniques beyond existing imaging techniques and demonstration of their ability to guide selection of therapies.

Disclosure

Authors acknowledge financial support by grants from the Research Council of Finland, the Finnish Foundation for Cardiovascular Research, the Sigrid Jusélius Foundation, and the State Research Funding of Turku University Hospital. Mia Stähle was supported by the European Atherosclerosis Society, Orion Research Foundation, and Turku Collegium for Science, Medicine and Technology, University of Turku. Antti Saraste discloses speaker or consultancy fees from Abbott, Astra Zeneca, BMS, Janssen, Novartis and Pfizer outside of the submitted work. Juhani Knuuti discloses consultancy fees from GE Healthcare and Synetkik and speaker fees from GE Healthcare, Bayer, Lundbeck, Boehringer-Ingelheim, Pfizer and Merck, outside of the submitted work.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRedit authorship contribution statement

Antti Saraste: Writing – original draft, Writing – review & editing. **Mia Stähle:** Writing – original draft, Writing – review & editing. **Anne Roivainen:** Writing – original draft, Writing – review & editing. **Juhani Knuuti:** Writing – original draft, Writing – review & editing.

Acknowledgments

The authors acknowledge financial support from the Research Council of Finland, Finnish Foundation for Cardiovascular Research, Sigrid Jusélius Foundation, and State Research Funding of Turku University Hospital. Figure 3 was created with BioRender.com.

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