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New Promising Targets for Imaging in Cardiovascular Diseases

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Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, driven by complex and dynamic molecular processes such as inflammation, fibrosis, metabolic dysregulation, thrombosis, and vascular remodeling. While conventional imaging techniques provide valuable anatomical and functional information, they fail to capture these underlying pathophysiological mechanisms at the molecular level. Molecular imaging, particularly with PET and SPECT, offers the potential to noninvasively visualize and quantify these processes, enabling earlier diagnosis, better risk stratification, and more precise treatment guidance. Despite substantial progress in clinical cardiology, there is a growing need for novel radiotracers that can target key disease-driving mechanisms beyond traditional perfusion or viability imaging. Emerging radiopharmaceuticals now enable the assessment of myocardial fibrosis (e.g., collagen-targeted and MMP-targeted tracers), cardiomyocyte stress responses (e.g., oxidative stress, unfolded protein response, endothelin signaling), and metabolic alterations (e.g., fatty acid, ketone, and glucose metabolism). Additionally, new tracers are being developed for thrombosis, vascular inflammation, plaque instability, and even for innovative targets such as cellular senescence and gut-derived inflammatory pathways. These developments reflect a paradigm shift towards imaging-driven phenotyping of cardiovascular disease. This review provides a comprehensive overview of the latest advances in molecular imaging tracers for cardiovascular applications, with a focus on their biological rationale, preclinical and clinical evidence, and translational challenges. We categorize tracers by their mechanistic targets and highlight their potential for integration into precision cardiology.

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Introduction

Molecular imaging has reshaped the landscape of cardiovascular diagnostics by enabling noninvasive visualization of pathophysiological processes at the cellular and subcellular level. Unlike traditional anatomical imaging techniques, such as echocardiography or computer tomography (CT), molecular imaging allows the assessment of dynamic biological phenomena such as inflammation, metabolic alterations, fibrosis, and apoptosis.[1] Positron emission tomography (PET) and single-photon emission tomography (SPECT) have become central to cardiovascular research and increasingly to clinical practice, driven by the development of specific radiotracers targeting key disease mechanisms.[2,3]

While [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) PET imaging has established its role in detecting inflammatory activity, it

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suffers from several limitations, including nonspecific uptake and high myocardial background signal.[4] Given the complexity of cardiovascular diseases, which involve diverse and often overlapping processes such as immune cell activation, fibrotic remodeling, endothelial dysfunction, and metabolic dysregulation,[5] there is the need for novel imaging targets that can more accurately capture the heterogeneity of these conditions.

This review focuses on recent advances in the identification and imaging of new molecular targets involved in the pathogenesis of cardiovascular disease (Fig. 1). We highlight emerging PET and SPECT radiotracers designed to evaluate pathophysiological processes, thus providing an updated perspective on how molecular imaging may refine disease stratification, guide targeted therapies, and improve prognostic evaluation in cardiovascular medicine.

Inflammation and Immune Activation

Activation of the immune system and local inflammation are hallmark features of cardiovascular diseases, spanning

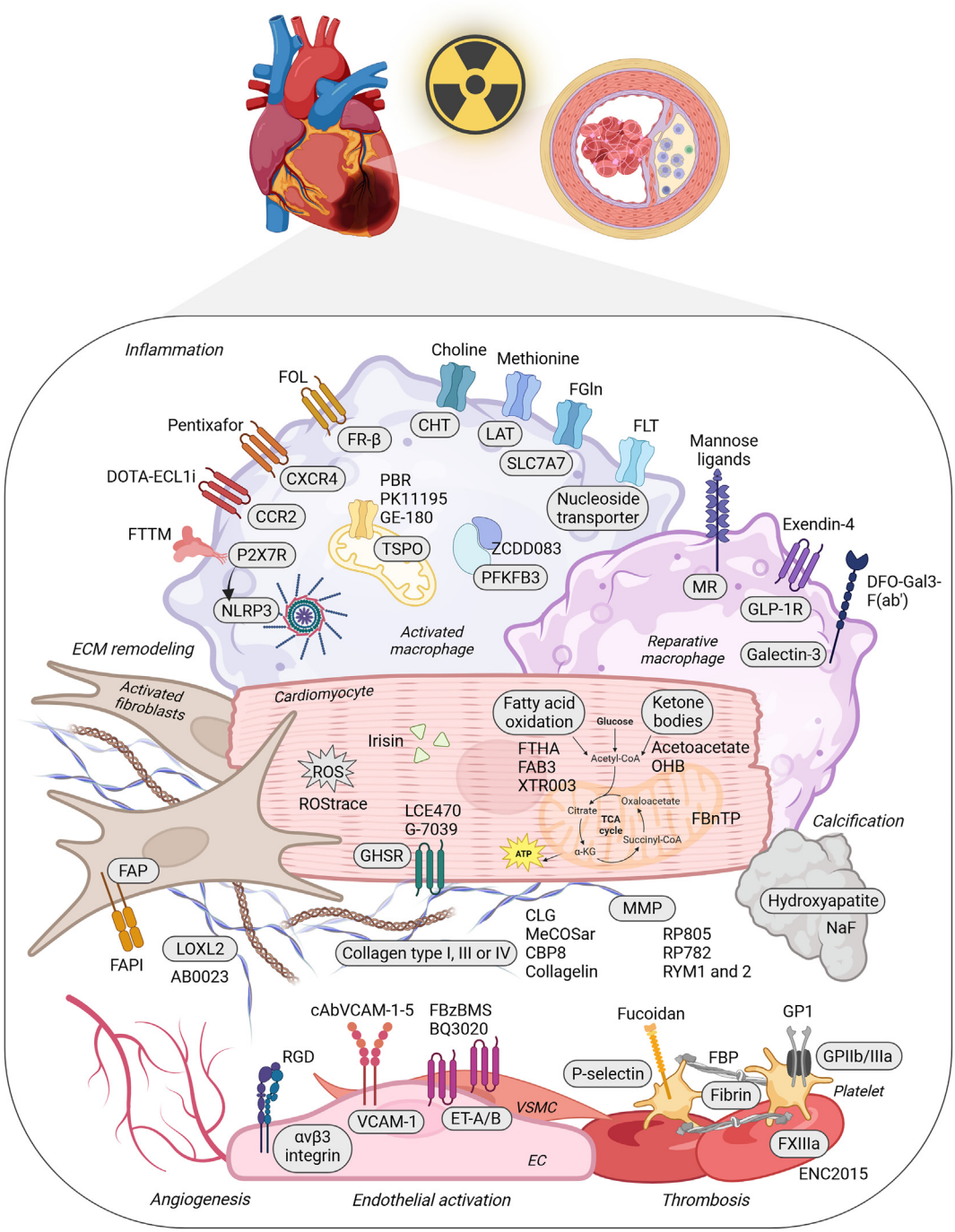

Figure 1 Representative image summarizing the many faces of possible targets in nuclear cardiology. Created with BioRender: Stahle M 2025. https://BioRender.com/ssfi6za.

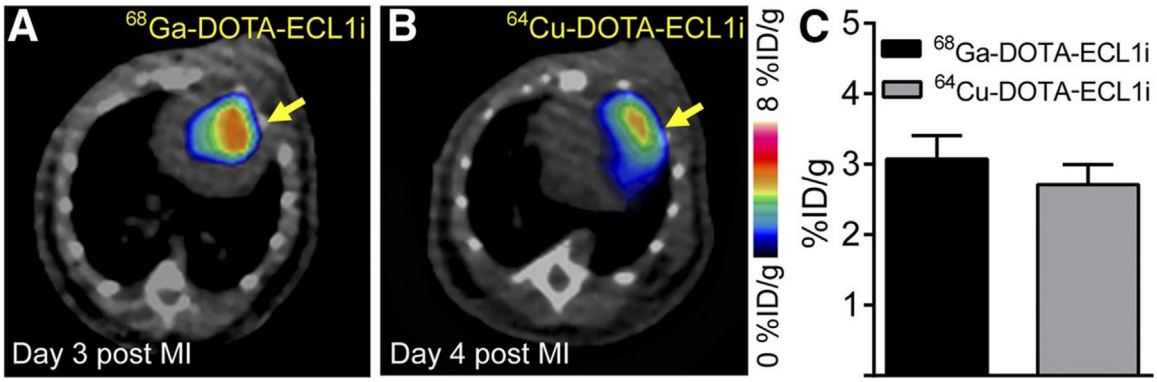

Figure 2 ^{64}Cu-DOTA-ECL1i compared with ^{68}Ga-DOTA-ECL1i-mediated imaging of CCR2 in injured heart. Representative PET/CT images (transverse plane) of ^{68}Ga-DOTA-ECL1i acquired at day 3 (A) and ^{64}Cu-DOTA-ECL1i acquired at day 4 (B) after MI in same mouse show comparable PET signals (C) in same infarcted region of heart. Reprinted without modifications from.[19]

endothelial dysfunction, atherosclerosis, acute myocardial infarction (AMI), cardiomyopathies, and chronic heart failure (HF). Inflammatory cell activity critically contributes to disease progression and poor outcomes.[6] Noninvasive molecular imaging plays a pivotal role in detecting and quantifying cardiovascular inflammation, enabling outcome prediction and targeted immunotherapy against specific leukocyte subsets.[7] As ^{18}F-FDG and SSTR2 PET tracers are established clinical markers,[4] they are not further discussed here.

Inflammation typically progresses through an acute pro-inflammatory phase, clearing cell debris, followed by a reparative phase that stabilizes plaques or forms post-AMI scar tissue. Imbalance in these phases—persistent inflammation or impaired resolution—can lead to rupture-prone plaques or adverse left ventricular (LV) remodeling,[6] making immune cells ideal imaging targets.

Tissue injury triggers local inflammation and rapid recruitment of peripheral immune cells. Chemokines and their receptors mediate early leukocyte recruitment.[6,8] The CXCR4-targeted tracer ^{68}Ga-pentixafor binds broadly to activated leukocytes and is the most validated pro-inflammatory PET agent, with uptake in plaques[9-12] and infarcted myocardium post-AMI.[13-17] Its signal predicts adverse cardiac events,[17] and CXCR4 blockade improves outcomes in animal models.[13] CCR2, expressed by pro-inflammatory monocytes/macrophages, can be imaged with ^{68}Ga- or ^{64}Cu-DOTA-ECL1i[18-20] (Fig. 2). Uptake peaks at day 4 postinjury in mice[18] and may persist for months in patients, correlating with impaired wall motion,[20] though its prognostic value is under investigation.

The NLRP3 inflammasome is another key pro-inflammatory target, triggering cytokine release and systemic CRP elevation.[6] The PET tracer ^{18}F-FTTM binds to P2 × 7R and has identified inflamed plaques in mice.[21] Activated macrophages also express TSPO, targetable with tracers like ^{18}F-PBR111,[22] ^{11}C-PK11195,[23] and ^{18}F-GE-180,[24-26] with signals found in plaques[22,23,25,27] and infarcts,[24,26,28] though clinical use is limited by high myocardial background. Folate receptor β (FR-β), upregulated in activated macrophages, shows promise with ^{18}F-FOL in atherosclerosis and myocarditis models.[29,30]

Immune cell metabolism also shifts during inflammation. Increased phospholipid metabolism (^{11}C-/^{18}F-choline[31-33]), glutamine uptake (^{18}F-FGln[34]), glycolysis (^{18}F-ZCDD083[35]), and proliferation (^{18}F-FLT[36]) have been visualized in atherosclerotic macrophages. Amino acid metabolism via ^{11}C-methionine imaging has shown potential in myocardial infarction and myocarditis models.[37-39]

As inflammation resolves, reparative immune cells such as anti-inflammatory macrophages secrete IL-10 and TGF-β, modulating fibrosis and immune suppression.[6,8] These cells express CD206, targetable by labeled mannose analogs in rodent models.[40-42] GLP-1R, detected by ^{68}Ga-NODAGA-exendin-4, is also expressed in reparative macrophages.[43] Galectin-3, targeted by ^{89}Zr-DFO-Gal3-F(ab′), accumulates in plaques and binds IL-4/IL-10-activated macrophages.[44] Its plasma levels are associated with cardiac fibrosis and mortality in HF.[45]

Single-cell RNA-sequencing (scRNA-seq) has revealed distinct macrophage subtypes, including inflammatory, resident, and lipid-laden cells, defined by surface markers.[8,46] Although PET tracers for activated leukocytes exist, more subtype-specific agents are needed. Novel targets include TREM2 (foamy macrophages)[47] and TREM1 (enhancer of inflammation).[48,49] T and B cells also play growing roles in diseases like myocarditis, sarcoidosis, and vasculitis. Tracers targeting CCR5 (^{64}Cu-DOTA-DAPTA-comb[50]) and CD40 ligand (^{89}Zr-anti-CD40 mAb[51]) have shown promise in mice. Emerging anti-inflammatory therapies would benefit from matched tracers to optimize treatment timing and monitor efficacy.[52]

Myocardial fibrosis and Extracellular Matrix Remodeling

Myocardial fibrosis (MF)—the excessive accumulation of extracellular matrix (ECM) proteins, mainly fibrillar

collagens—is central to many cardiovascular diseases, including heart failure, hypertension, and postinfarction remodeling.[53] Pathological ECM deposition disrupts myocardial architecture, increases tissue stiffness, impairs excitation-contraction coupling, and contributes to heart failure progression.[54] ECM remodeling depends on a tightly regulated balance between collagen synthesis and degradation, mediated by a complex network of molecular markers.[55] Understanding these pathways is key to developing diagnostic and therapeutic strategies. Molecular imaging—particularly PET and SPECT with targeted tracers—offers a noninvasive window into fibrosis-related cellular and molecular processes.

Collagen turnover, the balance between synthesis and degradation, is fundamental to ECM remodeling.[56] Cardiac fibroblasts drive collagen production,[57,58] while matrix metalloproteinases (MMPs) mediate degradation. MMPs are regulated by tissue inhibitors of metalloproteinases (TIMPs), which prevent excessive ECM breakdown.[59] In fibrosis, increased collagen synthesis and altered MMP/TIMP ratios result in collagen accumulation, myocardial stiffening, and functional decline.[60]

The PET tracer [^{18}F]AlF-NOTA-PEG-HYNIC-CLG targets type I collagen and has shown promising results in cardiac and pulmonary fibrosis models.[61] It uses a collagen-binding peptide (CLG) conjugated to the [^{18}F]AlF chelation system via NOTA/HYNIC and a PEG linker for improved pharmacokinetics. Animal studies demonstrated significant uptake in fibrotic areas, aligning with histology. In a β_2-adrenergic receptor overexpression model, ^{64}Cu-T-peptide-MeCOSar (targeting collagen IV) showed elevated uptake in fibrotic hearts and detected early fibrosis.[62] Similarly, ^{68}Ga-CBP8 PET showed increased lung uptake in murine pulmonary fibrosis, correlating with collagen content.[63] A first-in-human study demonstrated favorable biodistribution and safety of ^{68}Ga-CBP8.[64] ^{64}Cu-Collagelin, which binds type I and III collagens, enabled specific fibrosis imaging in a rat MI model.[65]

Several tracers have been developed to image MMP activity.[66] The SPECT tracer ^{99m}Tc-RP805 demonstrated a fourfold uptake increase in infarcted myocardium one week after MI in pigs, remaining elevated and predictive of late remodeling.[67] Other MMP-targeted tracers, including ^{111}In-RP782 and ^{99m}Tc-RYM1, localized to high MMP activity zones after injury, correlating with inflammation and ECM remodeling.[68] ^{111}In-RP782 predicted adverse ventricular remodeling,[69,70] while ^{99m}Tc-RYM1 showed strong uptake in inflamed fibrotic myocardium (Fig. 3).[71] PET tracers like ^{64}Cu-RYM2 are in development, with preclinical data confirming specific MMP binding in aneurysmal and human aortic tissues, supporting potential clinical use post-MI.[72]

LOXL2, an enzyme responsible for collagen cross-linking, contributes directly to myocardial stiffening in fibrosis.[73] Under pathological stress, excessive cross-linking leads to rigid collagen accumulation, impeding diastolic relaxation and promoting HF.[74] Human data show strong correlations between collagen cross-linking and ventricular stiffness,[74] as well as between LOXL2 levels and diastolic dysfunction severity.[75] While no [^{18}F]-labeled LOXL2 PET tracers exist yet, preclinical SPECT studies using [^{111}In]In-DOTAGA-AB0023 in pulmonary fibrosis support the feasibility of noninvasive LOXL2 imaging,[76] paving the way for PET applications in cardiac disease.

Periostin, a matricellular protein upregulated after cardiac injury, modulates fibrosis and post-MI remodeling.[77,78] It promotes myofibroblast activity, ECM organization, and scar stabilization early after MI, reducing rupture risk.[79,80] However, persistent high Periostin levels contribute to maladaptive remodeling by exacerbating collagen accumulation and LOXL2-mediated stiffening.[81,82] Although Periostin-targeted PET tracers have shown promise in oncology,[83] their application in cardiac fibrosis remains to be explored. Given Periostin's regulatory role in remodeling, such tracers could support early detection and monitoring of myocardial fibrosis.

Cardiomyocyte Injury and Stress Response

In acute and chronic cardiovascular diseases, damage to cardiomyocytes is a key pathological event. In response to this damage, molecular stress signaling pathways are activated that aim to minimize damage, maintain cell function or, under certain circumstances, induce cell death. Accordingly, these processes offer promising targets for both therapeutic interventions and molecular imaging.

Oxidative stress is one of the earliest events that occurs in the context of myocardial injury. It is mainly caused by NADPH oxidases (NOX), especially NOX2 and NOX4, which produce reactive oxygen species (ROS) in the heart.[84] Excessive production of ROS may cause lipid, protein and DNA damage, which in turn contributes to inflammation, fibrosis and adverse remodelling.[85]

Furthermore, the endoplasmic reticulum executes the unfolded protein response (UPR) in response to an overload of misfolded proteins. This stress response leads to the activation of transcription factors such as ATF6 and molecular chaperones such as GRP78 (also known as BiP), which support protein folding and homeostasis.[86] However, chronic endoplasmic reticulum stress can also turn into an apoptosis-inducing response that exacerbates myocardial damage.[87]

Endothelin receptors, in particular ET-A and ET-B, play a crucial role in cardiovascular diseases. In the heart, ET-A is mainly responsible for vasoconstriction, hypertrophy and fibrosis, while ET-B can mediate vasodilation and endothelin-1 (ET-1) clearance, ET-1 being a vasoconstrictor peptide predominantly produced by endothelial cells.[88] An imbalance between ET-A and ET-B signaling has been associated with heart failure and pulmonary arterial hypertension.[89]

Heat shock proteins (HSPs), in particular HSP70 and HSP90, play a key role in the cellular stress response and act as molecular chaperones that stabilize and refold denatured proteins under oxidative or ischemic stress conditions.[90]

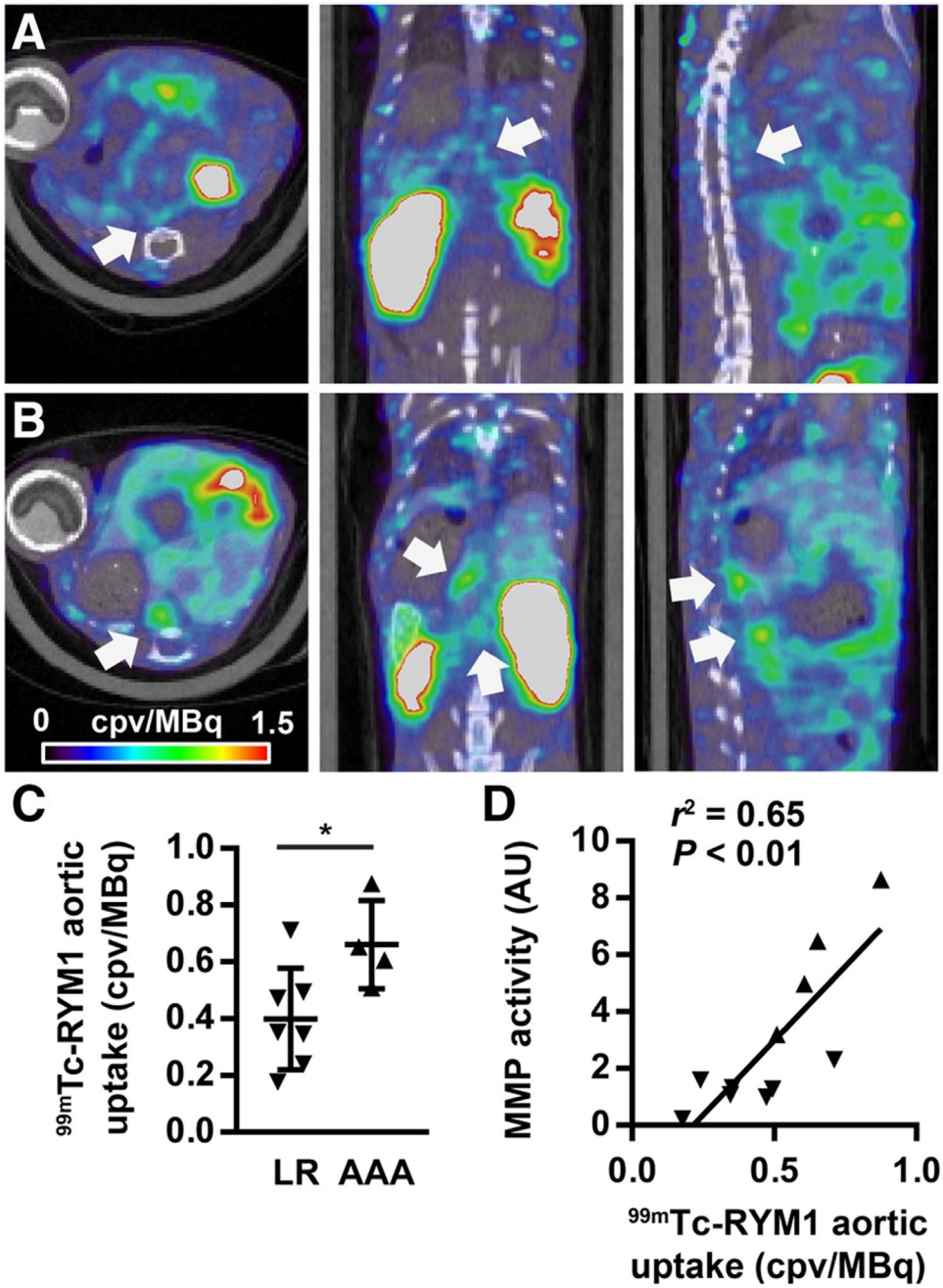

Figure 3 ^{9m}Tc-RYM1 imaging of AAA. (A and B) Examples of fused ^{99m}Tc-RYM1 SPECT/CT images of animals from the low remodeling (A) and aneurysm (B) groups, classified on the basis of visual in situ analysis of abdominal aorta. Transversal (left), coronal (middle), and sagittal (right) views are shown. Arrows point to areas of maximal tracer uptake in abdominal aorta. (C) Quantification of ^{99m}Tc-RYM1 signal in area of maximal tracer uptake in suprarenal abdominal aorta in low remodeling and AAA groups. *$P < 0.05$. (D) Correlation between ^{99m}Tc-RYM1 signal in vivo and MMP activity quantified by zymography ex vivo. AU = arbitrary units; cpv = counts per voxel; LR = low remodeling. Reprinted without modifications from.[71]

HSP90 is upregulated in the damaged myocardium and is involved in the stabilization of a number of signaling proteins.[91]

Novel radiotracers allow in vivo visualization of these stress responses. For example, [^{18}F]ROStrace is a PET tracer for visualizing ROS production that has been used to study oxidative stress in preclinical models of myocardial injury.[92]

Mitochondrial dysfunction is a typical phenomenon in ischemic and failing hearts and can be visualized with tracers that accumulate in depolarized or dysfunctional mitochondria, such as [^{18}F]fluorobenzyltriphenylphosphonium ([^{18}F]FBnTP), reflecting an impaired mitochondrial membrane potential.[93]

Endothelin receptor imaging is currently being investigated using fluorine-18-labelled ligands that selectively bind

to the above-mentioned ET-A or ET-B receptors. These PET tracers can provide information on the distribution and density of the receptors in diseases such as pulmonary hypertension.[94,95]

Finally, HSP-targeted tracers are being developed for PET and SPECT imaging. Radioactively labelled HSP90 inhibitors have shown promise for detecting regions of chaperone upregulation, with potential applications in myocardial infarction and myocarditis.[96]

In summary, oxidative stress, dysfunction of the endoplasmic reticulum, endothelin signaling and chaperone activity represent a complex orchestrated molecular response to cardiomyocyte injury. With the development of specific radiotracers, these processes can now be visualized in vivo, which could facilitate early diagnosis, disease monitoring and therapy stratification in cardiovascular medicine in the future.

Neurohormonal and Metabolic Pathways

G protein-coupled receptor kinase 2 (GRK2) is a key member of the GRK family.[97] It regulates receptor endocytosis and desensitization by phosphorylating activated GPCRs and promoting β-arrestin binding, thus modulating cellular signaling. In the cardiovascular system, GRK2 is especially important due to the central role of GPCRs, such as β-adrenergic and angiotensin receptors, in cardiac contraction, vascular tone, and remodeling.

A notable feature of GRK2 is its modular structure, allowing selective targeting of functional regions while preserving beneficial downstream signaling. This makes it an attractive theranostic target.[98] Although no GRK2-specific radiopharmaceuticals exist yet, a PET imaging agent could help identify patients with GRK2 hyperactivity before structural damage occurs, guide dosing of GRK2 inhibitors, and monitor disease progression or treatment efficacy.

The heart's high energy demand requires constant ATP production.[99] Fatty acids and glucose are the main energy sources, but substrate flexibility is essential for cardiac function.[100] In heart failure, ketone bodies become a critical energy source. For example, 3-hydroxybutyrate (3-OHB) can improve cardiac output by 40% and left ventricular ejection fraction by 8%, making it a promising therapeutic target.[101] Imaging ketone metabolism with PET tracers enables dynamic assessment and biodistribution quantification.

Etienne et al. developed [^{11}C]-Acetoacetate to image ketone metabolism in early heart failure in rats, demonstrating its value as a cardiovascular PET tracer.[102] Thien et al. administered [^{11}C]β-hydroxybutyrate ([^{11}C]OHB) to healthy volunteers, finding high cardiac uptake and favorable biodistribution.[103] These studies support the use of ketone-based tracers for assessing metabolic adaptations in heart disease.

Fatty acid oxidation, which supplies about 80% of cardiac ATP, is another crucial imaging target.[104,105] The PET tracer 14-[^{18}F]fluoro-6-thia-heptadecanoic acid ([^{18}F]FTHA) has been widely used,[106,107] though its specificity is limited, prompting interest in new tracers.[108] Jun et al. introduced an [^{18}F]-labeled fatty acid binding protein (FABP3) inhibitor, which showed high cardiac uptake and excellent metabolic stability in rats.[109] In a phase I trial, Mou et al. validated XTR003, a novel fatty acid tracer with high initial uptake and long myocardial retention, suggesting its potential for assessing fatty acid metabolism.[110]

Irisin, a 12-amino acid myokine regulated by PGC-1α, is involved in cardiovascular inflammation and oxidative stress,[111-113] and may serve as a prognostic biomarker.[114] Lv et al. radiolabeled irisin with ^{125}I for SPECT/CT in mice, showing its elimination through the liver, gallbladder, and kidneys, with low but stable cardiac uptake.[115] These data provide a foundation for future irisin-targeted imaging probes.

Ghrelin, a 28-amino acid peptide and GHS-R ligand first identified in 1999, plays a role in cardiovascular homeostasis, regulating glucose metabolism, adipogenesis, and thermogenesis.[116,117] Ghrelin has been shown to reduce cardiac hypertrophy,[118] improve hemodynamics in heart failure,[119] and prevent arrhythmias after myocardial infarction.[120] Therefore, quantitative imaging of GHS-R is important for assessing therapeutic outcomes.

Sullivan et al. developed [^{18}F]LCE470, a PET tracer with high GHS-R affinity (0.33 nM). Uptake correlated with receptor density, supporting its use for detecting myocardial GHS-R changes post-MI.[121] Fowkes et al. used N-succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]SFB) to radiolabel a peptidomimetic GHS analog, producing [1-Nal^{4},Lys^{5}(4-[^{18}F]-FB)] G-7039. The tracer showed high purity, good radiochemical yield, and potential for detecting diseases linked to ghrelin receptor overexpression.[122]

Thrombosis and Platelet Activation

Hemostasis is a highly complex and tightly regulated physiological process aimed at maintaining vascular integrity and preventing bleeding. However, pathological thrombosis can occur if the inhibitory and anticoagulant factors are not able to counterbalance the strongly activated hemostatic pathway to ensure proper healing and lysis. Pathological thrombosis, i.e. vascular occlusion, is a critical event in several cardiovascular diseases, including AMI, stroke, deep vein thrombosis, and pulmonary embolism.[123]

Thrombi can be classically divided into two types: arterial, platelet-rich thrombi ("white clots"), and venous thrombi consisting mainly of red blood cells and fibrin ("red clots"). Arterial thrombosis typically results from the disruption of atherosclerotic plaques. When the fibrous cap of the plaque ruptures or the endothelial monolayer erodes, the subendothelial matrix and thrombogenic material, including collagen and tissue factor (TF), are exposed to arterial circulation.[124] Exposed collagen triggers the rapid recruitment and activation of platelets, whereas TF initiates thrombin generation. Interactions of the platelet glycoprotein VI and glycoprotein

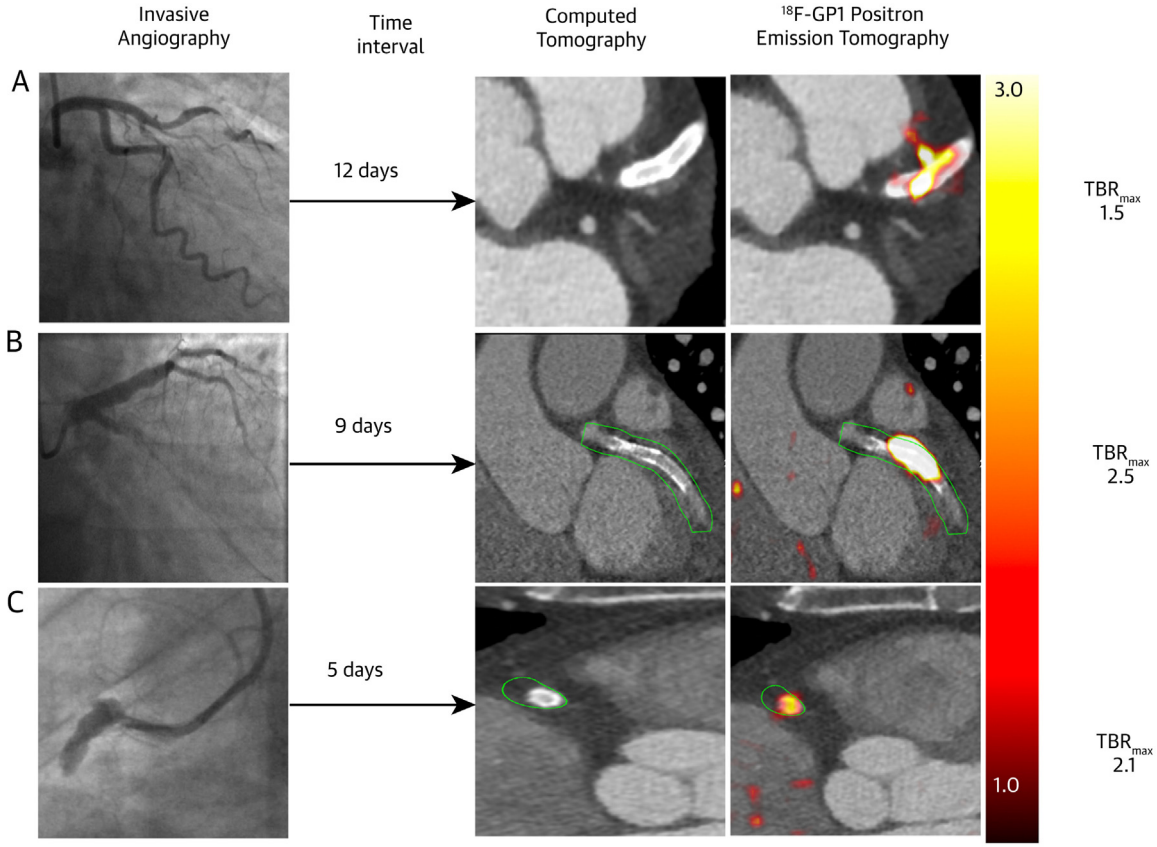

Figure 4 Three exemplar cases of ST-segment elevation myocardial infarction. Anterior (A), lateral (B), and inferior (C) myocardial infarction and corresponding ^{18}F-GP1 uptake from the corresponding culprit artery. Right to left: invasive coronary angiogram, CT angiogram, and ^{18}F-GP1 positron emission tomographic and CT angiogram. ^{18}F-GP1 uptake was noted only in the infarct artery. TBRmax = maximum target-to-background ratio. Reprinted without modifications from.[128]

Ib-IX-V receptors with collagen and von Willebrand factor, respectively, are crucial for platelet adhesion and aggregation at the site of injury. This process activates the blood coagulation cascade, leading to the conversion of fibrinogen to fibrin by thrombin, and eventually resulting in the formation of an arterial thrombus. In contrast, venous thrombus formation is primarily triggered by blood stasis, hypoxia, or inflammatory stimuli, rather than vessel wall injury. Therefore, endothelial activation has a key role in the development of venous thrombi.[123]

Acute thrombosis can be localized by filling defects or alterations in blood flow using ultrasound or invasive or non-invasive contrast-enhanced angiography techniques. However, these imaging approaches lack sensitivity and specificity for detection of thrombus and do not provide information on hemostatic activity. To address these limitations, new PET imaging tracers targeting key components of thrombus formation have been evaluated in preclinical and translational clinical studies.[125] The most extensively studied target is the glycoprotein IIb/IIIa receptor, also known as $\alpha_{IIb}\beta_3$ integrin that is specifically expressed on the surface of activated platelets and binds to its natural ligands, fibrin or fibrinogen.[126] A novel radiotracer, ^{18}F-labeled fiban-class ligand (^{18}F-GP1), binds to the glycoprotein IIb/IIIa receptor with high affinity and has shown promise for imaging both arterial[126-129] and venous thrombi[130] (Fig. 4). In patients with AMI, ^{18}F-GP1 accurately identified intracoronary thrombus in the culprit artery.[128] . Beyond coronary and carotid arteries, ^{18}F-GP1 has been successfully applied to image intramyocardial hemorrhage, left ventricular thrombus,[128] atrial appendage thrombus,[131] and bioprosthetic aortic valve thrombus.[132]

Another key biomarker of acute thrombosis is fibrin that is present in fresh arterial and venous thrombi. Fibrin-binding probes, ^{64}Cu-FBP7[133] and ^{64}Cu-FBP8,[134] have demonstrated feasibility in detecting arterial and venous thrombi in experimental animal models. Moreover, PET imaging with ^{64}Cu-FBP8 showed that the uptake was more prominent in younger thrombi compared to older ones.[134] These findings were confirmed in the observational first-in-human study, where ^{64}Cu-FBP8 successfully detected acute to subacute left atrial appendage thrombi.[135]

Other targets evaluated in preclinical and pilot clinical studies include coagulation factor XIIIa (FXIIIa) and P-selectin. FXIIIa strengthens fibrin crosslinking during thrombus formation. The FXIIa-targeting tracer ^{18}F-ENC2015 demonstrated selective binding to acute thrombus in both an ex vivo human model and an in vivo rodent model of arterial thrombosis.[136] However, this tracer has not entered clinical development due to high radiation exposure to the kidneys

observed in preclinical dosimetry studies. Adhesion molecule P-selectin in turn is expressed on activated platelets and interacts with leukocytes to form stable platelet-leukocyte aggregates during the early phase of thrombogenesis.[137] While the P-selectin targeting SPECT tracer ^{99m}Tc-fucoidan showed potential in visualizing thrombi in animal models of abdominal aortic aneurysm and endocarditis,[137] the first-in-human study did not support further clinical investigation related to deep vein thrombosis.[138] Recently, the TF-targeted radiotracer ^{18}F-ASIS has been successfully used to image tumors in a phase I clinical trial.[139] This tracer would be particularly interesting to evaluate in the context of thrombosis.

Taken together, novel tracers have deepened our understanding of the underlying pathogenesis in thrombotic diseases and hold potential for early detection and characterization of thrombosis. This advancement would also help to develop new more specific treatments beyond conventional antiplatelet and anticoagulant drugs. However, the narrow time window for detecting active thrombosis poses a challenge, requiring proper planning in study design and patient selection for future clinical trials.

Vascular Pathobiology and Plaque Instability

Atherosclerosis is the cause of most cardiovascular events and represents a multifactorial disease characterized not only by lipid deposits but also by chronic inflammation, vascular remodeling, and calcification. Crucial for the transition from stable to vulnerable plaques are endothelial dysfunction, integrin-mediated angiogenesis, and pathological calcification. These processes exhibit specific molecular mechanisms that can be visualized with specific radiotracers, potentially opening new avenues for risk stratification and monitoring of atherosclerotic disease progression.

Endothelial dysfunction is a central event in the pathogenesis of atherosclerosis. Proinflammatory adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and E-selectin are upregulated in response to cytokine signals and promote the adhesion and migration of monocytes into the subendothelial space.[140] These molecules are not only inflammatory markers but also promote plaque initiation and progression.[141]

Another significant factor in plaque vulnerability is neoangiogenesis within plaques, which is often induced by hypoxia and oxidative stress. This neoangiogenesis is regulated by integrins, which are transmembrane receptors that mediate cell adhesion and signal transduction.

Integrins such as $\alpha v\beta 3$, $\alpha 4\beta 1$, and $\alpha 5\beta 1$ are overexpressed on activated endothelial cells and macrophages, promoting not only vascular remodeling but also leukocyte infiltration and plaques haemorrhage.[142,143]

Vascular calcification, which was previously considered a passive degenerative process, is now understood as an actively regulated biological event involving osteogenic signaling pathways. The calcium-sensing receptor (CaSR) expressed on vascular smooth muscle cells (VSMCs) plays a pivotal role by modulating cellular responses to extracellular calcium levels and contributing to the differentiation of VSMCs into osteoblast-like cells.[144] This process distinguishes microcalcification, which is associated with plaque instability, from macrocalcification, which is observed in more stable lesions.

Molecular imaging has made it possible to specifically visualize these pathophysiological events. Radioactively labelled ligands targeting VCAM-1, e.g. the [^{18}F]VCAM-1 tracer, enable the in vivo detection of endothelial activation and early vascular inflammation.[145]These tracers have shown potential to identify inflamed plaques before structural changes become overt in anatomical imaging.

For the detection of vascular calcifications, PET imaging with [^{18}F]sodium fluoride ([^{18}F]NaF) has been established as the reference method due to its ability to bind to hydroxyapatite. Currently, however, new alternatives with improved specificity are being investigated. These aim to distinguish metabolically active microcalcifications from passive calcium deposits, thereby improving the accuracy of risk assessment.[146]

Integrin-targeted imaging, particularly with [^{68}Ga]RGD-based PET tracers, enables the visualization of $\alpha v\beta 3$ expression and thus active neoangiogenesis in plaques. These tracers are related both to histological markers of neovascularization and macrophage density, which represent key factors of vulnerable plaques.[147,148] In recent research, dual integrin-targeting ligands are being investigated for a more comprehensive characterization of inflammatory and remodeling processes in atherosclerosis.

There are currently no studies specifically describing [^{18}F]-labeled calcium-sensing receptor (CaSR) ligands for PET imaging to differentiate active from passive vascular calcification. However, several studies have demonstrated that the calcium-sensing receptor (CaSR) is a promising molecular target for distinguishing active, regulated calcification from quiescent mineral deposits.[149]

The pathobiology of the vessels and the instability of the plaques are characterized by various molecular processes such as endothelial activation, integrin-mediated angiogenesis, and regulated calcification. Using novel specific radiotracers these mechanisms can now be studied. As a result, molecular imaging not only enhances our mechanistic understanding of atherosclerosis but could also represent a new approach for early diagnosis, risk prediction, and therapy monitoring.

Markers of Cellular Senescence

Cellular senescence, defined as a stable and irreversible arrest of the cell cycle, plays a pivotal role in the pathophysiology of cardiovascular diseases (CVDs). This phenomenon represents a critical barrier against the uncontrolled proliferation of damaged cells, yet its persistent presence contributes deleteriously to tissue dysfunction and chronic inflammation, particularly in the cardiovascular system. In vascular and

cardiac tissues, cellular senescence is precipitated by a confluence of interrelated molecular mechanisms, including oxidative stress, DNA damage, telomere attrition, and inflammatory signaling.[150,151] Cellular senescence is not only a key driver of atherosclerosis,[152] but also an independent risk factor for myocardial infarction and an important cause of high mortality after myocardial infarction.[153] Therefore, it is intuitively essential to recognize s hallmarks and potential biomarkers of cardiovascular senescence.

One of the most commonly used biomarkers is senescence - associated β - galactosidase (SA - β - gal), which is expressed at a higher level in senescent cells. SA-β-gal is a glycoside hydrolase that catalyzes the hydrolysis of the glycosidic bond of beta-galactoside.[154] As the most commonly used senescence-associated biomarker, β-gal has been successfully used for molecular imaging at the cellular and organismal levels for senescent cell visualization.[155] Xiang et al. designed a novel PET imaging probe, 68Ga-Bgal, which showed high sensitivity and specificity both in vivo and in vitro, providing a new imaging technique for real-time quantitative detection of cellular senescence.[156] However, SA - β - gal is not entirely specific to senescent cells, as it can also be induced by other stress conditions, how to enhance the agent's specificity remains an issue to be addressed in the future design.

Cell - cycle regulators such as p16INK4a are also frequently used as biomarkers of cellular senescence. In a study on senescent coronary vascular smooth muscle cells, the over expressions of p16INK4a causes senescence of vascular smooth muscle cells, which leads to progression of coronary atherosclerosis.[157] Another study showed that, compared with the healthy elderly people, older patients with heart failure had higher expression levels of p16INK4a compared with healthy older adults, suggesting that p16INK4a -induced senescence and cell death characterize heart failure in aging.[158] To date, there is no PET molecular probe directly targeting P16 or its metabolites, but it still has great potential as a well-defined target in a variety of cardiovascular diseases such as atherosclerosis and heart failure as an theragnostic target.

Nicotinamide adenine dinucleotide (NAD+) is a core metabolite involved in energy and redox homeostasis as well as DNA repair and protein deacetylation reactions.[159] The decrease of NAD+ causes mitochondrial dysfunction, a decrease in ATP synthesis, a decrease in myocardial contractility, and accelerated cardiac cell senescence.[160] Silence-regulated proteins (SIRT) are nicotinamide adenine dinucleotide (NAD+)-dependent enzymes that regulate energy metabolism, mitochondrial activity, and senescence.[161] It has been shown that the loss of sirtuin activity and NAD+ levels with age is associated with the pathogenesis of several cardiovascular diseases, including atherosclerosis, endothelial dysfunction, acute cardiac syndromes, cardiomyopathy, myocardial hypertrophy, and heart failure.[162] To date, there has been one study using PET to molecularly image NAD and/or its analogs. ADAM et al. designed an ^{18}F-labeled NAD analog, ([^{18}F]-SuPAR), for monitoring Poly (ADP ribose) polymerase (PARP) activation status to assess DNA damage.[163]

Microbiome-Cardiovascular Axis (Emerging Concept in Imaging)

Recent research has highlighted the gut-cardiac axis, particularly microbial metabolites such as short-chain fatty acids (SCFAs), lipopolysaccharides (LPS), peptidoglycans, and trimethylamine N-oxide (TMAO), which result from bacterial fermentation of dietary fibers.[164] TMAO, derived from choline, phosphatidylcholine, and L-carnitine via gut microbial metabolism, is converted in the liver by FMO1 and FMO3. High TMAO levels are associated with atherosclerosis, thrombosis, and myocardial infarction.[165,166]

LPS, a component of gram-negative bacteria like *E. coli*, enters the bloodstream through the gut when permeability increases. It binds to Toll-like receptor 4 (TLR4), triggering pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6,[167,168] while suppressing anti-inflammatory responses. LPS and peptidoglycans are elevated in obesity and type 2 diabetes,[169] and linked to carotid atherosclerosis.[170] LPS comprises lipid A, a core oligosaccharide, and a variable O-antigen, with lipid A being the TLR4-recognized component.[171]

Disruption of gut barrier integrity allows microbial products into circulation, activating monocytes and macrophages and contributing to atherosclerosis. Mitochondrial function is essential for maintaining this barrier. Neutrophils and eosinophils secrete PGLYRP-1, which binds bacterial peptidoglycans and triggers inflammation. Elevated serum PGLYRP-1 is linked to acute coronary syndrome and subclinical atherosclerosis.[172,173]

Low-grade metabolic endotoxemia, induced by TMAO and LPS, produces inflammation at concentrations much lower than in sepsis. Despite this, LPS's potent immunogenicity makes even small amounts clinically significant. Research on high-affinity LPS binders could support anti-inflammatory therapies or endotoxin clearance.

Imaging low-grade bacterial inflammation is challenging due to low bacterial receptor expression and nonspecific tracer retention. [^{18}F]-FDG, though commonly used, lacks specificity for infection and cannot differentiate between sterile inflammation, cancer, or early infection.

New radiotracers aim to overcome these limitations. [^{18}F]-LPS-binding probes may target endotoxins in inflammation or circulation. Fluorine-18-labeled D-alanine derivatives, such as D-[^{18}F]-CF_3-ala, are incorporated into bacterial peptidoglycan but not mammalian cells, providing high-contrast images.[174] [^{18}F]-fluorodeoxysorbitol (FDS), derived from [^{18}F]-FDG, selectively targets gram-negative enterobacteria like *E. coli*, avoiding uptake in gram-positive bacteria or cancer cells.[175] FDS is easy to synthesize, has high specificity, low background, and a safe decay profile.

[^{18}F]-OP-801, a hydroxyl dendrimer PET tracer, detects activated macrophages in LPS-induced inflammation and could identify macrophage activity at atherosclerotic sites.[176] Another tracer, [^{18}F]-4FN, is redox-sensitive and accumulates in tissues with high oxidative enzyme activity (e.g., MPO, NOX2), offering better specificity than [^{18}F]-FDG for inflammation.[177]

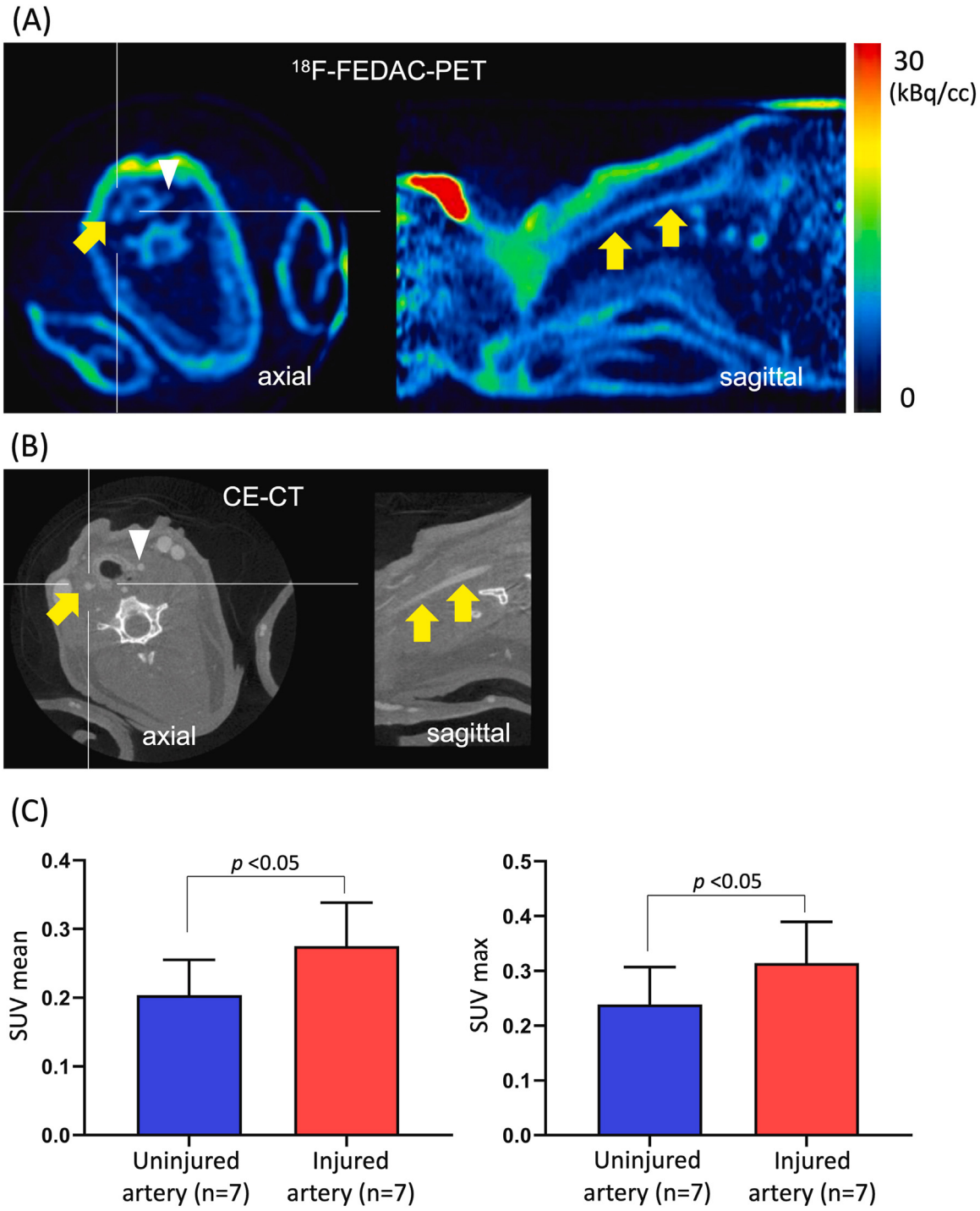

Figure 5 ^{18}F-FEDAC-positron emission tomography and contrast-enhanced computed tomography of a rabbit atherosclerosis model. (A) Representative axial and sagittal images of ^{18}F-FEDAC-positron emission tomography. The axial image shows higher ^{18}F-FEDAC uptake along the right side of the trachea (arrow) corresponding to the injured right carotid artery, compared to the left side of the trachea (arrowhead) corresponding to the uninjured left carotid artery. The sagittal image matching a white vertical line in the axial image shows high ^{18}F-FEDAC uptake which corresponds to the right carotid artery (arrows). (B) Representative axial and sagittal images of contrast enhanced computed tomography. The contrast enhanced uninjured left (arrowhead) and injured right (arrow) carotid arteries show no significant difference in the luminal size on the axial image. The sagittal image corresponding to white vertical line in the axial image shows the right carotid artery (arrows). (C) Standardized uptake value on body weight (SUVbw) of uninjured left and injured right carotid arteries. n = 7 in each, Wilcoxon signed rank test. Reprinted without modifications from.[178]

TSPO, located on the outer mitochondrial membrane, is overexpressed in activated macrophages and involved in cellular stress responses. Its role in cardiovascular inflammation has driven the development of TSPO-targeting tracers for imaging conditions like MI, myocarditis, sarcoidosis, and atherosclerosis. Macrophages from individuals with subclinical atherosclerosis show increased TSPO expression. [^{18}F]-labeled TSPO tracers such as [^{18}F]-FEDAC visualize atherosclerotic lesions in rabbits and humans, with higher uptake in diseased tissues (Fig. 5).[178] [^{18}F]-PBR111 identifies macrophage populations in early lesions and shows increased uptake in atherosclerotic mice.[22] [^{18}F]-PBR06 has been used for PET/CT to assess macrophage infiltration.[179]

[^{11}C]-PK11195 selectively binds TSPO and can distinguish between symptomatic and asymptomatic carotid plaques using PET/CT. Symptomatic plaques show higher uptake and lower CT attenuation, indicating vulnerability.[23,180]

In conclusion, imaging the gut-heart axis offers a promising tool in cardiovascular diagnostics. Novel PET tracers targeting gut-derived metabolites, endotoxins, immune cells, and TSPO may enable early detection and monitoring of inflammation-related cardiovascular disease. Future work will focus on clinical validation and integration into precision medicine.

Future Directions and Translational Challenges

While the field of molecular imaging tracers in cardiovascular disease is characterized by a rapid evolution, still the translation of promising targets from bench to bedside remains constrained by multiple challenges.

One of the central limitations is the difference in tracer pharmacodynamics, such as altered affinity for human versus murine receptor isoforms, which complicate the translation of data obtained in animal studies to the clinical scenario. Considering that the vast majority of new tracers are still in the preclinical phase of development, it is not unrealistic to foresee that only a small proportion will reach the phase of clinical research, and even fewer will prove effective in clinical practice.

Nonetheless, the clinical potential of targeted cardiovascular imaging remains substantial. The ability to noninvasively visualize e.g immune activation (CXCR4, TSPO), ventricular remodeling (MMPs, LOXL2), or mitochondrial dysfunction opens a door for early phenotyping of disease subtypes and risk stratification beyond anatomical imaging.

As the field moves toward precision medicine, the ability to noninvasively visualize pathophysiological mechanisms in vivo can help identify high-risk individuals before irreversible organ damage occurs.[181] Moreover, integration with therapeutic pathways, such as the use of CCR2 tracers to identify patients eligible for monocyte-targeted interventions, represents a true theragnostic paradigm.[182]

Molecular imaging may guide treatment selection, for instance, identifying patients most likely to benefit from anti-inflammatory or anti-fibrotic therapies, and monitor therapeutic response more sensitively than structural imaging or serum biomarkers.[183] In diseases like myocarditis, cardiac sarcoidosis, or postinfarct remodeling, PET tracers targeting immune and fibroblast activity could provide critical prognostic insights and allow for dynamic therapy adjustment.[184,185]

In the long term, integrating molecular imaging into cardiovascular workflows will depend on the demonstration of clinical utility, cost-effectiveness, and standardization across institutions. In this context, the future of cardiovascular imaging will not be defined solely by technological innovation, but by the ability to translate biological insight into actionable clinical decisions. Future research must therefore focus on improving the quantitative robustness of tracer uptake metrics, validating imaging endpoints as predictors of outcome, and aligning tracer development with therapeutic innovation to accelerate adoption in clinical cardiology.

Artificial intelligence (AI) is playing an increasingly important role in nuclear cardiac imaging, offering powerful ways to increase the potential of new molecular tracers. By improving image quality,[186] segmentation, and quantification, AI can accelerate workflows, enhance diagnostic accuracy, and integrate multi-modal data to better predict disease presence and patient risk.[187] Studies have already demonstrated AI's ability to outperform human experts in tasks like diagnosis coronary artery disease,[188] left ventricular segmentation and ejection fraction estimation,[189] and to more accurately predict outcomes such as abnormal myocardial perfusion and the need for coronary revascularization.[190,191] As novel tracers expand our ability to characterize cardiovascular diseases at a molecular level, AI will be essential for extracting clinically meaningful insights and enabling more personalized patient management.

In conclusion, recent advances in molecular imaging have uncovered a broad spectrum of novel targets that reflect key biological processes in cardiovascular diseases, including inflammation, fibrosis, metabolic dysregulation, and thrombosis. The development of dedicated PET and SPECT tracers for these targets offers new opportunities for early disease detection, mechanistic insight, and precision-guided therapy. While challenges in translational validation, regulatory approval, and standardization persist, the integration of these imaging tools into clinical workflows holds considerable promise to refine risk stratification, guide targeted interventions, and monitor therapeutic efficacy across a range of cardiovascular conditions. Continued interdisciplinary efforts will be essential to realize the full potential of these next-generation imaging strategies in clinical cardiology.

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

Mia Ståhle: Writing – original draft. **Cristina Popescu:** Writing – original draft. **Christoph Rischpler:** Writing – original draft. **Han Zhang:** Writing – original draft. **Samia Massalha:** Writing – original draft. **Leonor Lopes:** Writing – original draft. **Axel Rominger:** Conceptualization. **Federico Caobelli:** Conceptualization, Supervision, Writing – original draft.

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