Utility of positron emission tomography for drug development for heart failure

Lampros Papadimitriou, MD, PhD,[a] Peter M. Smith-Jones, PhD,[b] Chaudhry M. S. Sarwar, MD,[c] Catherine N. Marti, MD,[d] Kavitha Yaddanapudi, MD,[e] Hal A. Skopicki, MD, PhD,[a] Mihai Gheorghiade, MD,[f] Ramin Parsey, MD, PhD,[b] and Javed Butler, MD, MPH, MBA[a] *Stony Brook, NY; Atlanta, GA; and Chicago, IL*

Only about 1 in 5,000 investigational agents in a preclinical stage acquires Food and Drug Administration approval. Among many reasons for this includes an inefficient transition from preclinical to clinical phases, which exponentially increase the cost and the delays the process of drug development. Positron emission tomography (PET) is a nuclear imaging technique that has been used for the diagnosis, risk stratification, and guidance of therapy. However, lately with the advance of radiochemistry and of molecular imaging technology, it became evident that PET could help novel drug development process. By using a PET radioligand to report on receptor occupancy during novel agent therapy, it may help assess the effectiveness, efficacy, and safety of such a new medication in an early preclinical stage and help design successful clinical trials even at a later phase. In this article, we explore the potential implications of PET in the development of new heart failure therapies and review PET's application in the respective pathophysiologic pathways such as myocardial perfusion, metabolism, innervation, inflammation, apoptosis, and cardiac remodeling. (Am Heart J 2016;175:142-52.)

The cost for the development of a new pharmaceutical agent has been estimated to be at least $800 million.[1] The drug development process takes well over a decade to move from basic discoveries to animal testing, proof of principle and proof of concept human studies; and finally phase III trials assessing the clinical benefits. Many agents with promising pharmacology and early-phase data fail in the later stages to show clinical benefit. Development of new medications for heart failure (HF) has been particularly challenging. Phase II trials in HF rely on echocardiographic or other surrogate markers like functional capacity or biomarkers to guide the potential for clinical benefit in the later stages of drug development. In many attempts, however, despite such surrogate markers showing benefit, they did not translate into tangible results in registration trials yielding neutral effects on survival. Many reasons for this disconnect are hypothesized and highlight the need for alternate or incremental strategies to assess of the effects of an investigational drug to better inform subsequent large-scale trials.

Emerging applications of positron emission tomography (PET) hold promise in this regard, and the technology has been widely embraced by the oncological community. Positron emission tomography imaging is the use of specific radiotracers, which can report on molecular events at the cellular level and could be classified into broad areas according to their target and function into receptors, proteins/enzymes, antibodies, metabolic agents, nucleoside analogs, and labeled drugs.[2,3] Moreover, PET is widely accepted as being a quantitive tool where as the older technology single-photon emission computed tomography (SPECT) offers mainly qualitative information. In this review, we describe the implications of PET in cardiovascular system, related HF pathophysiology, and highlight its potential role in HF drug development.

Positron emission tomography in drug development

Positron emission tomography is a 3-dimensional noninvasive tomographic imaging modality that allows in vivo imaging of physiological and pathological processes involving molecules tagged with positron-emitting radionuclides. These molecules can target defined receptors or cellular transport mechanisms. Receptors are usually proteins located on cellular membranes or in the cytoplasm, which, when activated by specific ligands,

From the [a]Cardiology Division, Stony Brook University, Stony Brook, NY, [b]Department of Psychiatry, Stony Brook University, Stony Brook, NY, [c]Hospital Medicine, Stony Brook University, Stony Brook, NY, [d]Cardiology Division, Emory University, Atlanta, GA, [e]Department of Radiology, Stony Brook University, Stony Brook, NY, and [f]Center for Cardiovascular Innovation, Northwestern Feinberg School of Medicine, Northwestern University, Chicago, IL.

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Reprint request: Javed Butler, MD MPH, MBA, Division of Cardiology, Stony Brook University, Health Sciences Center, SUNY, T-16, Room 080, Stony Brook NY 11794.
E-mail: javed.butler@stonybrookmedicine.edu

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Table I. Most common radiotracers and their use in cardiovascular studies

Radionuclide	Half-life	Cardiac use
[^{15}O]	2.06 min	Yes
[^{64}Cu]	12.7 h	Yes
[^{124}I]	4.2 d	Yes
[^{13}N]	10 min	Yes
[^{11}C]	20.4 min	Yes
[^{89}Zr]	78.41 h	No
[^{18}F]	110 min	Yes
[^{68}Ga]	67.6 min	Yes
[^{82}Rb]	1.25 min	Yes

trigger a second response through a variety of mechanisms. Other processes imaged by PET include fatty acid (FA) metabolism, nucleotide incorporation into DNA, and blood flow. The recognition and anatomical allocation of such targets depicts the disease pathophysiology and highlights potential therapeutic targets. Ligands that cause downstream changes after the receptor binding are called agonists, whereas those that block changes and prevent other agonists to bind to the receptor are called antagonists. The imaging of these structures becomes possible with the attachment of a positron emitter to either a natural substrate of the receptor or to a receptor-targeted novel medication. There are a wide variety of radiolabels with different half lives available, but the most commonly used in humans are ^{18}F with ^{11}C, ^{68}Ga, ^{64}Cu, ^{124}I, ^{13}N, and ^{15}O as shown in Table I.[4–7]

The involvement of PET in drug development occurs in 2 forms. The first consists of the *microdose studies*, which are similar to pharmacokinetic studies assessing absorption, distribution, metabolism, and excretion of a new agent, and applied to early-phase studies.[7,8] A microdose is defined as a dose less than 1/100th of the dose predicted to have a pharmacologic effect and with a maximum dose of ≤100 μg. In order to have valid and accurate results, it is important to know the biologic properties of the new compound in terms of its affinity to other binding sites, whether there is a transmembrane transport, what is the fraction of the agent binding to protein fraction of the agent, and if the infused compound follows a linear model in its concentration and metabolism.[8] Positron emission tomography has the advantage of imaging receptor systems with the use of subnanomolar concentrations of an investigated agent.

The second area is assessing the pharmacodynamic or dose-finding studies to assess the effect of the novel agent measuring the receptor occupancy.[8,9] This process involves coadministration of a labeled and nonlabeled (cold drug) agent and these compete for binding to the target. Reduced radioactivity in the area of interest when increased levels of unlabeled drug are administered indicates high occupancy of the investigational drug (Figure 1).[8]

In molecules with high affinity to target, PET can be performed with the coinfusion of a cold drug. To assess the pharmacodynamics of receptor binding, 3-compartmental model is applied; the free ligand in the plasma, the nonspecifically bound and the bound ligand, with their kinetic constants constitute and confine the interaction between the 3 compartments.[10,11] There are limitations to this method which derive from (1) existence of other binding sites, (2) endocytosis of the complex drug-receptor and related downstream changes, (3) circulation of radiolabeled molecules from the metabolism of the novel agent, and (4) in cerebrovascular drugs, brai-blood barrier poses an extra parameter over the 3-compartment model, which may have safety concerns for HF drug development.

It is estimated that less than 1 in 5,000 compounds at the preclinical stage will be developed into a Food and Drug Administration (FDA)–approved drug. Any tool that helps in screening unsuitable drugs has the potential to reduce the costs of developing new drugs. Table II summarizes the potential implications of PET throughout the development process of a new medication.

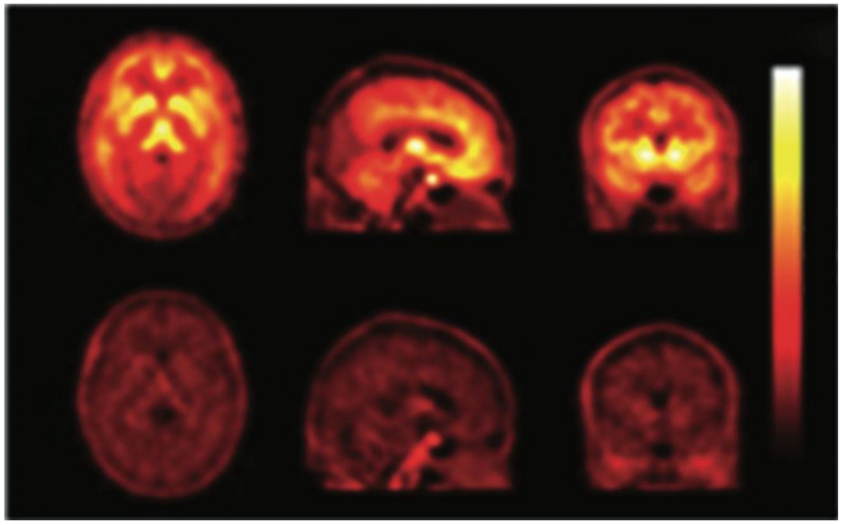
For drug development, there are 2 PET radiopharmaceuticals that may be used. Substituting natural ^{12}C with ^{11}C, or ^{19}F with ^{18}F, can develop a copy of test drug, and this can be monitored for distribution of the test drug at the tracer or therapeutic level. The second PET tracer would be one of a number of well-characterized radioligands that are specifically used to monitor the binding of the test drug to the target of interest as well as to compare the test drug to other agents that target the same system.

In the preclinical setting, the PET version of the candidate molecule can be used in biodistribution studies to determine if it is reaching the tissue of interest and the potential off target accumulation. Positron emission tomography can also be used with a carrier amount of the ^{12}C- or ^{19}F-labeled drug to see the effect of drug mass on the pharmacokinetics. Positron emission tomography can also be used with one of a number of well-characterized radiopharmaceuticals, which target a specific receptor or transport system to see the pharmacodynamics of the unlabeled drug candidate.

For the first time in human studies, PET can provide information on the pharmacokinetics and distribution of the new drug. For this phase, the FDA allows limited studies at a subpharmacologic dose (typically microgram or nanomole amounts) when supported with a limited toxicologic data set. This exploratory investigational new drug mechanism allows the investigator to rapidly determine if the drug targets its intended target and as such is a critical selection criterion for further development and can be used to optimize the dose range to be evaluated in subsequent clinical testing.

Many phase I/II studies fail because the drug is tested in the wrong population. Positron emission tomography microdosing studies have the potential to select optimal subjects who would benefit most from the therapy. In addition, if the PET studies are performed along with traditional phase 1 dose escalation study, it can help to

Figure 1



Positron emission tomography occupancy studies regarding a receptor in human brain. The upper set of images shows the uptake of a radiolabaled drug. Brighter regions define increased radioisotope concentration. In the lower set of images, PET was performed after the administration of cold drug competing for the same binding site. Reprinted with permission from Matthews et al.[9]

Table II. Implications of PET in drug development

Preclinical development
▪ Biodistribution studies confirming that a drug candidate reaches the target tissue and does not accumulate in nontarget sites of potential toxicity
▪ Pharmacokinetics and occupancy measures to guide dose selection for early in vivo studies
▪ Use of PET as a biomarker for proof of pharmacology studies and/or to differentiate between drug-candidate efficacy data/behavior and toxicity
Phase 0 clinical studies (microdose studies)
▪ Validation that pharmacokinetic and distribution from preclinical studies can be extended to humans
▪ Occupancy analysis to get proper dose range for phases I and II
Phase 1 studies
▪ Primary opportunity is to use PET to help stratify patients based on the potential for treatment efficacy
▪ Understand the relationship of occupancy with toxicity
Phase 2 studies
▪ PET imaging can pick responders and nonresponders.
▪ Validate blood concentration as a surrogate for occupancy for phase III studies
Phase 3 studies
▪ Validate blood concentration as a surrogate for occupancy for phase III studies
▪ Imaging can pharmacologically differentiate the new drug (in trial) from marketed drugs or competitor compounds.
Clinical use of a PET radiopharmaceutical
▪ Differentiate between available treatments
▪ Detect disease or associated pathology earlier
▪ Improve disease classification or diagnosis and related drug choice (and dose)
▪ Identify/monitor disease progression and treatment

resolve the issue of target occupancy with any toxicity. Importantly, the use of PET during phase I/II trials can be a critical selection criterion for any drug candidates before they enter the phase III testing. The microdosing studies can be applied during the phase III studies to ensure the selection of the optimal patients. Positron emission tomography radiotracers specific for the experimental drug target can be used in phase III testing to differentiate the pharmacology of the agent with competitor compounds.

Finally, when the new drug becomes approved, PET can continue to be a patient selection tool as an FDA-approved radiopharmaceutical drug.

Positron emission tomography imaging of HF pathophysiology

Myocardial metabolism

Alterations in myocardial energy metabolism has been well described in HF.[12] Normal myocardium uses mainly

FAs as fuel. In conditions of increased wall stress and oxygen demand, there is an increase in myocardial oxygen consumption.[13] "Aerobic" FA is a substrate to anaerobic glucose utilization and FA uptake in ischemic regions is decreased. (*R*,*S*)-[^{18}F]fluoro-6-thiaheptadecanoic acid (FTHA) has been proposed as a PET tracer of the β-oxidation pathway. Initial results with animal models were promising, but uptake and retention in myocardium were not sensitive to the inhibition of β-oxidation by hypoxia.[14] [^{18}F]fluoro-4-thia-palmitate ([^{18}F]FTP) is structurally modified palmitate analog designed to overcome the back diffusion of nonoxidized [^{11}C] palmitate under ischemic conditions in imaging cardiac FA metabolism.[15] Because dietary oleate (18:1) is preferentially oxidized relative to palmitate (16:0) and stearate (18:0), it is anticipated that an oleic acid analog of [^{18}F]FTP might show a higher specificity for mitochondrial FA oxidation than [^{18}F]FTP itself. [^{18}F]Fluoro-4-thia-oleate demonstrated slower myocardial clearance and higher heart to blood, heart to lung, and heart to liver radioactivity concentration ratios.[15] In mild to moderate ischemia, β-oxidation ceases and anaerobic metabolism supervenes. Glucose becomes the primary substrate for increased anaerobic glycolysis and for continued, albeit diminished, oxidative metabolism.[16] [^{18}F]Fluoro-2-deoxy-d-glucose ([^{18}F]FDG) has been used to demonstrate the accelerated myocardial glucose metabolism.[17] [^{18}F]FDG can be considered an ideal radiotracer in that it mimics natural glucose through its active transport through the GLUT1 transporter and subsequent phosphorylation inside the cell. Once phosphorylated, the FDG-6 phosphate product is unable to freely diffuse out of the cell product and the position of the ^{18}F label at 2′ site makes it stable to further metabolism. The ^{18}F activity is effectively trapped inside the cell and the uptake is simply proportional to the GLUT1 transport and phosphorylation rates.

A decrease in FA metabolism and increased use of glucose as substrate in ventricular hypertrophy have been shown by PET with increased FDG uptake.[18] Similarly, decreased FA uptake and oxidation has been shown using PET with [^{11}C]palmitate and [^{11}C]glucose as radiotracers in nonischemic HF.[19] However, in a study with ischemic and nonischemic HF, Taylor et al[12] investigated the alterations in myocardial FA use in the nonischemic regions using PET with FTHA and showed that myocardial FA uptake in HF is higher than normal heart, whereas myocardial glucose uptake rates are lower. This controversy regarding the preference in human myocardial metabolism in HF has been attributed to other comorbidities that may coexist like diabetes, obesity, and insulin resistance, and more data are needed in to have a clear picture.[20] Hence, therapies targeting this shift in energy substrate in the failing heart can be developed and evaluated using PET.

Myocardial perfusion imaging

Myocardial perfusion imaging detects blood flows through the heart and can provide pathophysiologic insights into HF pathophysiology. There are 3 PET radiotracers that are used, including [^{15}O]water, [^{13}N]ammonia, and [^{82}Rb]rubidium chloride. The physical half-life of [^{15}O]water is 2.06 minutes.[21] The short half-life requires an onsite cyclotron. [^{15}O]water has been used for the quantification of myocardial blood flow (MBF) and coronary flow reserve (CFR) assessment.[22] However, it is not approved by the FDA for clinical use and is primarily used for measuring MBF in research.[21] The half-life of ^{13}N is 9.96 minutes and typically requires an onsite cyclotron for production of [^{13}N] ammonia.[21] Its use has been validated in MBF and CFR and is approved for clinical use. The half-life of ^{82}Rb is 1.25 minutes and it requires an onsite generator.[21] Although the low myocardial extraction fraction of ^{82}Rb does not render it ideal for absolute quantification of MBF and CFR, it has been widely validated for this purpose[23,24] and provides useful information in clinical setting.[25–27]

Flurpiridaz F-18 is a novel myocardial perfusion imaging tracer that is a structural analog of pyridaben, a known inhibitor of the reduced nicotinamide adenine dinucleotide/ubiquinone oxidoreductase known as mitochondrial complex-1 (MC-1).[21] In a submitochondrial assay, [^{18}F]flurpiridaz binds to MC-1 with high affinity and demonstrates high myocardial uptake for perfusion deficits. It exhibits rapid uptake in the myocardium, prolonged retention, and superior extraction compared with thallium and technetium.[28] Uptake and washout kinetics of [^{18}F]flurpiridaz in rats demonstrated a rapid uptake, with a time to half-maximal uptake of 35 seconds, and slow washout with an efflux half-time greater than 120 minutes.[29] This allows for fast and sustained accumulation in the heart. [^{18}F]flurpiridaz is currently in commercial development and is undergoing phase III trials. Three other MC-1 inhibitor classes studied in animal models are [^{18}F]RP1003 fenazaquin; [^{18}F]RP1004 or pyridaben, which demonstrated superior profile with minimal washout and less background interference; and [^{18}F]RP1005: Chromone.[30] [^{18}F]MC1-27 is a series of fluorinated pyridazinone derivatives with half minimal (50%) inhibitory concentration values ranging from 8 to 4000 nM for the MC-1. It has high cardiac uptake and minimal lung or liver interference.[31]

The combination of myocardial metabolism and perfusion could identify the presence of scarring in the myocardium. There are regions with no perfusion and FDG uptake, which are identified as scar, but importantly, there are regions with abnormal perfusion, which maybe scar or viable-hibernating myocardium. There have been several models developed calculating the percentage of the scar areas to establish prognosis[32–34] and may be useful for selection of subjects for novel therapies.

Inflammation

There are multiple imaging modalities that can detect and characterize the extent and severity of coronary atherosclerosis, but none identify patients who are at risk

for plaque rupture. Consequently, [^{18}F]FDG is being evaluated for the detection of biologically active atherosclerosis based on the premise that the tracer accumulates in activated macrophages, which are key inflammatory component of a plaque.[17] The increased uptake has been noted in animal models of atherosclerosis and, in humans, atherosclerosis of the carotid artery and aorta.[35-38] [^{18}F] attached to other compounds, such as FDG and sodium fluoride (NaF), has also been used to target and image active inflammatory atherosclerosis and micro-calcifications.[39-42]

Recently, the role of a transmembrane G-protein–coupled chemokine receptor, C-X-C chemokine receptor type 4 (CXCR4), involved in leucocyte chemotaxis, was investigated in mice model of acute myocardial infarction (AMI).[43] CXCR4 was labeled with[^{68}GA]-pentixafor, and PET demonstrated an increased uptake in the infarct region (along with the bone marrow). The radiosignal was attenuated after long-term treatment with enalapril and abolished with the infusion of a specific CXCR4 antagonist. The evidence of the involvement of this chemokine receptor in the inflammatory phase post-AMI, and the existence of an efficient CXCR4 blocker, may have therapeutic implications. However, current literature on the therapeutic use of this blocker has shown mixed results,[44,45] whereas there is an ongoing trial with another agent of this class (CATCH-AMI, ClinicalTrials.gov, NCT01905475), which may further elucidate this field.

Cardiac remodeling

Remodeling is a response of the myocardium and vasculature to a range of hemodynamic, metabolic, and inflammatory stimuli.[46] Adaptive at first, when sustained, it becomes pathogenic. The endothelial cell senses the environment and signal modulations of vascular function to maintain homeostasis and host defenses against injury.[47] Inappropriate signaling from vascular endothelial cells leads to arterial remodeling and causes atherosclerosis and hypertension.[46]

Endothelin. Endothelin receptors are transmembrane proteins that are distributed throughout the body.[48] Endothelin exists in 3 isoforms and, in addition to vasoconstriction, are involved in cell proliferation and hormone production.[49] The endothelins act through 2 receptors: subtype-A (ETA) and subtype-B (ETB). The first selective PET radioligands were the ETA-selective antagonist [^{11}C]PD156707 and the ETB-selective agonist [^{18}F]BQ3020.[50,51] ETA receptor antagonists have been extensively studied for treatment in heart disease.[52,53] Both [^{11}C]BMS-5p3 and ^{18}F-(*N*-[[29-[[(4,5-dimethyl-3-isoxazolyl) amino]sulfonyl]-4-(2-oxazolyl)[1,19-biphenyl]-2-yl] methyl]-*N*,4-fluorobenzamide) ([^{18}F]FBzBMS 5) bind selectively to the ETA receptor in vivo.[49,54] ^{18}F-labeled analog of FBzBMS 5, which is an endothelin receptor antagonist, was reported to adequately image the expression of ETA receptors even in infarcted regions of animal myocardium, demonstrating a reduced uptake after the site blockage with different doses of oral bosentan (Figure 2).[54]

Integrins. Integrins represent proteins that are involved in cell migration, proliferation, survival, and differentiation.[55] [^{18}F]fluorogalacto-RGD has high affinity for α_γ and β_3 integrin receptors, and has been developed as a PET ligand for monitoring myocardial repair after infarction.[56]

Matrix metalloproteinases. Matrix metalloproteinases (MMPs) are a group of extracellular degradative enzymes that have a pivotal role in ventricular remodeling.[57] The induction of MMP transcription is increased by activation of protein kinase C, a process that is activated by catecholamines, angiotensin II, and endothelin.[58,59] Noninvasive hybrid SPECT/computed tomography (CT) imaging approach for assessing MMP activation with ligand [^{99m}Tc]RP805, all in conjunction with cine magnetic resonance (MR) for investigation of ventricular deformation, has been studied. Matusiak et al[60] successfully labeled nanomolar affinity MMP with ^{18}F PET radioligand in an in vitro study of human bronchial and breast epithelial cancer cells.

Angiotensin-converting enzyme. Inhibiting angiotensin-converting enzyme (ACE) decreases primary pulmonary hypertension and delays pulmonary vascular remodeling. Qing et al[61] used radiolabeled [^{18}F]fluorocaptopril in PET to show that the total mass of pulmonary ACE appears to be significantly reduced in pulmonary hypertension and that only low doses of ACE inhibitors may be needed to block the effects of ACE on vascular remodeling.

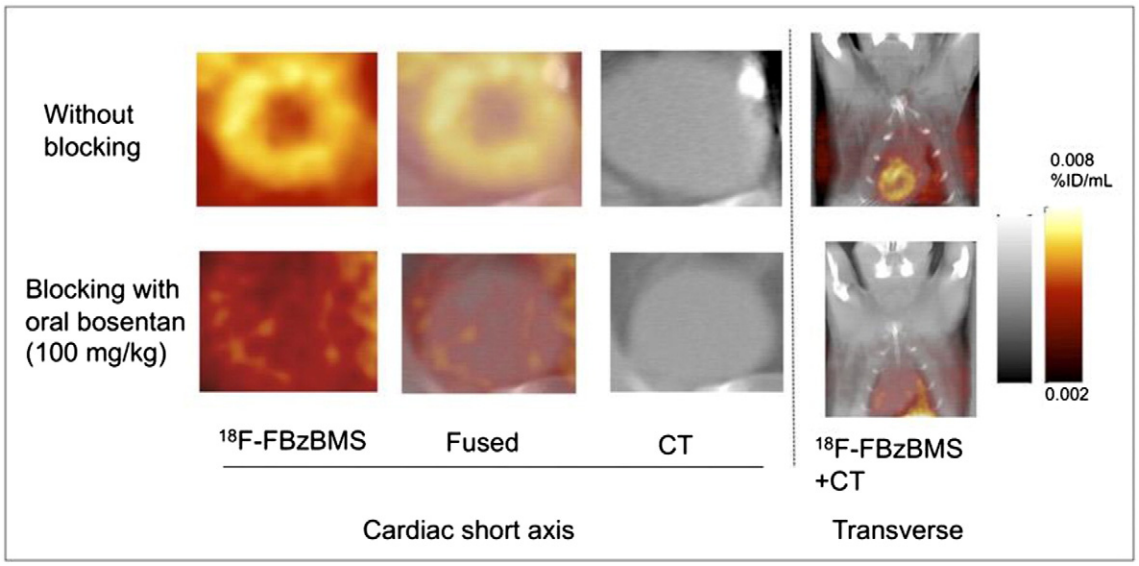
Angiotensin II type 1 receptors

The involvement of a separate myocardial renin-angiotensin-aldosterone system has been implicated in the postinfarct remodeling process, with the PET imaging of an angiotensin II type 1 receptor (AT1R)–specific labeled substrate [^{11}C]-2-butyl-5-methoxy-methyl-6-(1-oxopyridin-2-yl)-3-[[2-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl]-3H-imidazo[4,5-b]pyridine ([^{11}C]KR31173). However, it seems that there are species-specific differences in the AT1R postinfarct up-regulation because in rats, there is an increase uptake in the infarct area,[62] although in pigs, it is in both infarct and remote myocardial regions.[63] AT1R imaging was also proven to be safe in healthy humans and provide valid data regarding its blockage with the use of angiotensin receptor blockers, such as olmesartan.[63] Thus, there are extensive potentials for the study, but also for the regulation of remodeling, through the pathway of AT1R.

Cardiac innervation

The role of sympathetic activation in HF is well known. Disorders of cardiac innervation can be detected by radiotracers that target sympathetic and parasympathetic nerve terminals or postsynaptic receptors. The sympathetic nervous system is the predominant autonomic component in the ventricles. The available presynaptic sympathetic radiotracers include [^{11}C]hydroxyephedrine, [^{11}C]epinephrine, [^{11}C]phenylephirine, and [^{18}F]dopamine, whereas [^{11}C]CGP12177 and [^{11}C]GB67 are postsynaptic

Figure 2



In vivo PET and CT images in healthy rats after the infusion with the radiolabel [^{18}F]FBzBMS. Upper images show [^{18}F]FBzBMS myocardial uptake, which is significantly diminished after pretreatment with oral bosentan (lower images). There is no [^{18}F]FBzBMS uptake in adjacent organs, that is, lung and liver. ID, injected dose. This research was originally published in *J Nucl Med*. Higuchi et al.[54]

radiotracers.[17,56] The most commonly used tracer for imaging the presynaptic adrenergic function is [^{123}I] metaiodobenzylguanidine (MIBG) [^{123}I], which is not catabolized by monoaminooxidase and localizes at the presynaptic nerve endings. *N*-[3-bromo-4-(3-[^{18}F]fluoro-propoxy)-benzyl]-guanidine [^{18}F]LMI1195, shares similarities with [^{123}I]MIBG based on its benzylguanidine structure. The high specificity of [^{18}F]LMI1195 for the norepinephrine transporter has been shown.[64,65] Other ^{18}F-labeled MIBG analogs are in development.[66,67] ^{11}C-meta-hydroxyepinephrine (HED) ([^{11}C]HED) is another PET radiotracer with similar properties to MIBG but provides a higher resolution and sensitivity, while depicting the regional heterogeneity of myocardial uptake. Ischemic HF patients who developed cardiac arrest had greater denervated, but viable myocardium.[68]

Apoptosis

Myocyte apoptosis is related to worsening HF[69,70] and has been evaluated by radiolabel imaging of annexin V and caspases. Phosphatidylserine is a phospholipid in the internal cell membrane, which during apoptosis is externalized to the outer cell membrane and binds to several proteins including annexin V.[71] Annexin V, which has been labeled with ^{99m}Tc, was reported to have an increased uptake in regions of infarcted myocardium of rats.[72,73] Another area where the PET imaging of annexin V showed promising findings in animals is with chemotherapy-induced cardiomyopathy.[74] Development of PET annexin V tracers[75,76] will provide a better spatial resolution of the myocardium and provide the potential for the design and development of relevant studies.

Role of PET in HF drug development

Positron emission tomography imaging provides a promising noninvasive modality for therapeutic agents affecting myocardial metabolism. The use of PET metabolic imaging provides superior detection sensitivity in the evaluation of different targets and pathways at the cellular and subcellular level. The use of PET will bring the focus of targeting therapy in HF to the myocardium. Compared with developing new treatments for encountering the several maladaptive processes in HF, the orientation to the myocardial abnormalities has a higher chance of transitioning myocardium into recovery.[77,78]

At the preclinical stage, imaging with radiolabeled investigational drugs would allow for the study of pharmacokinetic behavior and its accumulation at the target vs nontarget tissue. Such studies could provide information if in fact the agent is reaching its target and also identify potential toxicity.[79] Investigational drug analogs used against a validated radioligand selective for the same biological target could provide quantitative measures of receptor occupancy. Such data could guide design optimal dosing and timing schedules in trials, thereby improving their efficiency and cost-effectiveness. The use of FDG as a radiotracer for glucose metabolism and viability detection in heart is well established. Although myocardial metabolism and viability are the

mainstay in cardiac PET imaging, the development of newer radioligands like rubium chloride ([^{82}Rb]$RbCl_2$), [^{15}O] water, [^{13}N] ammonia, and [^{18}F]FTHA can be used in conjunction with drugs to study their effects in early-phase trials.

Overall there are 4 main areas for the application of PET in HF drug development: (*a*) to provide information on the biodistribution of a drug, (*b*) to predict efficacy of drug candidates, (*c*) to monitor the effectiveness of therapy in early drug development phases, and (*d*) as a method for prescreening patient populations for clinical trials.[80]

Biodistribution

Biodistribution of a drug requires radiolabeling the drug itself. Bergström et al[81] developed a radiosynthesis of [^{11}C]-zolmitriptan for studying drug biodistribution. Similarly, Roche[82] used a radiolabeled antibody against human epidermal growth factor receptor-3, [^{89}Zr] RO5479599, to provide information on their trial of RO5479599 alone or in combination with erlotinib or cetuximab in patients with human epidermal growth factor receptor-3–positive solid tumors. Zofenopril, an ACE inhibitor, in its active form zofenoprilat, was labeled with [^{11}C] and was shown to have cardiac accumulation, in addition to the uptake in tissues with high levels of angiotensin converting enzyme (ACE), such as lungs and kidneys and in organs involved in drug metabolism, like liver and gall bladder.[83] In cardiovascular research, PET can give the opportunity to image the direct interaction of the potential medication with the myocardium at a cellular level. Particularly in HF, subjects have several comorbidities, such as renal and hepatic dysfunction; thus, the potential of investigating the toxicity of novel agents (by exploring their biodistribution in other tissues) in minimal doses enhances the safety and the compliance of the participants.

Drug efficacy and effectiveness

PET can be used to study the receptor occupancy of drugs. A radiolabeled biomarker of the receptor is developed which is structurally different from the drug under study to ensure that any displacement of the tracer be attributed to the drug. Nyberg et al[84] used a radioligand (*S*,*S*)-[^{18}F]FMe-NER-D2 for the norepinephrine transporter to show that norquetiapine, a metabolite of quetiapine, also has high affinity for the 5-hydroxytryptamine$_{1A}$ and dopamine D2 receptors, which may account for its efficacy in various psychiatric disorders other than its antipsychotic action. In an animal study, candesartan was labeled with [^{11}C] ([^{11}C] methyl-candesartan) and the pharmacokinetics were investigated regarding changes in the AT1Rs in the kidney.[85] Lisinopril was labeled with ^{99m}Tc to monitor the up-regulation of ACE in various tissues and, thus, the progression of the failing heart.[86] The effectiveness of the oral angiotensin receptor antagonist valsartan vs the intravenous agent SK-1080 in blocking the myocardial AT1R was investigated in rats, by comparing the uptake of the AT1R-specific radioligand [^{11}C]-2-butyl-5-methoxy-methyl-6-(1-oxopyridin-2-yl)-3-[[2-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl]-3H-imidazo[4,5-b]pyridine ([^{11}C]KR31173).[62] As collateral analysis, it was shown that the intravenous agent achieved a complete blockage of the AT1R compared with the partial effect of oral valsartan.[62]

By exploring the uptake of a labeled HF medication in the cardiovascular system and its corresponding effect to the myocardial receptors, effectiveness can be assessed thoroughly and can lead to the successful transfer of novel medications from an early to a later phase of development (Figure 3).

Prescreening patients

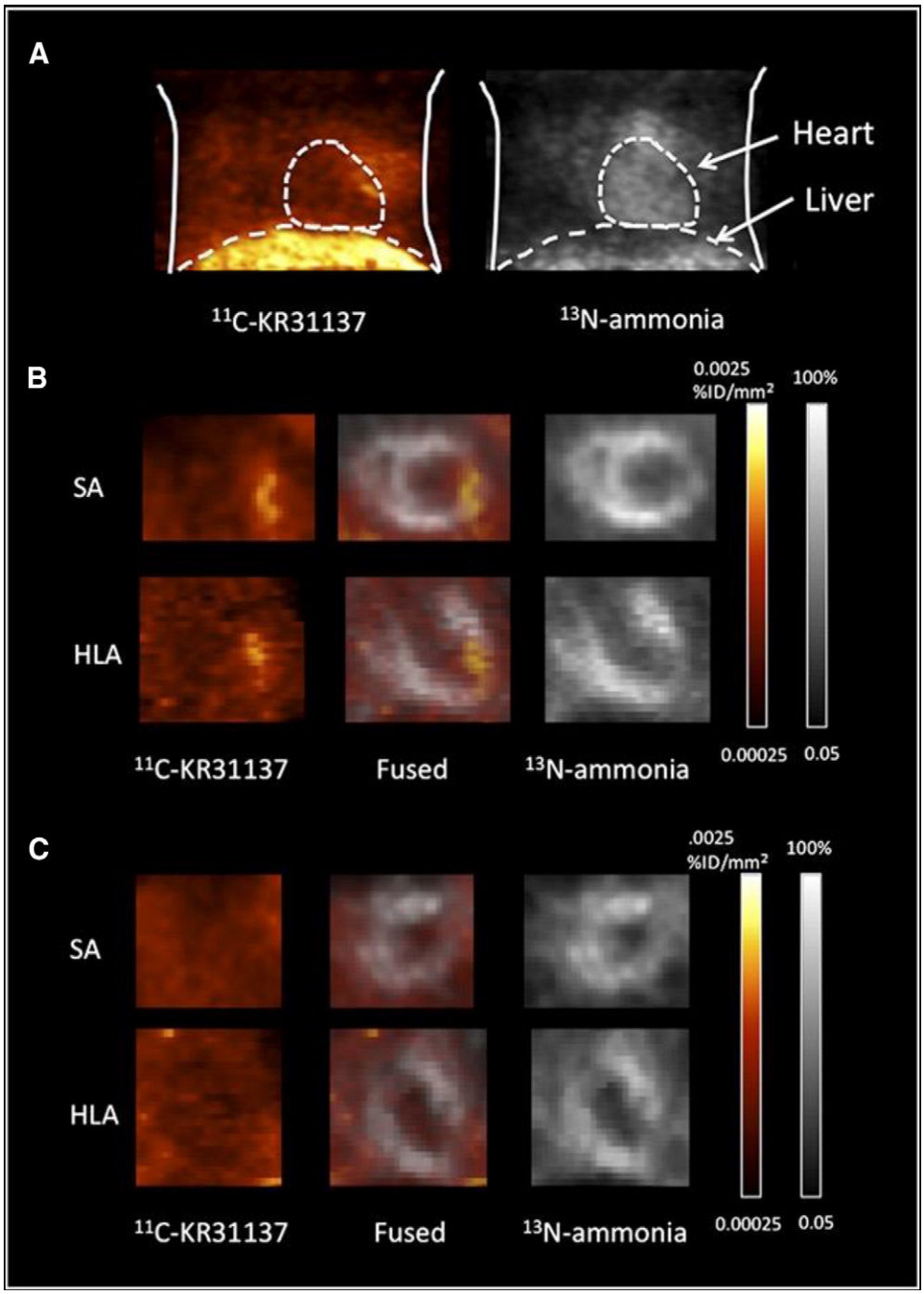
Positron emission tomography imaging may help select HF patients for specific therapies. A β-adrenoreceptor (β-AR) antagonist, [^{11}C]CGP12177, was used to measure the baseline density of the β-AR in subjects with idiopathic dilated cardiomyopathy. Patients with low levels of β-AR had greater improvement in ejection fraction after the treatment with carvedilol.[87] Imaging of cardiac innervation has also been used to risk stratify HF patients. The PAREPET study investigated the prognostic role of the quantification of cardiac denervation by using [^{11}C]HED in 204 subjects with ischemic cardiomyopathy. After 4 years, sympathetic denervation was associated with sudden arrest independent of ejection fraction and infarct volume, and thus, these patients could benefit from a defibrillator.[68] Accordingly, a multiparametric [^{18}F]FDG PET reported to predict the responders and nonresponders to cardiac resynchronization therapy.[88]

Positron emission tomography has the potential of providing significant insights into HF pathophysiology by better characterizing the myocardial substrate. Positron emission tomography can differentiate the regional state of myocardium from normal to dysfunctional but viable to viable. This in turn would contribute detecting HF patients more amenable to recovery or to determine the best timing to move to more advanced therapies and to develop new therapies targeting the myocardium.[78,89] The development of direct markers of fibrosis in animals by attaching the radioligand [^{68}Ga] to collagelin, a cyclic peptide with micromolar affinity to collagen, provides an example of such potential.[90]

Combination studies

Positron emission tomography provides higher-quality image, shorter scans, and higher temporal resolution than SPECT. Positron emission tomography combined with MR or CT gives the added benefit of functional information from PET added with anatomical information from MR or CT. Magnetic resonance delivers better soft tissue contrast with less radiation and is more sensitive for imaging myocardium. Integration of PET with MR in the presence of functional MR through MR spectroscopy,

Figure 3



In vivo PET images of rat myocardium. One week after a technically induced myocardial infarction after the administration of the radiopharmaceuticals ^{11}C-KR31137 and ^{13}N-ammonia. **A**, Anterior maximum-intensity-projection chest view. **B**, In the middle set of views, there is an increased ^{11}C-KR31173 uptake in segments with reduced myocardial perfusion by ^{13}N-ammonia. **C**, In the lower images, the infusion with AT1R blocker SK-1080 results in the absence of increased ^{11}C-KR31173 uptake. HLA, horizontal long axis; SA, short axis. This research was originally published in *J Nucl Med*. Higuchi T et al.[62]

diffusion-weighted imaging, and perfusion imaging can provide important metabolic and functional information.[91] There have been 2 approaches with PET/MR. The first consists of the 2 tests done separately, which is cost and time inefficient, and renders problems with matching the 2 sets of images related to patient repositioning and time lag. An alternate approach is using a single machine and performing the test at one time.

Safety and radiation exposure

Radiation protection and assessment of worker exposure to ionizing radiation, emitted mainly by the isotope ^{18}F, are important issues. The total effective dose to the patient from a PET/CT is ≈10 mSv. The majority comes from internal irradiation due to radiopharmaceuticals and the minority is due to the CT scan (low-dose CT scan ≈2-4 mSv). For comparison, the average background effective radiation dose is 3 mSv, a stroke protocol CT delivers 14 mSv, and an angiogram aorta CT deliver 24 mSv.[92] Compared with PET/CT, PET/MR reduces the exposure of ionizing radiation. However, PET/MR may be associated with a higher-radiation exposure for the technicians performing the examination, as patient positioning takes considerably longer, particularly when attaching and connecting the MR surface coils, during which the technician is near the gamma-emitting patient.[91]

Limitations of PET in HF drug development

The cost of PET is higher compared with echocardiography but has the potential to save unwarranted phase III clinical trials. Most of the radioligands used as investigational drug analogs have shorter half-lives and may require an on-site cyclotron; however, virtually all clinically useful tracers can be converted to ^{18}F analogs for wide dissemination. Aside from time needed to train staff to use drug-specific radiotraces and interpret PET, the time needed to develop radiotracers for use in drug testing poses a considerable burden for nuclear medicine centers. Finally, cross-laboratory standardization is needed for wide use.

Conclusion

Positron emission tomography is a mature imaging technique, with continuously growing acceptance worldwide. Beyond its applicability in diagnosis, stratification, and understanding of pathophysiology in oncology and neurology/psychiatry, the growth of radiochemistry and of novel combined molecular imaging technologies opens new horizons in cardiology and in HF, in particular. The evolution of PET could help either in the early-phase drug trials, by confirming the successful drug–tissue target interaction, or in phase II/III trials with the more convenient determination of effectiveness, efficacy, and safety and the preselection of more appropriate candidates for these emerging treatments. This might boost the transition of new under investigation agents to later-phase trials and production, by reducing the temporal and financial burden, thus providing earlier access to more promising therapies for millions of patients worldwide.

Disclosures

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