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Novel Myocardial PET/CT Receptor Imaging and Potential Therapeutic Targets

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Abstract

Purpose of the Review Activation of myocardial cannabinoid type 1 receptors (CB1-R) and/or angiotensin II type 1 receptors (AT1-R) likely plays an important mechanistic role in determining the left-ventricular remodeling process in systolic heart failure. We provide an overview on novel radiotracer probes and positron emission tomography (PET)/computed tomography (CT) imaging to noninvasively probe the expression of myocardial CB1-R and/or AT1-R.

Recent Findings Recent translational investigations have demonstrated the feasibility of ^{11}C-OMAR or ^{11}C-KR31173 and PET/CT to image and quantify myocardial CB1-R and/or AT1-R expression, respectively. There is an increasing understanding of the mechanisms of activated myocardial CB1-R and/or AT1-R to influence the left-ventricular remodeling process in systolic heart failure in different disease entities.

Summary The review summarizes contributions of PET to image myocardial CB1-R and AT1-R expression that may have the potential to serve as a target to tailor preventive medical care in the individual patient.

Keywords Angiotensin II type 1 receptors · Angiotensin-converting enzyme · Cannabinoid type 1 receptor · Heart failure · Left-ventricular remodeling · Obesity · Positron emission tomography

Introduction

The continuous steady increase in the prevalence of obesity in industrialized nations has reached a level as high as ~ 30%. This "obesity epidemic" contributes to a multitude of diseases, including the 20% prevalence of type 2 diabetes mellitus in the USA [1]. As obesity is recognized as a risk factor of cardiovascular morbidity and mortality, its increasing prevalence constitutes a major public health problem [1]. Of particular concern, obesity also reflects major risk factor for the initiation and progression of heart failure. Despite standard medical treatment of heart failure patients with B-blockers, angiotensin-converting enzyme (ACE) inhibition, angiotensin II type 1 receptor (AT1-R) blockers, and aldosterone antagonists, that have been demonstrated to beneficially alter morbidity and mortality, 5-year mortality rates for ischemic and nonischemic heart failure still remain high as 50% [2, 3]. The mechanisms by which obesity initiates and accelerates cardiovascular disease remain largely unexplored. Several potential pathogenic mechanisms have been postulated to contribute to the manifestation of left-ventricular dysfunction, such as altered circulatory state (increases in left-ventricular pre- and afterload) associated with left-ventricular remodeling, insulin

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resistance induced excessive myocardial fatty acid uptake promoting cell dysfunction and myocyte apoptosis, insulin-like growth factor 1, and leptin stimulation of myocyte proliferation and differentiation [2, 4, 5]. In particular, activations of the renin–angiotensin–aldosterone system (RAAS) as well as the myocardial cannabinoid type 1 receptors (CB1-R) via endocannabinoids may trigger myocardial dysfunction in obesity [6••, 7•]. Imaging of myocardial AT1-R and CB1-R expression with PET has raised much interest as the noninvasive identification of an upregulation of the myocardial receptors in various disease entities that may reflect novel biomarkers of cardiac risk to develop heart failure and to predict its response to preventive medical care [6••, 8••, 9••, 10•]. This review aims to summarize contributions of PET to image noninvasively myocardial CB1-R and AT1-R expression in different disease entities, to the understanding of cardiac remodeling and heart failure development, diagnostic and prognostic implications, and as an emerging target to gear preventive medical care.

Myocardial Cannabinoid Type 1 Receptor

In the last decade, it has been appreciated that the endocannabinoids and cannabinoid (CB) receptors do not play only a critical role in the regulation of brain function, food intake, energy balance, and metabolism but also in the cardiovascular system [11, 12, 13•, 14•, 15•]. Increasing evidence signifies that the activation of the CB1-R of endothelial cells of the coronary artery, cardiomyocytes, and inflammatory cells, stimulates MAPK, increases reactive oxygen species and inflammation, all of which may favor the initiation and progression of atherosclerosis and cardiac dysfunction [6••, 7•]. Obesity has been unraveled as an independent cause of an abnormal functioning of the coronary circulation, which is commonly deemed as an early functional precursor of coronary artery disease (CAD) process and a feature observed in systolic and diastolic heart failure [13•, 16–20]. The latter may also outline a mechanistic link between the function of the coronary endothelium and cardiomyocytes and potentially to myocardial receptor expressions [21, 22]. More recent evidence [6••] also suggests that increases in adipose-derived endocannabinoids, may exert not only pro-atherosclerotic effects, favoring the development of CAD, but they may also promote cardiac dysfunction by receptor signaling via CB1-R. In a diabetic obese mouse model, activation of myocardial CB1-R by endocannabinoids did lead to cardiac dysfunction via mitogen-activated protein kinases (MAPK) activation, angiotensin II receptor type 1 (AT1-RC) expression/signaling, advanced glycation end product (AGE) accumulation, oxidative/nitrate stress, inflammation, and fibrosis [6••]. In view of these findings and a known dysregulation of the endocannabinoid system in obesity [7•], someone could assume that increases in body weight may alter myocardial CB1-R expression that could reflect a mechanistic link between obesity and the initiation of obesity-related cardiomyopathy.

A specific radiotracer ^{11}C-OMAR is commonly used for PET brain imaging to identify alterations in CB1-R such as in schizophrenia [23]. More recently, the application of ^{11}C-OMAR and PET imaging in the identification of CB1-R has been extended also to the heart in the advanced obese state [8••]. In a seminal investigation, the feasibility of targeted imaging of myocardial CB1-R and its potential upregulation in obese mice with translation to humans using ^{11}C-OMAR and micro-PET/CT imaging was evaluated [8••]. As a first step, the bio- distribution of ^{11}C-OMAR and its potential uptake in the heart in obese mice was investigated. As we assumed an increase in myocardial CB1-R expression with increasing body weight, we did investigate ^{11}C-OMAR bio-distribution in obese mice in order to ascertain the highest photon counts from the heart of sacrificed mice as determined with a ɣ-counter camera. Following intravenous injection of ^{11}C-OMAR in obese mice, the highest accumulation was seen in the heart, followed by the cerebellum, thalamus, and blood at 5 min. At this time point of course, ^{11}C-OMAR blood pool activity likely contributed to the heart signal. Yet, after an initial peak of the ^{11}C-OMAR signal, it remained constant between 5 and 15 min for the heart, cerebellum, thalamus, and blood. Subsequently, the ^{11}C-OMAR declined at 30 min, while between 30 and 90 min, the accumulation of ^{11}C-OMAR and its signal of the heart, brain regions, and blood remained widely constant. Thus, between 30 and 90 min, there was a significant ^{11}C-OMAR uptake in the heart that was three times higher than the one of the blood pool, outlining CB1-R expression in the obese mouse heart. Someone could have argued, however, that the observed ^{11}C-OMAR uptake in the heart may be non-specific and also related to radiometabolites of ^{11}C-OMAR. Thus, proof of myocardial CB1-R specificity of ^{11}C-OMAR was needed. For this endeavor, a myocardial CB1-R receptor blocking study with 5 mg/kg rimonabant in obese mice as compared with vehicle was conducted. At this blocking dose, the decrease of ^{11}C-OMAR uptake in the cerebellum and thalamus was about 68%, respectively, while a bit less pronounced for the blood and myocardium by 55% and 58%, respectively. Although that the blockage of ^{11}C-OMAR uptake in the myocardium by 55% is less than for brain imaging studies of about 75% [23], it signifies predominant CB1-R specific binding of ^{11}C-OMAR in the heart. This consideration is also emphasized by the observation that in the rimonabant blocking study, the observed baseline-to-block ratio was about 2.4. This exceeds by far the receptor binding potential of a radiotracer threshold of 1 and thus is suitable for quantification with PET imaging [24]. Overall, the myocardial CB1-R blocking study with rimonabant provides proof of a predominant

specificity of ^{11}C-OMAR to identify myocardial CB1-R expression albeit some non-specific binding to other CB receptor and/or radioactive metabolites of ^{11}C-OMAR may have occurred. Finally, ^{11}C-OMAR and dynamic micro-PET/CT were applied in order to visualize and quantify myocardial CB1 receptor expression in obese and normal-weight mice. For these micro-PET/CT studies, mice were divided into two test groups; lean control C57Bl/6J mice with a median weight of 26.7 (range 24.9–31.1) gram and obese *ob*/*ob* mice with a median weight of 46.2 (range 35.0–81.3) gram. On visual analysis, myocardial OMAR uptake was clearly detectable and regionally homogenous in mice (Fig. 1a, b). As can be seen, there is relatively higher ^{11}C-OMAR myocardial uptake in the obese compared with the lean mouse that is also reflected by the time activity curves (TAC) (red: arterial input function and green: myocardial uptake response) to quantify the OMAR retention index (Fig. 1a). This is also reflected by a higher TAC course in the obese than in the lean mouse. Quantification of myocardial OMAR retention index demonstrated significantly higher values in obese than in normal-weight mice (8.29%/min [range 2.12 to 15.14%/min] vs. 0.13%/min [0.00 to 0.16%/min]; $p \leq 0.009$). Thus, there was a marked increase in myocardial CB1-R uptake in obese as compared with lean mice, outlining indeed a myocardial CB1-R up-regulation in obese mice. Importantly, these in vivo findings by ^{11}C-OMAR and dynamic micro-PET/CT were

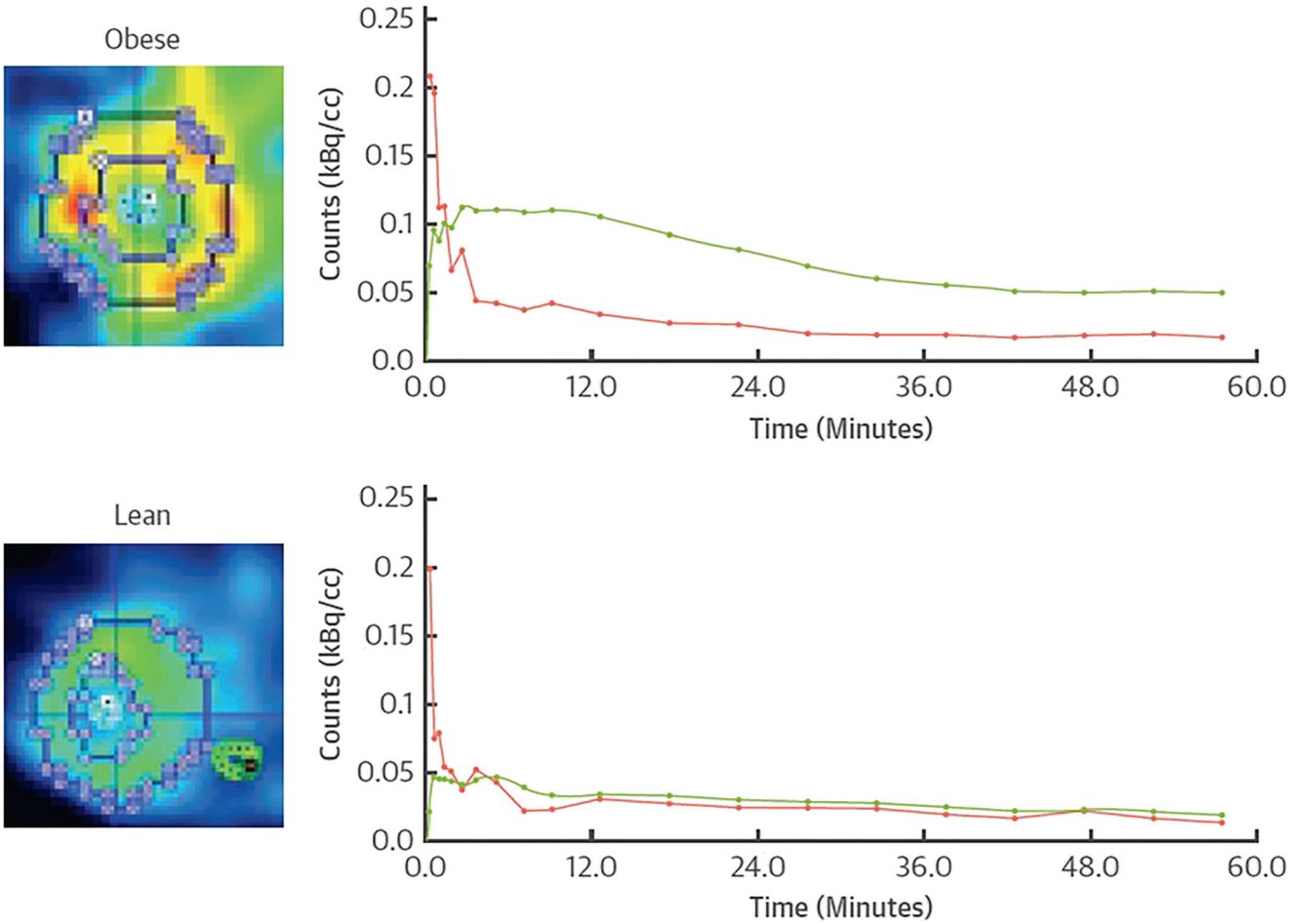


Fig. 1 Myocardial CB1-R imaging with ^{11}C-OMAR and PET/CT. **a** ^{11}C-OMAR and micro PET/CT transaxial fusion images in an obese mouse (top left). Corresponding myocardial kinetics of ^{11}C-OMAR with time-activity curves (TACs) for arterial blood pool (pink) and myocardium (green) (top right). Transaxial fusion micro PET/CT image of left-ventricular ^{11}C-OMAR uptake in a lean mouse (bottom left) and corresponding TACs (bottom right). As can be realized, ^{11}C-OMAR myocardial uptake, reflecting a noninvasive probe of CB1-R expression, is more evident in the obese when compared with the lean mouse. This is also mirrored by a higher TAC course in the obese than in the lean mouse. **b** Droplet digital polymerase chain reaction (ddPCR) fluorescence-activated cell sorting plots of CB1-R and CB2-R expression (negative control for CB1-R) in hearts of lean and obese mice and in the mouse brain (positive control for CB1-R). **c** Short-axis PET/CT (top left) of the left mid-ventricular myocardium applying ^{11}C-OMAR in individuals with advanced obesity (AOB) but no other traditional cardiovascular risk factors. Corresponding myocardial kinetics of ^{11}C-OMAR (top right) with time-activity curves (TACs) for arterial blood pool (pink) and myocardium (green). In addition, short-axis PET/CT image of the left mid-ventricular myocardium in a healthy lean participant as a control subject (CON) (bottom left) and corresponding TAC (bottom right). As can be seen, the ^{11}C-OMAR myocardial uptake in AOB is more pronounced than lean CON that is also reflected corresponding myocardial TAC course. (Reprinted from: Valenta I et al. J Am Coll Cardiol Imaging 2018;11:320-32, with permission from Elsevier) [8••]

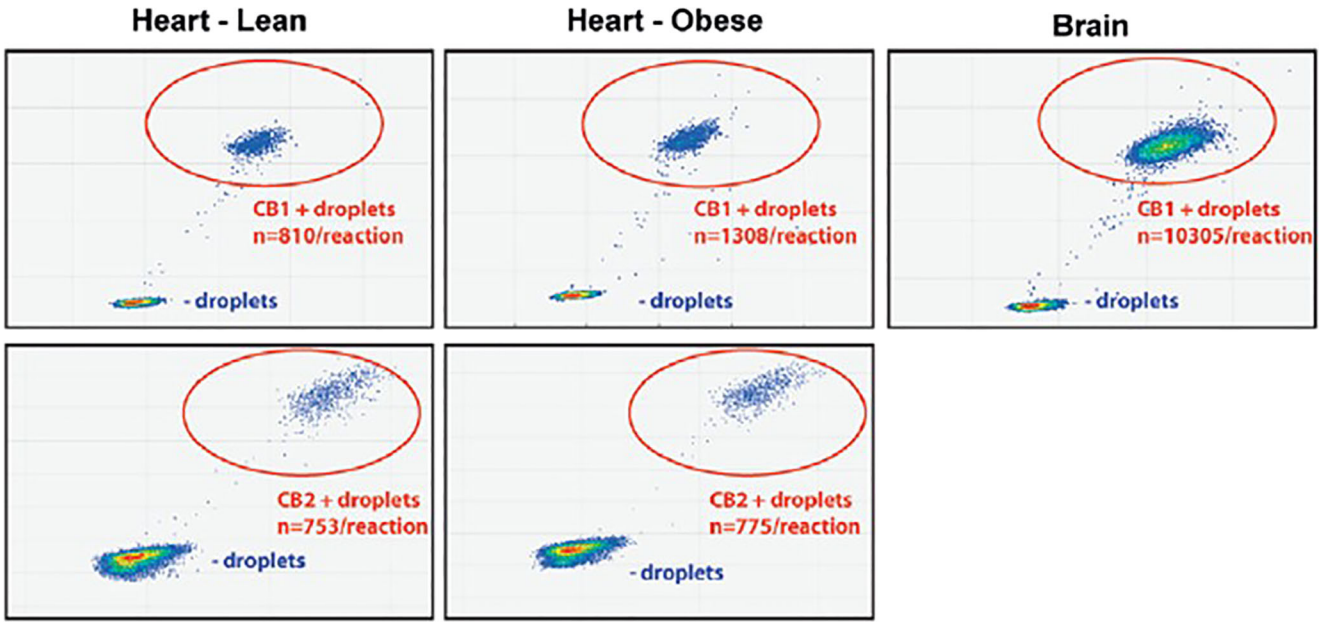
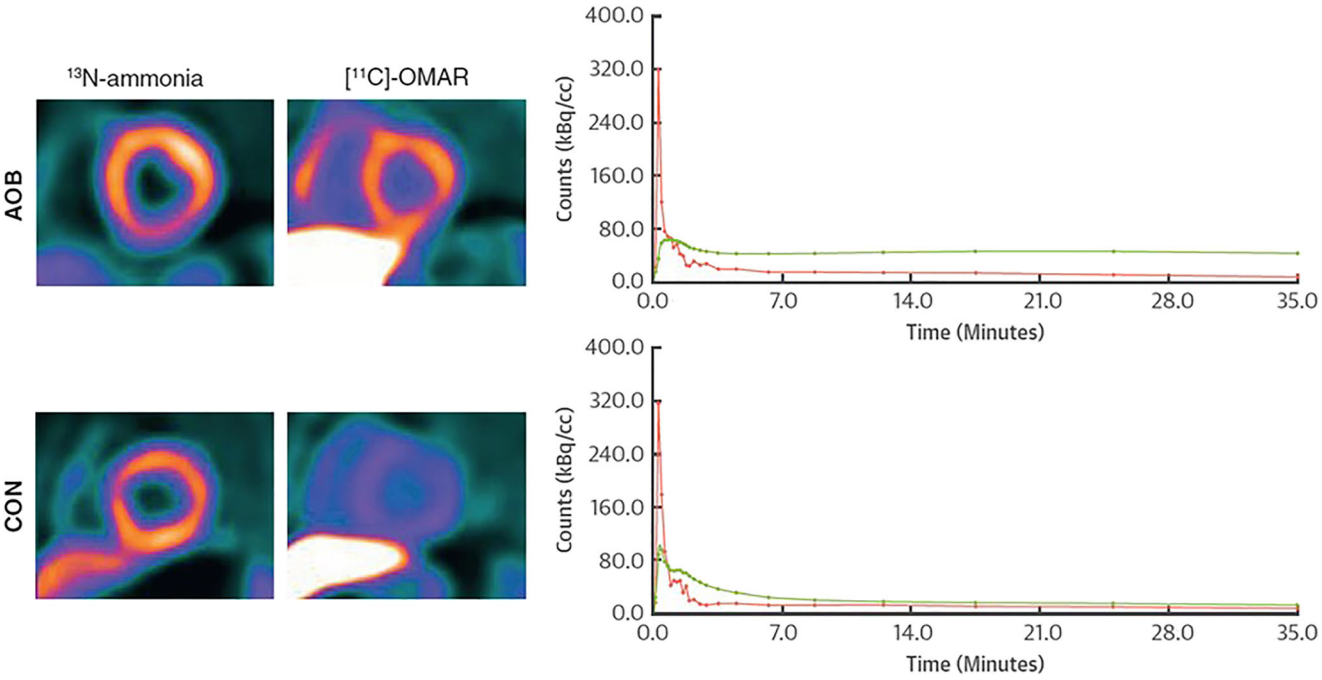


Fig. 1 continued.

validated with absolute quantification of myocardial CB1-R gene expression with droplet digital PCR and in situ hybridization (Fig. 1b). And indeed, quantification of myocardial CB1-R gene expression by droplet digital PCR signified a distinct upregulation of CB1-R not paralleled by findings in lean mice (Fig. 1b) that corresponded with an increase in ^{11}C-OMAR retention on PET images in obese mice (Fig. 1a). In addition, in order to visualize the alterations in myocardial messenger RNA expression, RNA in situ hybridization was conducted that unraveled a distinct myocardial increase of the CB1-R transcript in obese hearts. Finally, the study protocol with ^{11}C-OMAR and PET imaging was translated and applied to seven individuals with advanced obesity (AOB) (BMI ≥ 38 kg/m^2) and to five normal-weight participants as control group (CON) (BMI < 25 kg/m^2). Each study individual underwent ^{13}N-ammonia and ^{11}C-OMAR PET/CT to noninvasively assess myocardial perfusion at rest as visual reference and CB1-R expression, respectively. As expected, resting ^{13}N-ammonia retention on PET/CT images was homogeneous in AOB and CON. In regard to the visualization of myocardial



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CB1-R with ^{11}C-OMAR, the signal was widely homogenous throughout the left ventricle but higher in AOB than in CON (Fig. 1c). Quantification with time activity curves (red: arterial input function and green: myocardial uptake response) also signifies a higher OMAR retention index in AOB. This is appreciated by the results of the absolute left-ventricular retention of ^{11}C-OMAR that was significantly higher in AOB than in CON (median 5.68%/min [range: 1.88 to 6.89%/min] vs. 0.47%/ min [0.13 to 1.31%/min]; $p \leq 0.006$), signifying indeed myocardial CB1-R upregulation in AOB in comparison with normal-weight CON. Thus, in vivo imaging, applying ^{11}C-OMAR and PET/CT in mice and humans could demonstrate for the first time an upregulation of myocardial CB1-R in the advanced obese state that was be confirmed with absolute quantification of myocardial CB1-R expression in mice with digital PCR and RNA in situ hybridization [8••]. The increased myocardial expression of CB1-R messenger RNA in obese mice was not only seen in cardiomyocytes but also in part endothelial cells, vascular smooth muscle cells, and fibroblasts. Since it was impossible to separate the cardiac ^{11}C-OMAR PET signal among these cardiovascular cells, a minor portion of the ^{11}C-OMAR signal likely originated from the coronary vessels and fibroblast that, however, is neglectable as in situ hybridization outlines. The observed up-regulation of myocardial CB1-R, however, may indeed represent a mechanistic link between obesity and the initiation and/or progression of obesity-related heart failure. If this assumption holds true in future experimental and clinical investigations, then new medical therapy strategies may target to block the myocardial CB1-R, e.g., with peripherally restricted CB1 antagonists, in those morbidly obese patients not undergoing gastric bypass surgery, or those with relapse into advanced obesity after successful gastric bypass surgery, or those with non-morbid obesity.

It is of interest to note that ^{11}C-OMAR, like other CB1-R radiotracers such as ^{18}F-MK-9470, ^{18}F-FMPEP-d2, ^{11}C-MePPEP, and ^{11}C- SD5024, has been commonly used for CB1-R imaging in the brain. These positron emission tomographic radiotracers are structurally related to the CB1-R inverse agonist rimonabant (SR141716) and possess high lipophilicity [25, 26]. The lipophilicity of ^{11}C-OMAR leads to a pronounced uptake of ^{11}C-OMAR in the liver that may compromise the analysis of the myocardial ^{11}C-OMAR uptake in the inferior and inferoseptal wall. Such a limitation of ^{11}C-OMAR radiotracer characteristics calls for the development of less lipophilic CB1-R radiotracer ligand with improved imaging characteristics [26]. The CB1-R affinity of ^{11}C-OMAR, however, ranges from Ki = 2.1 to 11 nmol/l [27]. This affinity in conjunction with the relative fast kinetics of ^{11}C-OMAR affords shorter brain and cardiac positron emission tomographic scans compared with other radiotracers, which commonly need 90 to 120 min of data acquisition. Overall, further developments in CB1-R radiotracers are certainly desirable to further reduce the high lipophilicity of ^{11}C-OMAR and to increase its affinity to the CB1-R for an optimal diagnostic yield for the noninvasive detection and characterization of myocardial CB1-R in individuals with increasing body weight. Such an optimal diagnostic yield appears to be critical for an accurate evaluation of myocardial CB1-R expression in relation to increasing body weight. It remains to be investigated whether there is a proportional or disproportional increase in myocardial CB1-R expression over the whole spectrum of increasing body weight. For example, if there is a disproportional increase in myocardial CB1-R expression with increasing body weight, then a certain threshold of body weight may apply that is likely to be associated with a marked upregulation of myocardial CB1-R expression. This likely could afford the identification of those individuals that may benefit most from medical and/or behavioral interventions related to weight gain, diet, and physical activity striving to reduce effectively myocardial CB1-R expression.

Scintigraphic Imaging from Myocardial Angiotensin-Converting Enzyme to Angiotensin II Type 1 Receptors

The renin–angiotensin and kallikrein–kinin systems are not only systemically, but also locally, active in the myocardium [3]. This local myocardial production of angiotensin is assumed to play a critical role, apart from the effects of circulating angiotensin levels in the circulation, in the remodeling process of the left ventricular myocardium in various cardiac disease states [3]. Previous experimental investigations [28•] have demonstrated the feasibility of ^{18}F-radiolabeled ACE inhibitor, ^{18}F-captopril, to image ACE in vivo in the lung, kidney, and aorta. In a seminal paper by Dilsizian et al. [29••], this concept was extended to using ^{18}F-fluorobenzoyl-lisinopril (FBL) in the heart. In an elegant study, the presence and distribution of ACE activity in relation to collagen replacement were determined in three explanted human hearts in individuals undergoing heart transplantation. All explanted hearts were incubated in vitro with the radiotracer ^{18}F–FBL, with and without lisinopril. Subsequently, tissue radioactivity was recorded as a function of position in photo-stimulating luminescence units, while immunohistochemistry studies were conducted with mouse monoclonal antibody against ACE, and polyclonal antibody against the human AT1R. Indeed, the investigators were able to demonstrate specific binding of ^{18}F–FBL to ACE, and moreover, the binding of FBL was heterogeneous in infarcted, peri-infarcted, and remote, non-infarcted myocardial regions. In this respect, ACE binding in peri-infarcted segments proved to be about 1.3-fold greater than binding in remote, non-infarcted regions. This heterogeneous

distribution was also noted with AT1R immunoreactivity. ACE activity and AT1R immunoreactivity were increased in the juxtaposed regions of replacement fibrosis that confirms the central role in the initiation and progression of the remodeling and scarring process of the collagen matrix in ischemic heart failure patients. In the following, these findings were expanded to the application of technetium-99 m–labeled lisinopril (Tc-Lis) in conjunction with micro single-photon emission computed tomography (SPECT)/computed tomography (CT) to noninvasively image over-expression of human ACE-1 in the heart of transgenic rats as compared with wild type controls [10•]. And indeed, on micro SPECT/CT, myocardial ACE-1 uptake was best displayed in transgenic rats and fivefold higher than in control rats after intravenous injection of Tc-Lis. The myocardial uptake of Tc-Lis also closely correlated with post-mortem analyzed myocardial ACE enzyme activity emphasizing the accuracy of this novel noninvasive molecular imaging approach. In addition, blocking studies of myocardial Tc-Lis with pretreatment of cold lisinopril demonstrated a high specificity this radiotracer to myocardial ACE-1 (Fig. 2). These initial groundbreaking observations [10•, 29••] opened a new field in the noninvasive identification of patients with increased myocardial ACE activity likely to undergo an adverse myocardial remodeling process with transition to heart failure. Such observations for scintigraphic myocardial ACE imaging with ^{18}F–FBL or Tc-Lis were also expanded to the noninvasive imaging of myocardial angiotensin II type 1 receptor (AT1-R) with positron emission tomography (PET). Activation of myocardial angiotensin II type 1 receptor (AT1-R) by angiotensin II has been widely appreciated to play a key role in the initiation and development of various heart failure conditions [4, 9••]. Stimulation of myocardial AT1R may lead to hypertrophic growth, interstitial myocardial fibrosis, progressive loss of contractile proteins, and defective excitation-contracting coupling manifesting in a progressive decrease of systolic function [3]. Treatment with angiotensin-converting enzyme inhibitors (ACE-I) or AT1-R blockers have been proven beneficial in the prevention and/or delay of left-ventricular remodeling paralleled by reductions in clinical symptoms, frequency in hospitalization, and mortality in systolic heart failure patients [30]. Conversely, there

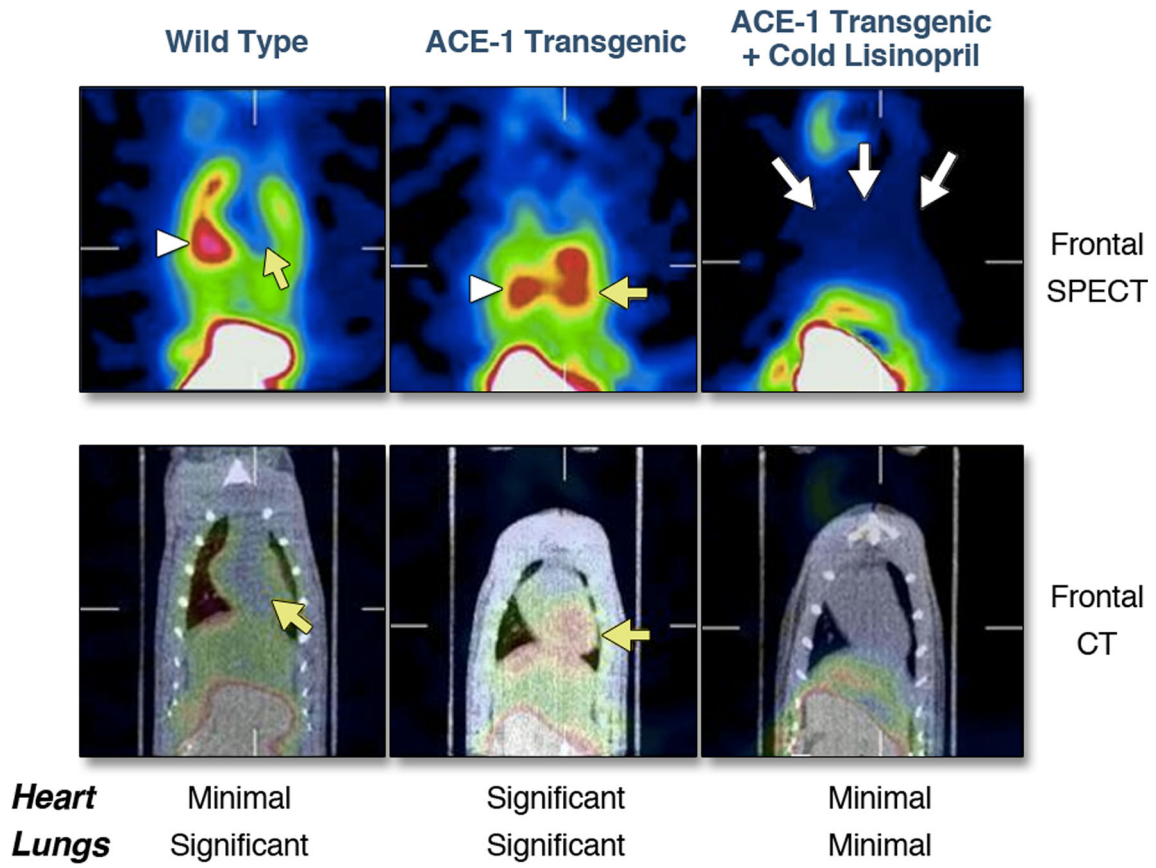

Fig. 2 ACE-1 activity determined with micro SPECT/CT. Micro SPECT/CT with delineation of myocardial technetium-99 m–labeled lisinopril uptake 60 min after tracer administration, in a control animal (left), angiotensin-converting enzyme (ACE)-1 over-expressing transgenic animal (middle), and a transgenic animal after cold lisinopril administration (right). White arrowhead signifies demonstrates intense lung uptake, while yellow arrows indicate myocardial ACE-1 activity. White arrows stress a substantial reduction in technetium-99 m–labeled lisinopril uptake after pretreatment with non-radiolabeled lisinopril application. (Reprinted from: Dilsizian V et al. JACC Cardiovasc Imaging 2012;5:409-8, with permission from Elsevier) [10•]

may be a distinct variability in individual treatment responses to ACE-I and/or AT1-R blockers, ranging from marked improvement in clinical symptoms to no identifiable or even worsened treatment response [30]. The underlying mechanisms of the observed variability in treatment responses to ACE-I and/or AT1-R blockers remain obscure but have been related in part to differences in race, ethnicity, comorbid conditions, co-medication, myocardial tissue components of the renin-angiotensin system, and a genetic susceptibility [31, 32]. Recent advances in radiotracer developments [9••, 33••] have put forth ^{11}C-KR31173 and PET/CT imaging as a promising approach to visualize and quantify myocardial AT1-R. Such an approach could proof unique in cardiovascular prognostication in the treatment response to ACE-inhibitors and/or AT1-R blockers in systolic heart failure patients. Higuchi et al. [33••] were first to demonstrate the feasibility of ^{11}C-KR31173 and PET/CT to image upregulated myocardial AT1-R in the region of myocardial infarction in a rat model. Evidence of the specificity of ^{11}C-KR31173 was also provided by blocking studies with SK-1080, a potent AT1-R antagonist, and valsartan. This resulted into a complete or partial blockage (≈ 60%) of the myocardial ^{11}C-KR31173 signal, respectively. Conversely, application of enalapril had no blocking effects on the myocardial ^{11}C-KR31173. Subsequently, Fukushima et al. [9••] translated these observations to an infarction model in the pig and healthy humans. ^{11}C-KR31173 blocking studies with the AT1-R blocker olmesartan provided proof of the specificity of this novel radiotracer for myocardial AT1-R imaging (Fig. 3). Also here, the application of ^{11}C-KR31173 and PET/CT unraveled an upregulation of AT1-R expression in the area of myocardial infarction relative to the remote myocardium in the pig model. Interestingly, the AT1-R expression in the remote myocardium of the pig infarction model was higher when compared with the mild and physiologic myocardial AT1-R expression in healthy humans that may also suggest an inflammatory activation or mild upregulation of myocardial AT1-R expression going beyond the region of myocardial infarction affecting the remote myocardium and thereby likely also the remodeling process [34–38]. Substantial binding of ^{11}C-KR31173 to AT1-R expressions of increased myofibroblasts in the region of myocardial infarction, however, need to be taken into account [37]. As the imaging signal derived from myocardial ^{11}C-KR31173 uptake cannot separate between myofibroblasts and cardiomyocytes, the exact contributions of these cell lines to the signal in the infarcted regions still remain to be explored [3, 9••, 33••]. Despite the promising results of ^{11}C-KR31173 and PET/CT in imaging and quantifying myocardial AT1-R expression in normal and abnormal conditions, further evaluation of the feasibility and practicability of this PET imaging approach in different forms of heart failure development is warranted.

Furthermore, apart from measuring noninvasively AT1-R expression with ^{11}C-KR31173 and PET/CT, it would be of additional interest to investigate angiotensin-converting enzyme (ACE)-1 upregulation in the myocardial tissue in order to acquire more mechanistic insight in the myocardial RAS activation in various cardiovascular disease entities. Combining both noninvasive imaging methodologies to display myocardial AT1-R and ACE-1, therefore, could indeed represent a unique pathway to gain novel in vivo insight in pathophysiology and molecular mechanism in various cardiac disease entities of RAS activation [3, 9••, 10•].

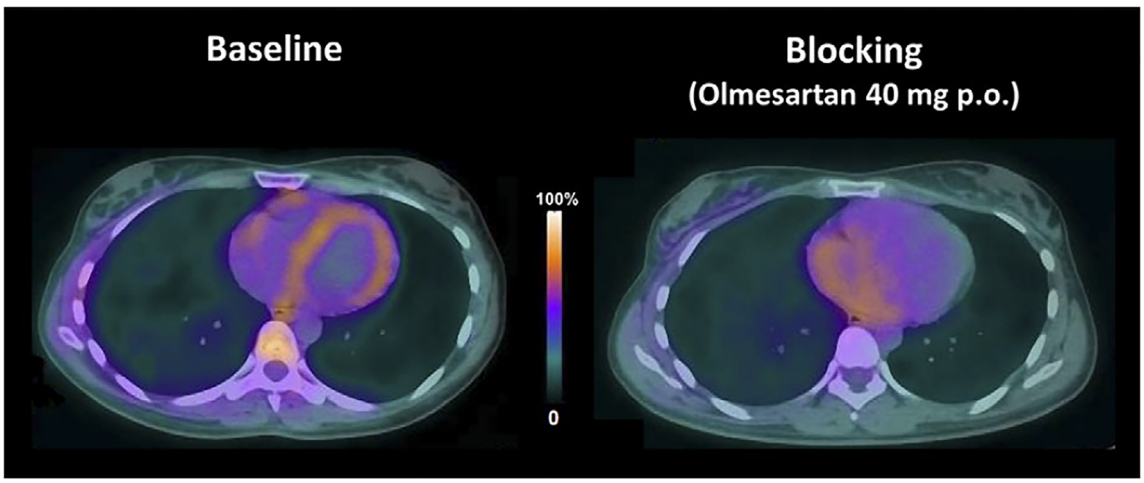

Fig. 3 Myocardial AT1-R imaging with ^{11}C-KR31173 and PET/CT imaging. Baseline transaxial PET/CT images in the mid-ventricular myocardium demonstrate homogeneous uptake of ^{11}C-KR31173 in left-ventricular myocardium (left side). Repeat imaging 3 h after an oral (p.o.) dose of 40-mg olmesartan for specific blocking of AT1-R signifies complete absence of the radiotracer signal in the myocardium, unraveling the specificity of ^{11}C-KR31173 for AT-R imaging (right side). Some minor radiotracer blood pool activity of atria and ventricles, however, is noted. (Reprinted from: Fukushima K et al. J Am Coll Cardiol 2012;60:2527-34, with permission from Elsevier) [9••]

Conclusions

In vivo imaging of myocardial CB1-R and/or AT1-R expression with novel radiotracer probes and PET/CT may have the potential to afford image-guided and "individualized" medical therapy in the prevention and/or reduction of the progression of systolic heart failure manifestation due to various disease conditions. Treatment doses of preventive medical pharmacotherapy could be adapted according to imaging findings of myocardial CB1-R and/or AT1-R expressions as determined with PET/CT. For example, instead of a standard medical dose, according to the quantified myocardial CB1-R and/or AT1-R receptor expressions, the doses needed for optimal receptor blockade may be even lower with less potential adverse side effects (safety in clinical use). In some case, so-called non-responders, higher doses of pharmacotherapy may be needed to achieve complete suppression of the signal and, thus, optimal preventive treatment effect to improve patient outcome. While these considerations may be intuitively attractive, it warrants further validation and clinical testing.

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Compliance with Ethical Standards

Conflict of Interest Ines Valenta, Pal Pacher, and Vasken Dilsizian declare that they have no conflict of interest.

Thomas H. Schindler reports personal fees from advanced accelerator application (AAA), Geneva, Switzerland.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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