Imaging of myocardial inflammation with somatostatin receptor based PET/CT — A comparison to cardiac MRI

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ABSTRACT

Background: Acute myocarditis as well as post-ischemic myocardial inflammation are generally associated with a profound activation of the immune system. Current established imaging techniques such as cardiac MRI reliably demonstrate signs of acute myocardial injury. However, detection of mediating cells such as macrophages is currently limited to experimental settings. We aimed to investigate the feasibility of somatostatin receptor (SSTR) based positron emission tomography/computed tomography (PET/CT) for detecting inflammatory lesions in patients after acute myocardial infarction or acute peri-/myocarditis.
Methods: 12 patients with active peri-/myocarditis (n = 6) or sub-acute myocardial infarction (n = 6) underwent SSTR-PET/CT and cardiac MRI within 3–10 days after onset of symptoms. The AHA 17-segment model of the left myocardium was used for visual localization of inflamed myocardium for both imaging modalities. Tracer uptake of infarcted/inflamed myocardium was assessed as mean and maximum standardized uptake value (SUV_{mean} and SUV_{max}) and compared with both remote myocardium and left ventricular (LV) cavity.
Results: SSTR-PET/CT revealed areas with increased cardiac tracer uptake in all patients. In the 17-segment model, PET/CT yielded 55 and MRI 47 positive segments. Overall, concordance of the 2 modalities was 85.3% (174/204 segments analyzed). In 9.3% (19/204), more positive segments were identified by PET/CT, whereas in 5.4% (11/204), MRI detected more positive segments.
Conclusions: The imaging patterns of SSTR-directed radiotracers and MRI in vivo show a close spatial relation of macrophage concentration and structural changes. This suggests the possibility of a new potential biomarker that predicts cardiac remodeling and, hence, progression towards heart failure. Prospective trials are warranted.

1. Introduction

Macrophages and monocytes play a pivotal role in healing processes of the myocardium [1]. After infarction, they are crucial effectors in orchestration of the balance between inflammation and its resolution [1–5]. Delayed healing has been reported for areas of microvascular obstruction due to impaired macrophage recruitment [1,5]. In myocarditis, the macrophage-triggered immune response is mandatory to fight viral or other agents [6]. Although endomyocardial biopsy remains the gold standard for establishing the diagnosis of myocarditis, its sensitivity is variable and might be as low as 10–35% [7,8].

Magnetic resonance imaging (MRI) is the gold standard in cardiovascular imaging and plays an unequaled role in the non-invasive diagnosis of myocardial inflammation and healing. Contrast-enhanced T1- and T2-weighted sequences allow structural assessment. T2-weighted sequences reveal intra-myocardial edema associated with acute inflammation [9]. The differentiation between acute myocarditis and (sub-)acute infarction is based on distinct features in T2-weighted and contrast-enhanced images. Whereas inflammation can occur throughout the heart and is usually limited to the epi- and myocardium, ischemia also affects the (sub-)endocardium and is confined to the area supplied by the culprit vessel. Microvascular obstruction, an indicator of severe tissue damage, can be detected in re-perfused infarct areas as signal void due to slow contrast penetration secondary to endothelial swelling and embolization by cell debris [10].

Myocardial inflammation can also be visualized effectively using the glucose analog ^{18}F-fluorodeoxyglucose (^{18}F-FDG) in positron emission tomography (PET) as glucose metabolism is activated by enhanced

expression of glucose transporters and production of glycolytic enzymes in inflammatory cells [11]. Its use in endocarditis as well as in myocarditis has been reported [12–14]. However, specificity of PET with ^{18}F-FDG is hampered by physiologic ^{18}F-FDG accumulation in healthy myocardium [15]. Activated macrophages have been described to overexpress somatostatin receptor subtypes 1 and 2 (SSTR) on their cell surface during differentiation of monocytes [16,17]. Since these receptors display active binding sites, specific SSTR-targeted radiotracers such as ^{68}Ga-DOTA-TATE or -TOC may be used to directly identify activated macrophages. Recently, inflammation of large arteries has been detected by PET imaging of the somatostatin receptor (SSTR) subtype 2 by demonstrating increased tracer uptake in large vessel artherosclerotic plaques [18,19]. Detection of myocardial inflammatory activity would facilitate making the diagnosis of acute myocarditis in patients in whom conventional imaging is inconclusive and/or endomyocardial biopsies unyielding or not achievable. Furthermore, assessment of macrophage kinetics after ischemic damage as well as spatiotemporal monitoring of inflammatory activity might gain new insights into the pathophysiology of inflammation and offer a new promising target for both patient monitoring and therapy assessment.

As SSTR-targeted radiotracers for PET/CT imaging are more specific for inflammation and lack physiologic myocardial uptake, they might prove well-suited for specifically visualizing myocardial inflammation. Therefore, we investigated the concept of macrophage detection with SSTR-PET/CT in comparison to cardiac MRI in patients with sub-acute myocardial infarction and acute peri-/myocarditis, respectively. Our hypothesis was that SSTR-PET/CT provides complementary information to MRI for imaging myocardial inflammation.

2. Materials and methods

2.1. Subjects and study design

From December 2013 to June 2014, a total of 12 patients (7 males and 5 females, mean age, 52 ± 10 years: range, 33–70 years) with the suspicion of inflammatory heart disease underwent both SSTR-PET/CT as well as cardiac MRI on a compassionate use base. Six patients (all male) presented after myocardial infarction diagnosed according to current national and international guidelines [20]. The remaining 6 patients (5 female, 1 male) suffered from acute pericardial or myocardial inflammation as defined by Lake Louise criteria [9]. Imaging was performed within 3–10 days after the onset of symptoms (mean, 7 ± 3 days; delay between PET and MRI, 3 ± 3 days).

German federal laws accept the use of the radiotracer ^{68}Ga-DOTA-TOC under conditions of the pharmaceutical law. The local ethics committee granted compassionate use of ^{68}Ga-DOTA-TOC-PET/CT in a limited number of pilot patients. Written informed consent was obtained prior to imaging from all patients.

2.2. Preparation of ^{68}Ga-DOTA-TOC

^{68}Ga-DOTA-TOC was prepared using a modification of the method described previously by Breeman et al. [21] using a SCINTOMICS module (Scintomics, Fürstenfeldbruck, Germany). The synthesis was carried out on a computer-assisted synthesis module (Scintomics, Fürstenfeldbruck, Germany). The labeling procedure was optimized concerning amount of peptide, reaction time and reaction temperature. Radiochemical purity was determined by gradient HPLC (Scintomics, Fürstenfeldbruck, Germany).

2.3. PET imaging

PET scans were acquired using an integrated PET/CT scanner (Siemens Biograph mCT 64, Siemens, Knoxville, USA) consisting of a LSO full-ring PET and a 64-slice spiral CT. 104 ± 30 MBq of ^{68}Ga-DOTA-TOC was injected. After a period of 60 min, transmission data were acquired using low-dose CT of the thorax (80 mAs, 120 kV, 512×512 matrix, 5 mm slice thickness, increment of 30 mm/s, rotation time of 0.5 s, and pitch index of 0.8). Consecutively, PET emission data were acquired in three-dimensional mode with a 200×200 matrix with 10 min emission time. After decay and scatter correction, PET data were reconstructed iteratively with attenuation correction using a dedicated software (HD PET, Siemens Esoft).

Images were first inspected visually by two experienced nuclear medicine physicians (CL and AKB). For quantification of increased tracer uptake, a visual score using the terms "mild", "moderate" and "intense" was used. Areas of increased ^{68}Ga-DOTA-TOC accumulation were documented using the 17-segment AHA heart model [22].

For semi-quantitative analysis, the axial PET image slice with maximum cardiac uptake was selected. A standardized 15 mm circular region was placed over the area with the peak activity. This first ROI was used to derive maximum (SUV_{max}) and mean standardized uptake values (SUV_{mean}). SUV_{max} and SUV_{mean} were also derived in normal reference regions defined by two distinct methods: (1) a second ROI (diameter of 15 mm) in a remote region of the left ventricular wall without late-gadolinium-enhancement (LGE) in the corresponding MRI data (if applicable) and (2) another ROI with a diameter of 25 mm in the left ventricular cavity. Signal-to-background ratios were calculated for each method.

For inter-individual comparison, 20 consecutive oncologic patients (12 males; 8 females; mean age, 53 ± 13 years) with no history of coronary artery disease or other known cardiac disease undergoing SSTR-PET/CT (120 ± 27 MBq ^{68}Ga-DOTA-TOC) for staging purposes were enrolled. In this patient cohort, imaging started 45–60 min after tracer injection with 2 min emission time per bed position. As for the infarction/myocarditis cohort, cardiac uptake was defined by placing a ROI with a diameter of 15 mm in the left lateral ventricular wall.

2.4. MRI imaging

MRI was performed on a 1.5 T scanner (Achieva 1.5 T, Philips Healthcare, Best, The Netherlands), using a 32 element phased array coil for radiofrequency reception. Sequences were gated to the heart cycle via a four lead vector cardiogram. The protocol included a morphologic study based on balanced turbo field echo sequences for documentation of standard cine long and short axis views (FOV 380 mm, flip angle 60°, TE 2.6–3.0 ms, TR 130–158 ms). A T2-weighted multi-echo gradient echo sequence was used for imaging myocardial edema in both long and short axes (FOV 370 ms, NSA 2, TE 90 ms, TR 2000–3600 ms, TR (beats) 3). Late enhancement imaging was performed 9 to 12 min after antecubital intravenous administration of 0.15 mmol/kg of a gadolinium based contrast agent (Gadobutrol, Bayer HealthCare, Leverkusen, Germany). An inversion recovery T1 turbo field echo sequence was used, and the inversion time was adjusted to completely null the myocardial signal.

Image analysis was performed using the Extended Workspace software (EWS, Philips Healthcare, Best, The Netherlands) and followed European standards [23]. In analogy to PET, all LGE scans were segmentally analyzed with regard to scar distribution within the myocardium according to the 17-segment model.

2.5. Statistical analysis

Quantitative data are presented as median, range, and mean $\pm$ SD. The Wilcoxon signed rank test and the Mann–Whitney test were used for paired and unpaired comparisons of quantitative parameters. Statistical analyses were performed using SPSS Statistics software for Windows (version 22.0, SPSS Inc., Chicago, USA). All statistical tests were performed two-sided and a p-value < 0.05 was considered statistically significant.