[68Ga]Pentixafor-PET/CT for imaging of chemokine receptor 4 expression after myocardial infarction [Letter]

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[^{68}Ga]Pentixafor-PET/CT for Imaging of Chemokine Receptor 4 Expression After Myocardial Infarction

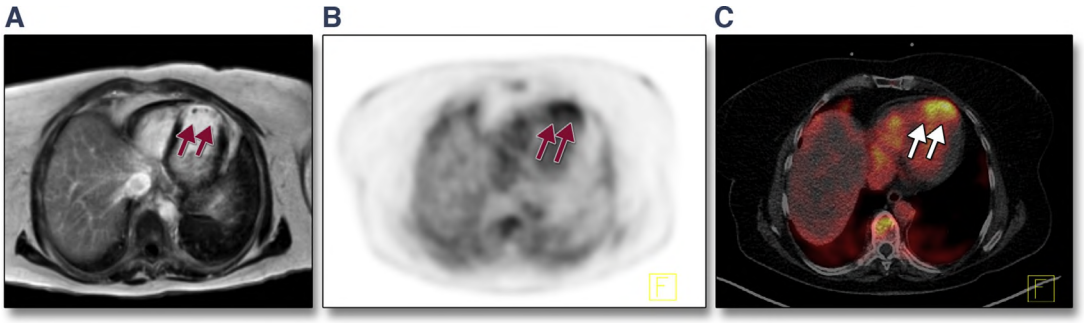
Due to the inability of myocytes to regenerate, acute and sustained ischemia usually results in irreversible myocardial damage and subsequent remodeling processes. Chemokine receptor 4 (CXCR4)/stromal cell-derived factor (SDF)-1α play a pivotal role in the recruitment and homing of stem and progenitor cells to the infarct zone (1). Prolonged myocardial SDF-1α expression after infarction has been demonstrated to result in beneficial outcomes (2) Additionally, CXCR4 is normally expressed on various immune cells and therefore is involved in the orchestration of post-infarct inflammation and its resolution (3).

Recently, a radiolabeled CXCR4 ligand ([^{68}Ga] Pentixafor) for positron emission tomography (PET) imaging has been developed (4). This is the first report of noninvasive detection of CXCR4 expression in the human myocardium after acute myocardial infarction.

Seven patients (4 men and 3 women, mean age 62 ± 14 years) with (sub)acute myocardial infarction underwent imaging with cardiac magnetic resonance (CMR) (n = 6) and Pentixafor-PET (all, 126 to 161 MBq/patient) within 5 to 10 days after symptom onset (mean 8 ± 2 days; delay between PET and CMR 1.0 ± 0.5 days). All patients gave written informed consent before imaging. Static PET scans were acquired 60 min post-injection using an integrated PET/computed tomography (CT) scanner (Siemens Biograph mCT 64, Siemens, Knoxville, Tennessee). CMR was performed on a 1.5-T scanner (Achieva 1.5T, Philips Healthcare, Best, the Netherlands) including steady-state free precession cine, T2-weighted turbo spin echo, and multishot inversion recovery turbo field echo sequences.

Images were first inspected visually. For quantification of increased tracer uptake, a visual score using the terms *mild*, *moderate*, and *intense* was employed. Affected areas were documented using the 17-segment American Heart Association heart model. For semiquantitative analysis, a 15-mm circular region was placed over the infarcted areas to derive maximum standardized uptake value (SUV_{max}) and

FIGURE 1 Increased ^{68}Ga-Pentixafor Uptake in Acute Myocardial Infarction Affecting the Left Anterior Descending Artery



Axial slices of both **(A)** contrast-enhanced multishot inversion recovery turbo field echo cardiac magnetic resonance (CMR) and **(B)** CXCR4-positron emission tomography (PET), as well as **(C)** fused PET/computed tomography. Images reveal increased ^{68}Ga-Pentixafor uptake in the apex that consistently matches myocardial damage in CMR **(arrows)**.

mean standardized uptake value (SUV_{mean}). For reference, a second region of interest (diameter of 15 mm) was placed in a remote region of the left ventricular wall. Signal-to-background ratios were calculated.

Acute myocardial infarction was diagnosed by elevated cardiac enzymes, ST-segment elevations, and coronary angiography. The left anterior descending coronary artery was affected in 5 patients, and the right coronary artery, in 2 subjects. All patients were on antihypertensive medications (including beta-blockers, hydrochlorothiazide, and calcium channel blockers) and underwent mechanical revascularization within 20 h after symptom onset. On CMR, infarcts comprised 7% to 30% of the myocardium; left ventricular ejection fractions ranged from 37% to 67%.

Pentixafor-PET was visually positive in 3 of 7 patients (CMR available in 2 of 3). Overall, retention of the radiotracer was rated mild (5 segments) or moderate (5 segments). No segment was rated intense. CXCR4-PET and CMR were concordantly positive in 9 of 10 segments with no PET-positive, CMR-negative segments (**Figure 1**). The remaining 4 patients did not show increased tracer accumulation.

Of note, there was no substantial difference between the "positive" (days 5, 8, and 8) and "negative" (days 6, 8, 9, and 10) patients regarding the timing of imaging after onset of clinical symptoms.

SUV_{mean} in infarcted areas ranged from 2.0 to 3.3, and SUV_{max}, from 2.1 to 3.7, respectively. The SUV_{mean} and SUV_{max} ratios of lesion to remote myocardium were 2.1 ± 0.2 and 2.0 ± 0.4, respectively. Median troponin T and maximum creatine kinase levels were 2,106 pg/ml (range 1,285 to 13,058 pg/ml) and 1,065 U/l (range 631 to 3,570 U/l) in PET-positive patients compared with 670 pg/ml (range 36 to 1,936) and 538.5 U/l (range 386 to 1,933 U/l) in PET-negative subjects.

This is the first report to our knowledge of in vivo imaging of CXCR4 in the human heart after myocardial infarction. Enhanced chemokine expression could be observed in 3 of 7 patients, with tracer uptake 2-fold higher in the infarcted myocardium as compared with remote myocardium. Of note, PET-positive patients presented with higher troponin and creatine kinase levels than negative subjects. One might speculate that increased myocardial damage with hypoxia leads to CXCR4 up-regulation in order to initiate healing processes of the damaged myocardium (5). Interestingly, 4 patients proved Pentixafor negative in the presence of acute myocardial damage on CMR.

However, given the very limited number of observations, as well as the lack of histological proof, no final conclusions can be drawn yet, especially as the true source of the signal detected by Pentixafor-PET has not been identified yet. In general, both hematopoietic stem cells and neutrophils are potential cellular origins. Neutrophils are known to outnumber hematopoietic progenitors in acutely inflamed myocardium and may therefore be the likely source of the imaging signal. However, the timing of PET was somewhat late (mean 8 ± 2 days after onset of symptoms) because neutrophils are thought to dominate very early. Additionally, up-regulation of CXCR4 by cardiac myocytes has been demonstrated to occur after 36 to 48 h after acute infarction (5). Future studies including serial imaging starting at earlier time points are warranted.

Although the data would benefit from corroboration, further pre-clinical support is prevented by high specificity of the tracer for the human CXCR4, limiting all investigation to the human setting. New ligands enabling experiments in another species are not yet available.

In summary, this first proof-of-concept investigation demonstrates the general possibility to examine and quantify alterations in CXCR4 receptor density after myocardial infarction by means of Pentixafor-PET/CT.

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Please note: Please see the paper by Thackeray (page 1417) and the accompanying editorial comment by Nahrendorf and Swirski (page 1427) in this issue. Dr. Ertl is a consultant for Novartis. Dr. Wester is the chief executive officer of and shareholder in Scintomics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Lapa and Reiter contributed equally to this work as first authors. Drs. Bauer and Herrmann contributed equally as senior authors.

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