Characterizing the Inflammatory Tissue Response to Acute Myocardial Infarction by Clinical Multimodality Noninvasive Imaging

Bengel et al: Imaging Post-Infarct Inflammation

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Abstract

Background—Myocardial infarction (MI) triggers a systemic inflammatory response which determines subsequent healing. Experimentally, cardiac positron (PET) and magnetic resonance (CMR) imaging has been used successfully to obtain mechanistic insights. We explored the translational potential in patients early after MI.

Methods and Results—PET/CT and CMR were performed in 15 patients <7 days after first MI. CMR showed regional transmural late gadolinium enhancement (LE) and edema exceeding the area of LE. Using F-18 deoxyglucose with heparin pretreatment, metabolic rate of glucose (MRGlc) was significantly increased in infarct vs remote myocardium (median 2.0 vs 0.4mg/min/100ml; \( P=0.0001 \)). Infarct correlated with MRGlc in remote myocardium (\( \rho=0.64; P=0.01 \)), spleen (\( \rho=0.82; P=0.0002 \)) and bone marrow (\( \rho=0.57; P=0.03 \)), but not with muscle or liver. Regionally, FDG-score was highest in segments with LE vs edema only and remote (median 2.0 vs 1.8 vs 0.4; \( P<0.0001 \)). Patients requiring repeat intervention during preliminary follow-up of 11±5 months tended to have higher early post-MI MRGlc. Five patients with chronic, stable MI served as controls. Opposite to acute MI, MRGlc was lower in infarct (median infarct/remote ratio 0.6 vs 3.2 for acute MI; \( P=0.001 \)), and there was no correlation with bone marrow or spleen MRGlc.

Conclusion—Increased glucose utilization following heparin-induced suppression of myocyte uptake appears to mostly reflect inflammatory activity in damaged myocardium early after MI. Consistent with prior preclinical observations, and in contrast to chronic MI, this is associated with activity in spleen and bone marrow as sources of inflammatory cells. PET and CMR multimodality characterization of the acutely infarcted, inflamed myocardium may provide multi-parametric endpoints for clinical studies aiming at support of infarct healing.

Key Words: myocardial infarction, inflammation, positron emission tomography, F-18 deoxyglucose, magnetic resonance imaging
Early reperfusion by percutaneous coronary intervention (PCI) is the standard of care in acute myocardial infarction (AMI), but in some patients even optimal subsequent medical treatment cannot prevent ventricular remodeling and development of heart failure. This has triggered an increasing interest in novel therapeutic strategies targeting the early phase after AMI: It has been shown that AMI causes an inflammatory response, which needs to be balanced to ensure optimal wound healing. New molecular therapies directed at post-infarct inflammation are emerging, which aim at supporting regeneration through improved tissue repair. Success of such therapies will require detailed insights into the mechanisms underlying the inflammatory response. In this regard, noninvasive imaging can make a substantial contribution.

Recent preclinical studies have shown that post-infarct inflammation is detectable by positron emission tomography (PET) with the glucose analogue, F-18 deoxyglucose (FDG), when integrated with the late contrast enhancement signal from the infarct region in concomitant cardiac magnetic resonance (CMR) or computed tomography (CT) studies. Mechanistic studies have shown that progenitor cells and inflammatory cells are released from the bone marrow, migrate to the myocardium, and transiently accumulate in the spleen, which serves as a cell depot. Also, inflammation is not limited to infarcted myocardium, but also affects non-infarcted “remote” myocardium to a lesser degree, providing a rationale for remote remodeling.

But the use of FDG is complicated by the fact that its uptake may also reflect the presence of ischemically compromised, viable myocytes after AMI. In order to test the feasibility of FDG as an inflammatory marker in patients, we employed quantitative FDG
PET and CMR to obtain clinical insights into the biology of acutely infarcted, inflamed myocardium. Successful proof of principle may lay the groundwork for subsequent use in therapy monitoring.

Methods

Patients

Fifteen consecutive patients (13 male; 53±12 years) underwent myocardial FDG PET/CT, perfusion imaging and CMR within one week after their first acute myocardial infarction. All patients were treated by PCI, within 5.3±5.2 hours (range: 2-21) of symptom onset. Ten were stented in the LAD, one in the LCX and four in the RCA artery. CKmax was 3465±2094U/l (range: 247-6717). Angiographically, 9 had single-vessel, 6 two-vessel, and none triple-vessel disease. The mean time from reperfusion to CMR was 3±1 days (range: 1.2-6.1), and 4±2 days (range: 1.9-7.5) to perfusion/FDG imaging.

An additional group of 5 consecutive patients with chronic, stable MI (4 male; 72±9 years) underwent PET and CMR at 6.5±3.3 years after myocardial infarction. All showed stable symptoms of heart failure (2 NYHA II, 3 NYHA III) which were treated medically.

Noninvasive imaging was obtained for clinical purposes to determine successful reperfusion and ischemic compromise. Imaging data were retrospectively analyzed for the purpose of this study. General exclusion criteria were a history of prior acute coronary syndrome, symptoms or diagnostic proof of residual myocardial ischemia, and presence
of diabetes mellitus, heart failure, cardiomyopathy, or inflammatory diseases including myocarditis, sarcoidosis.

Within 11±5 months (range 4-19) after the acute event, the 15 AMI patients underwent a standardized telephone interview to evaluate outcome. This was approved by the local ethics committee and aimed at determination of symptoms of heart failure (NYHA class), angina pectoris (CCS class), new cardiovascular events (infarct or stroke), or additional intervention (bypass surgery or PCI).

Noninvasive Imaging

CMR. All examinations were performed on a 1.5T scanner (Magnetom Avanto, Siemens). Cine images of LV function were obtained using steady state free precession sequences. Extent and severity of myocardial edema were determined by T2-weighted triple inversion recovery sequences in corresponding slices. Then, late contrast enhancement (LE) was imaged by phase-sensitive inversion recovery sequences, 10-15 minutes after bolus injection of 0.15mmol/kg gadolinium-DTPA (Gadobutrol, Bayer Healthcare).

FDG PET/CT. For improved detection of infarct-induced presence of inflammatory cells, myocyte glucose metabolism was suppressed according to previously established protocols for detection of cardiac sarcoid. After an extended fasting period of >12 hours, 50 IU/kg of non-fractionated heparin were injected intravenously to increase plasma free fatty acid levels. Two patients with chronic MI did not receive heparin due to ongoing coumadin therapy. Fifteen minutes later, 360±44 MBq of 18F-FDG were injected and list-mode PET was obtained for 60 minutes using a Siemens Biograph Duo scanner. A low-dose CT was obtained for attenuation correction. List-
mode data were resampled to attenuation corrected, iteratively reconstructed, static (minutes 30-60) and dynamic images (22 frames: 12×10, 3×30, 3×300, 4×600 seconds).

Perfusion Imaging. Patients abstained from caffeinated drinks and food at least 12h before stress examination. Rest perfusion studies were obtained by $^{13}$N-ammonia PET/CT (381±98MBq; n=8 AMI pts), or $^{99m}$Tc-Sestamibi-SPECT/CT (329±25MBq; n=7 AMI pts and all chronic MI pts). Additionally, pharmacologic stress perfusion studies were obtained after regadenoson-induced vasodilation in 6/8 PET/CT sessions (422±83MBq $^{13}$N-ammonia) and in 6/7 AMI SPECT/CT sessions (654±260MBq $^{99m}$Tc-Sestamibi). Low-dose CT scans were obtained for attenuation correction of all studies. 20 minute list-mode PET data were resampled to attenuation corrected, iteratively reconstructed, static (10-20 minutes) and dynamic images (21 frames: 12×10, 6×30, 3×300 seconds). SPECT images were acquired for 25 minutes, 45 minutes after injection, and reconstructed iteratively with attenuation correction.

Data Analysis

CMR. Images were analyzed using CMR42 (Circle Imaging, Calgary, Canada). LV function was assessed by modified Simpson’s method. Volumes, ejection fraction and LV mass were obtained by delineation of inner and outer LV contours in enddiastolic and endsystolic frames. Additionally, using the AHA 17-segment model, regional edema, LE and microvascular obstruction (MVO) were graded based on the average transmurality of the signal, and regional wall motion was graded visually (table). Mean scores per segment were calculated and individual segmental scores were summed up to generate global scores. Assessment was done on agreement by two experienced observers blinded to all other study parameters.
Segmental Perfusion and FDG Uptake. Static $^{18}$F-FDG-PET images were visually analyzed by two independent observers, based on a scoring system using the AHA 17-segment model. Each segment was given a score from 0 to 4 for the magnitude of FDG uptake relative to blood pool (table). For perfusion studies, defect severity was scored, according to the standard summed score approach. Discrepancies between observers were resolved by consensus.

Quantitative Perfusion Analysis. For perfusion defect size quantification, polar maps of the LV were generated and normalized to their maximum using Munich Heart software. For both $^{13}$N-ammonia and $^{99m}$Tc-stestamibi a threshold of 60% relative to the maximum was chosen to define defect. Also, dynamic $^{13}$N-ammonia PET rest and stress images were quantitatively analyzed by generating myocardium and blood time-activity curves and applying a validated three compartment model to determine myocardial blood flow (MBF) at stress and rest, as previously described.

Quantitative Metabolic Analysis. Metabolic rates of glucose (MRGlc) were determined for infarcted and remote myocardium, bone marrow of vertebral bodies, spleen, liver and paravertebral skeletal muscle by using PMOD software and Patlak graphical analysis of dynamic FDG-PET images. Spherical volumes of interest (VOI, 2.5mm diameter) were placed in left atrium to determine arterial input function, in infarcted myocardium (hottest region), and 3-fold in remote myocardium. Guided by CT and fusion images (Figure 1), further VOIs were placed in bone marrow of three vertebral bodies and paravertebral skeletal muscle in the field of view, and a large VOI (8 mm) was placed in the spleen and liver. Using time activity curves from VOIs, MRGlc was estimated by assuming a standard lumped constant of 0.67.
Statistical Analysis

Statistical analysis was performed with MedCalc v12.7.0.0 (Ostend, Belgium). Due to small sample sizes, data are expressed as median and (25th-75th quartile) ranges. Spearman correlation was performed to describe the relationship between continuous variables. Interobserver reproducibility of ordinal segmental scores was assessed by kappa-statistics with 95% confidence intervals. Comparisons between groups of continuous variables were performed using Wilcoxon signed-rank and Mann-Whitney-U-test, as appropriate. The Bonferroni procedure was used in the case of multiple hypothesis tests. P<0.05 was considered as statistically significant. Analyses on the segmental level were based on the assumption of independence of segments within the same patient, as specified previously.

Results

Perfusion and CMR Tissue Characterization

In AMI pts, LVEF was 46(44-50)% and resting perfusion defect size was 33(15.0-42.0)% of LV. Stress perfusion imaging did not reveal significant ischemia in remote territories. CMR showed transmural LE in the infarct region in 12/15 patients, with a summed LE score of 22(16-28). Edema was present and tended to exceed the infarct area, with a summed score of 28(20-36) (P=0.05 vs LE score). Microvascular obstruction was observed in 10/15 patients, comprising a median of 4.0(0.0-5.0) segments.
In chronic MI pts, LVEF was 30(28-41)%, and resting perfusion defect size was 47(42-55)% of LV. CMR showed transmural LE in the infarct region in 3/5 patients, with a summed LE score of 15(12-24). No edema or microvascular obstruction was identified.

**Regional Glucose Utilization**

In the acute MI group, diet and heparin pretreatment resulted in good suppression of FDG uptake in remote myocardium, while regionally increased FDG uptake was detected in the hypoperfused infarct region in 12/15 patients (Figure 2). Summed FDG score was 19(12-25) and correlated significantly with the global scores for LE ($\rho=0.54; P=0.04$; Figure 3A) and edema ($\rho=0.76; P=0.002$; Figure 3B). Consistently, the mean FDG score was significantly elevated in segments with LE compared to those without (2.0(1.5-2.3) vs 0.6(0.3-0.7); $P=0.0001$). There was no significant difference in FDG score between LE segments with or without MVO (2.1(1.3-2.8) vs 1.8(1.0-3.0); $P=0.54$; figure 3C). Also, there was significantly increased FDG score in segments with edema compared to regions without, while there was no significant difference among edema segments with or without LE (2.0(1.5-2.6) vs 1.8(1.4-2.0) vs 0.4(0.0-0.5) for edema with LE vs edema without LE vs remote; $P=0.26$ for edema with LE vs edema without LE; $P<0.0001$ for edema with or without LE vs remote; figure 3D). Finally, FDG score tended to correlate with wall motion score ($\rho=0.42; P=0.12$). It was significantly elevated in segments with impaired wall motion (1.8(1.4-2.5) vs 0.5,0.4-0.8); $P=0.0008$).

In chronic MI patients, a reverse pattern was observed. Fasting and heparin yielded suppression of myocardial uptake and, if at all detectable, FDG uptake in the infarct region was lower than in remote myocardium (Figure 4). FDG scores in segments without LE were consistently higher than in those with LE, resulting in a ratio of 1.2(1.1-
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1.5), which was opposite to AMI (ratio of FDG scores in segments without relative to with LE: 0.3(0.1-0.4); \( P=0.001 \)). Unlike in AMI, summed segmental FDG score did not correlate with global LE score (\( \rho=0.1; P=0.93 \)).

Of note, interobserver reproducibility for segmental analysis was in good agreement for FDG PET (\( \kappa=0.93 \) [0.86- 1.00]) and CMR (LE: \( \kappa=0.72 \) [0.51-0.94]); edema: \( \kappa=0.88 \) [0.74–1.00]; MVO: \( \kappa=0.77 \) [0.50- 1.00]).

Quantitative MRGlc in Heart and Lymphoid Tissue

In AMI, consistent with visual regional analysis, quantitative MRGlc was significantly elevated in infarct versus remote myocardium (2.0(1.2 - 2.8) vs 0.4(0.2-1.2) mg/min/100ml;\( P=0.0001 \)). Infarct MRGlc was positively correlated with MRGlc in remote myocardium (\( \rho=0.64;P=0.01 \); Figure 5A) and showed a trend to an inverse correlation with time after reperfusion (\( \rho=-0.40;P=0.14 \); Figure 5B). There was no correlation with other parameters of myocardial damage, including perfusion defect size (\( \rho=0.28;P=0.32 \)), LVEF (\( \rho=0.13;P=0.65 \)), CKmax (\( \rho=0.17;P=0.54 \)), or with markers of systemic inflammation including blood leukocyte count (\( \rho=0.14;P=0.61 \)) or C-reactive protein (\( \rho=0.12;P=0.73 \)). Interestingly, however, glucose utilization in infarcted myocardium showed a significant positive correlation with MRGlc in lymphoid tissue, i.e. the spleen (\( \rho=0.82;P=0.0002 \); Figure 5C) and the vertebral bone marrow (\( \rho=0.57;P=0.03 \); Figure 5D), while it did not correlate with nonlymphatic organs such as skeletal muscle (\( \rho=0.34; P=0.21 \)) or liver (\( \rho=0.1; P=0.73 \)).

In contrast to AMI, MRGlc in chronic MI was consistently lower in infarct relative to remote myocardium, with an infarct/remote ratio of 0.6(0.5-1.1) vs 3.2(2.4-
6.4) for acute MI ($P=0.001$). Also, there was no correlation between infarct MRGlc and that of bone marrow or spleen in this group.

**Regional MRGlc and MBF**

In the subgroup of 8 AMI pts who had $^{13}$N-ammonia perfusion PET, MBF data were available and allowed for a preliminary analysis. Of note, rest MBF in remote myocardium tended to correlated with MRGlc ($r=-0.64$, $P=0.12$), while neither stress MBF in remote, nor rest or stress MBF in the infarct region showed a correlation.

**Follow Up in AMI Patients**

Two patients were lost to follow up. Among the remaining 13, no deaths occurred. At the time of the interview, 7 patients were in NYHA class I, 2 in class II, 3 in III and 1 in IV. CCS class was 0 in 8 patients, 1 in 2 and IV in 3. Seven patients underwent an additional coronary angiography. Five of these patients underwent PCI while, while two had no intervention. One patient had bypass surgery and only one patient suffered from re-infarction.

Patients without angina symptoms (CCS 0) at follow-up tended to have higher MRGlc in the infarct region ($2.4(1.5-3.2)$ vs $1.4(1.1-1.6)$ mg/min/100ml; $P=0.17$) and bone marrow ($1.1(0.9-1.5)$ vs $0.8(0.6-1.0)$; $P=0.106$) early after the event, compared to patients with angina at follow up (CCS 1-4). Also, those requiring additional intervention or bypass surgery (n=6) showed a trend towards higher MRGlc in remote myocardium than those without intervention (n=7) ($1.2(0.21-1.37)$ vs $0.3(0.23-0.47)$ mg/min/100ml; $P=0.23$). Overall, however, there was no significant association between early imaging results and subsequent outcome in this small sample of infarct patients.
Discussion

In summary, our study demonstrates a specific pattern of regionally increased glucose uptake in the area of acutely infarcted myocardium, early after reperfusion. Pretreatment with heparin (an approach commonly employed for clinical detection of cardiac sarcoid as an inflammatory disease) facilitated the identification of this increase, because it efficiently suppressed uptake of FDG in remote myocardium. Also, for the first time, our study demonstrates that the magnitude of increased glucose utilization in the infarct region is associated with activation of lymphoid tissue in spleen and bone marrow in humans.

These observations support the notion that regionally increased FDG uptake in the acutely infarcted myocardium may be -at least in part- a marker of tissue inflammation. Direct proof for this notion by tissue analysis cannot be obtained in a clinical study, but various prior experimental studies have confirmed a link between FDG uptake in the infarct region and inflammation, which is known to peak within a few days after the event. Other results give further support: Firstly, FDG uptake occurred in areas with transmural late gadolinium enhancement at CMR, suggesting extensive damage of myocytes. Secondly, there was a trend towards an inverse correlation between infarct FDG signal strength and time after reperfusion. While this relationship is influenced by multiple factors and probably not linear, the decline with time is consistent with the natural course of inflammation because imaging was likely obtained after the peak inflammatory activity. Thirdly, increased infarct uptake of FDG was associated with increased activity in remote myocardium, consistent with previous experimental observations of infarct and remote inflammation, and, more importantly, with activation
of bone marrow and spleen as lymphoid organs which are known to play a key role in the systemic immune response to myocardial damage. This relation could not be observed for the liver or the skeletal muscle as organs that are not involved in the inflammatory reaction. And finally, a small control group of patients with chronic MI showed a reverse FDG pattern with lower uptake in the infarct region relative to remote myocardium and no correlation with lymphoid tissue.

An alternative explanation for the regionally increased FDG uptake would be increased glucose utilization by viable myocytes in the infarct region. It needs to be pointed out that myocardial glucose utilization is a complex mechanism which may be stimulated by ischemic compromise, increased catecholamine levels and/or other stressors. Prior work has e.g. suggested that increased FDG uptake in the infarct region may represent residual viability, contributing to improved regional wall motion at follow up. This prior work, however, did not provide information about transmurality of the infarct from CMR, and it did not employ heparin-based suppression techniques for reduction of myocyte FDG uptake. In our study, CMR suggests extensive, transmural regional damage. Although late enhancement early after infarction may overestimate irreversible damage to some degree, the mass of residual viable myocardium is likely small and the contribution of viability to the elevated FDG signal may be limited. Likewise, the inflammatory nature of the elevated FDG signal early after AMI has recently been confirmed experimentally in rodents, where a good correlation with flow cytometry of infarct tissue for inflammatory cells was shown.

Another point of interest was the relationship between MVO and inflammation because MVO is a strong predictor of remodeling and may be a consequence of
FDG uptake in segments with MVO may be increased due to inflammation, or it may be reduced due to lack of perfusion, high tissue pressure or hemorrhage – the same factors which result in absence of contrast enhancement at CMR. The lack of difference in FDG uptake between infarct segments with and without MVO suggests that more severe inflammation on the one hand may be counterbalanced by reduced tracer delivery on the other hand.

Further insights into the viable infarct border zone are provided by CMR edema imaging. The edema signal consistently exceeded the area of delayed enhancement in acute but not chronic MI. Interestingly, FDG uptake was increased not only in the infarct region, but also in regions with edema only when compared to remote myocardium. This implies that the viable, but edematous infarct border zone may be ischemically compromised and/or involved in the inflammatory response. Consistent with the latter, the infarct border zone commonly shows intense neutrophil margination and infiltration and preclinical studies observed numerous monocytes/macrophages in the infarct border zone.

Finally, it is of note that increased FDG uptake did not correlate with other measures of myocardial damage such as perfusion defect size, LVEF or CKmax, or systemic markers of inflammation such as CRP or blood leucocyte count. Severity of functional compromise and cell damage, and systemic inflammatory response therefore are not strong determinants of the local tissue inflammatory reaction. This may confirm an independent value of myocardial inflammation imaging after acute infarction. Consistently, it has been assumed that infarct size, ventricular stress and infarct healing (inflammation) are independent determinants of ventricular remodeling. Also, some
studies observed an association between increased leukocyte count\textsuperscript{36, 37} or increased CRP\textsuperscript{38, 39} and adverse ventricular remodeling but there are also studies that match our result and likewise found no correlation between infarct size and inflammatory markers or markers of matrix remodeling\textsuperscript{40}.

Some limitations of the present study need to be recognized: First, the sample size in our study was small so that lack of a significant correlation does not rule out the existence of an association. It just shows that the relative strength of the association is less than that of parameters which correlated significantly. Second, the limitations stemming from complexity of the FDG signal cannot be completely resolved. Besides questions about the partial contribution of elevated FDG uptake from compromised but viable myocytes, we also had to assume the same lumped constant of 0.67 for all tissues, which is not proven to be correct and may partially bias the results. Third, patient follow up in our study is substantially limited in power due to the small sample size and lack of prospective nature. Confirmation in larger samples is necessary. Also, follow-up did not include repeated measures of ventricular function. But such repeated measures may not necessarily be helpful to resolve the issue of viable myocardium versus inflamed tissue as the origin of the FDG signal in the infarct region. While viable myocardium would improve in function, this could also be true for ventricles that have an intense, but overall more balanced inflammatory response leading to improved healing and less remodeling\textsuperscript{41}. And forth, we included a control group of patients with chronic, stable MI in order to support our conclusions. But results in this group must be interpreted with caution, too, not only because of the even smaller sample size, but also because glucose utilization in those subjects may be influenced by other pathomechanisms such as remodeling,
subclinical ischemia and/or heart failure. Nevertheless, the inverse pattern of FDG in infarct versus remote myocardium under heparin suppression in the chronic setting further suggests that elevated infarct activity is a phenomenon of the acute inflammatory phase.

In addition to the afore mentioned limitations of FDG as a myocardial inflammation marker and the relatively small sample size, it should be note that this study was not a prospective project and thereby may have been subject to inherent limitations and bias. It should nevertheless be seen as hypothesis-generating for subsequent work, and it may provide a rationale for projects aiming at monitoring of the effect of therapies seeking to modulate the inflammatory response to acute infarction in order to improve myocardial healing. Prior work from our group has e.g. shown that an accelerated but limited inflammatory response by very early treatment with eplerenone, a selective aldosterone antagonist, improves early infarct healing in rats. Furthermore, a recent report has shown some evidence for the anti-inflammatory impact of ACE-inhibitors through inhibition of monocyte mobilization from their splenic reservoir. These are examples where the multi organ inflammatory response after myocardial infarction is already influenced by the current therapy of myocardial infarction, and where molecular imaging of inflammation could provide further insights.

**Conclusion**

Multimodality imaging using quantitative clinical FDG PET following cardiomyocyte glucose uptake suppression with heparin, combined with multi-parametric CMR, confirms prior experimental data and provides noninvasive insights into the acutely infarcted, inflamed myocardium, and into the interrelation between myocardium and
lymphoid tissue activation. This initial study may serve as a foundation for future work focusing on the early prediction of risk of later remodeling and on the monitoring of new therapies aiming at modulation of the inflammatory response in order to support myocardial healing.

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**Disclosures**

The authors report no conflict of interest.
References


Table. Scoring Template for Regional Analysis According to AHA 17-Segment Model

<table>
<thead>
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<th>Score</th>
<th>Radionuclide Imaging</th>
<th>CMR</th>
<th>Wall Motion</th>
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<td>Perfusion (relative to LV max)</td>
<td>LE (% trans-mural)</td>
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<td>below/equal</td>
<td>Equal</td>
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<td>absent</td>
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</tbody>
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CMR, cardiac magnetic resonance imaging; FDG, F-18 fluorodeoxyglucose; LE, late gadolinium enhancement; MVO, microvascular obstruction.
Figure Legends

Figure 1. Multi-organ PET-CT analysis of glucose utilization. Shown are positron emission tomography (PET) images (right) and hybrid PET-computed tomography (CT) images (left) of the cardiac region, showing the positioning of regions of interest for quantitative analysis of glucose utilization in heart and lymphoid tissue.

Figure 2. Representative multi-parametric cardiac magnetic resonance (CMR) and positron emission tomographic (PET) images in a patient early after myocardial infarction and reperfusion. CMR of Gadolinium contrast late enhancement (Gd LE; top row) shows transmural tissue damage (bright) and subendocardial no-reflow (black), indicating microvascular obstruction in anteroseptal infarct region. T2-weighted images of edema (second row) show transmural edema (bright), exceeding the area of LE. PET perfusion images (third row) show perfusion defect in the infarct area with LE. Also, uptake of [18F]-deoxyglucose (FDG) is present in the infarct region under suppression of myocyte uptake by heparin, consistent with regional inflammation (bottom row).

Figure 3. Relationship between myocardial uptake of [18F]-deoxyglucose (FDG) under heparin suppression as a marker of regional inflammation, and parameters derived from cardiac magnetic resonance imaging. Global FDG score correlates (A) with late enhancement of gadolinium, and (B) T2-derived myocardial edema. Segmental FDG score (C) among segments positive for late enhancement (LE(+)) is not different if microvascular obstruction (MVO) is present (+) or absent (-) (P=0.54), and (D) is significantly elevated in segments positive for LE and edema (**P<0.0001) and segments positive for edema only (*P<0.0001) versus negative segments.
Figure 4. Short-axis gadolinium late enhancement magnetic resonance (CMR LE) and \[^{18}\text{F}\]-deoxyglucose positron emission tomography (FDG PET) images in representative patients with chronic (left) and acute infarct (right). The chronic infarct shows transmural enhancement in anterior and lateral wall, where FDG uptake is absent (arrows). The acute infarct also shows transmural enhancement in anterior and septal wall, including a subendocardial area of no reflow. FDG uptake is elevated in the acute infarct region (arrows). FDG PET studies are scaled to the same level of standardized uptake values (SUV) in both studies, showing high blood pool and low myocardial tissue uptake consistent with fasting and heparin preparation.

Figure 5. Quantitative metabolic rate of glucose (MRGlc; measured in milligrams of glucose per minute per 100 grams of tissue, mg/min/100g) under heparin suppression as a marker of inflammatory activity in myocardium and lymphoid tissue. MRGlc in infarct (A) correlates with MRGlc remote myocardium, (B) shows a trend towards inverse correlation with time after reperfusion, (C) correlates with MRGlc in spleen as an inflammatory cell depot, and (D) correlates with MRGlc in vertebral bone marrow as cell source.
Figure 2

CMR

Infarct (Gd LE)

Edema (T2)

Perfusion

PET

Inflammation (FDG w. Heparin)
Figure 3

A. 

B. 

C. 

D. 

Global FDG Score vs. Global Late Enhancement Score

Global FDG Score vs. Global Edema Score

FDG Score per Segment

FDG Score per Segment

LE (+) MVO (+) LE (+) MVO (-)

LE (+) Edema (+) LE (-) Edema (+) LE (-) Edema (-)

$\rho = 0.54$  
P = 0.04

$\rho = 0.76$  
P = 0.002

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Figure 4

Chronic Infarct
CMR LE  FDG PET
BASE

Acute Infarct
CMR LE  FDG PET
Apex

SUV0 SUV5  SUV0 SUV5
Figure 5

A. 

B. 

C. 

D. 

\[ \rho = 0.64 \quad P = 0.01 \]

\[ \rho = 0.82 \quad P = 0.0002 \]

\[ \rho = -0.40 \quad P = 0.14 \]

\[ \rho = 0.57 \quad P = 0.03 \]
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