Assessment of sympathetic reinnervation after transient myocardial ischemia by C11 hydroxyephedrine PET imaging


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Purpose: To investigate sympathetic nerve damage and reinnervation utilizing a rat model of myocardial transient ischemia and a catecholamine analogue PET tracer, C-11 hydroxyephedrine (HED).

Methods: Transient myocardial ischemia was induced by 20 min coronary occlusion and reperfusion in Male Wistar rats. Dual-tracer autoradiography was performed sub-acute (day 7, n=4) and chronically (>2 months, n=8) after ischemia, and in non-operated control rats (n=8) using C-11 HED as a marker of sympathetic innervation and Tl-201 for perfusion. Additional serial in-vivo cardiac C11-HED- and F-18 FDG-PET scans were performed at week 1 and after two months.

Results: After transient ischemia, a perfusion defect at the mid ventricular wall was clearly exceeded by a defect of C-11 HED at both the sub-acute and chronic phases. The sub-acute defect showed transmural pattern whereas the chronic phase defect was seen only on the endocardial portion. C-11 HED uptake ratios (vs. remote) at the endo- and epi-cardial portion of the scar were 0.26 ± 0.18 and 0.40 ± 0.28 (n.s.) at the subacute phase, and 0.35 ± 0.13 and 0.97 ± 0.10, (p<0.001) at the chronic phase, respectively. Tyrosine-Hydroxylase antibody nerve staining confirmed a denervation corresponding to the area of HED uptake defect. Serial in-vivo PET imaging visualized reduction of HED defect area at chronic phase consisted with autoradiography and histology.

Conclusions: Discrepant larger uptake defect with C-11 HED in comparison to the perfusion tracer after transient ischemia corresponded to the histologically identified area of denervation. Furthermore, we observed recovery of regional C-11 HED uptake from epi-cardial portion at chronic phase reflecting sympathetic reinnervation.

In vivo non-invasive evaluation of therapeutic hydrogels for modulation of post infarction remodeling: role of MMP-targeted SPECT myocardial imaging in a chronic porcine model

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Following myocardial infarction (MI) there is a maladaptive regulation of matrix metalloproteinases (MMPs) altering the ECM and function leading to adverse cardiac remodeling. Tissue inhibitors of MMPs (TIMPs) provide a therapeutic target for modulation of MMPs, and can be delivered locally by TIMP releasing hydrogels. SPECT/CT imaging of MMPs may provide a non-invasive approach to determine the effect of therapeutic hydrogels on MMP activation and remodeling.

Methods: MI was induced in pigs by LCX marginal branch ligation. Pigs were randomized to MI only (n=6), or therapy through regional injection of a degradable hyaluronic acid (HA) based hydrogel containing recombinant TIMP-3 (HA/TIMP-3)(n=6) or hydrogel (HA) alone (n=6). HA or HA/TIMP-3 were injected in risk area via myocardial injections. Hybrid SPECT/64-slice CT imaging performed 2-wk following MI after injection of an MMP-targeted tracer (99mTc-RP805) and 201Tl. Endocardial (EN) and epicardial (EP) contours were generated from ECG-gated contrast CT to assess wall thickness, thickening, and displacement. Hearts underwent ex vivo SPECT/CT imaging. LV was cut into 4mm slices, 8 pie, and EN and EP pieces for well counting. Myocardial uptake was expressed as % injected dose per gram of tissue.

Results: LV wall thickness and thickening were significantly improved in MI region in HA and HA/TIMP-3 groups compared to control MI. 201Tl was reduced in MI in all groups, although improved with HA/TIMP-3 therapy. MMP activity in MI region was increased by 75% in MI only group (p=0.02), and attenuated in the HA (p=0.20) and HA/TIMP-3 (p=0.42) groups.
Conclusions: HA and HA/TIMP-3 therapy prevented LV wall thinning and reduces loss of function in MI, and decreased MMP activation and increased perfusion as assessed with SPECT imaging.

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Quantification cardiac amyloid by cardiac computed tomography

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Purpose: To develop Dynamic Equilibrium Computer Tomography (DyneCT) to diagnose and quantify cardiac amyloidosis by measuring the myocardial extracellular Volume, ECV\textsubscript{ct}. Cardiac involvement determines outcome in patients with systemic amyloidosis. There is major unmet need for quantification of cardiac amyloid burden, which is currently only met in part through semi-quantitative DPD bone scintigraphy or Cardiovascular Magnetic Resonance (CMR), which measures ECV\textsubscript{cmr}. Other accessible tests are needed.

Methods: Twenty-six patients (21 male, 64 ± 14 years) with a biopsy proven systemic amyloidosis (ATTR n=18; AL n=8) were compared with twenty-seven patients (19 male, 68 ± 8 years) with severe aortic stenosis (AS). Patients underwent echocardiography, bone scintigraphy, NT-pro-BNP, Troponin measurement and CMR. DynECT was performed using a prospectively gated cardiac scan prior to and after (5 and 15 minutes) a standard iodotanid (1 mCi/kg) bolus to measure ECV\textsubscript{ct}; an additional 1 minute scan was added to aid cardiac wall segmentation. ECV\textsubscript{ct} was compared to the reference ECV\textsubscript{cmr} and conventional amyloid measures: DPD bone scintigraphy and clinical markers of cardiac amyloid severity (NT-pro-BNP, Troponin, LVEF, LV mass, LA and RA area).

Results: ECV\textsubscript{ct} and ECV\textsubscript{cmr} results were well correlated (r=0.85 vs r=0.74 for 5 and 15 minutes post bolus respectively). ECV\textsubscript{ct} was higher in amyloidosis than AS (0.54 ± 0.11 vs 0.28 ± 0.04, p<0.001) with no overlap. ECV\textsubscript{ct} tracked clinical markers of cardiac amyloid severity (NT-pro-BNP, Troponin, LVEF, LV mass, LA area, 6-minute-walk test), and DPD bone scintigraphy amyloid burden (p<0.001).

Conclusion: Dynamic Equilibrium CT, a 5 minute contrast-enhanced gated cardiac CT, has potential for non-invasive diagnosis and quantification of cardiac amyloidosis.

Abstract 220 Figure. Dynamic Equilibrium Computed Tomography

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Simultaneous multi-isotope imaging for leukocyte tracking using dedicated cardiac CZT SPECT. A new approach to reveal foci of endocarditis

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Purpose: To analyze features of atherosclerotic plaques in culprit and remote coronary lesions in patients with acute coronary syndrome without persistent segment ST elevation by multidetector computed tomography (MDCT).

Methods: We enrolled 70 patients with NSTE-ACS (47 with unstable angina and 23 with myocardial infarction), who underwent 64-slice MDCT before coronary angiography. We evaluated plaque type (soft, mixed and calcified), minimum CT density (HU), contour, length as well as presence of spotty calcium, ring-like sign and positive remodeling in all culprit lesions (Figure 1) and in non-culprit segments, if stenosis was >50%.

Results: In culprit lesions (n=70) compared to non-culprit lesions (n=144) frequency of soft plaques (60% vs. 43%, p=0.003), positive remodeling (70.2% vs. 54.3%, p=0.03) and uneven contour (91.7% vs. 68.7%, p=0.002) was significantly higher. The minimum plaque density was significantly lower and length of plaque was significantly higher in the culprit coronary segments (40.1 ± 25.3 HU vs 74.1 ± 116.8 HU, p=0.02 and 16.8 ± 13.4 mm vs 13.2 ± 6.9 mm, p=0.01, respectively). Receiver-operator characteristic curve analysis identified the optimal cutoff value of minimum plaque density and length for discrimination between culprit and non-culprit lesion as 40 Hounsfield units (HU) and 13.5 mm respectively. The prevalence of spotty calcium and ring-like sign was tended to be greater in culprit lesions, but statistical analysis did not show significant difference (p=0.12 and p=0.27 respectively).

Conclusions: The most specific features of culprit lesions in patients with ACS include positive vascular remodeling, minimum CT-density <40 HU, length >13.5 mm and presence of uneven contour.

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Extent and prognostic significance of scar and inducible ischaemia following primary PCI for STEMI with multivessel disease: Insights from the CvLPRIT Nuclear Substudy

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Introduction: In STEMI patients with multivessel disease, the randomised CvLPRIT study showed that complete revascularisation reduced MACE at 12 months compared to primary PCI (PCI) of the infarct-related artery (IRA) alone. CvLPRIT patients underwent MPS at 6-8 weeks, and we report the effect of revascularisation strategy on scintigraphic variables, and their association with subsequent cardiac events.

Methods: CvLPRIT randomised STEMI patients from seven UK centres (2011–2013). Following IRA-only or complete revascularisation, patients received contemporary medical therapy. Stress-rest SPECT MPS was performed at 6-8 weeks, with semi-quantitative analysis centrally. Summed scores were converted to 4LV. Clinicians were blinded unless ischaemia exceeded 20%LV (0 patients), or MPS was indicated symptomatically. MAEC at 9–12 months comprised death, recurrent MI, heart failure, or ischaemia-driven revascularisation.

Abstract 222 Figure 1. Culprit lesion

Conclusions: The most specific features of culprit lesions in patients with ACS include positive vascular remodeling, minimum CT-density <40 HU, length >13.5 mm and presence of uneven contour.
Results: Randomised groups were comparable (Table). Patients with complete revascularisation had smaller infarcts than those with IRA only PCI. The extent of inducible ischaemia was limited and similar between groups. 13/194 patients (6.7%) suffered MACE following MPS, but no scintigraphic variable was predictive (eg ischaemia no event v event 1.5% v 2.9%, P=0.72).

Conclusions: Compared with IRA-only PCI, complete revascularisation reduced infarct size but not the extent of inducible ischaemia at 6–8 weeks. Ischaemia was limited and did not predict MACE at 12 months.

Abstract 223 Table. Characteristics of randomised groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>IRA only (n=101)</th>
<th>Complete revasc (n=104)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>62.7 (11.0)</td>
<td>62.6 (10.1)</td>
<td>0.91</td>
</tr>
<tr>
<td>Male (%)</td>
<td>84 (83%)</td>
<td>91 (88%)</td>
<td>0.38</td>
</tr>
<tr>
<td>IRA = LAD (%)</td>
<td>33 (33%)</td>
<td>34 (33%)</td>
<td>0.76</td>
</tr>
<tr>
<td>MACE pre MPS</td>
<td>9 (8%)</td>
<td>2 (2%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Stress defect (%LV)</td>
<td>13.2 (7.4, 19.1)</td>
<td>13.2 (7.4, 16.2)</td>
<td>0.16</td>
</tr>
<tr>
<td>Rest defect (%LV)</td>
<td>10.3 (5.9, 17.7)</td>
<td>8.8 (4.4, 14.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Ischaemia (%LV)</td>
<td>0%</td>
<td>49 (49%)</td>
<td>0.91</td>
</tr>
<tr>
<td>0.1–4.9%</td>
<td>30 (30%)</td>
<td>29 (28%)</td>
<td></td>
</tr>
<tr>
<td>5.0–9.9%</td>
<td>15 (15%)</td>
<td>16 (17%)</td>
<td></td>
</tr>
<tr>
<td>≥10%</td>
<td>6 (6%)</td>
<td>8 (8%)</td>
<td></td>
</tr>
<tr>
<td>Resting EF</td>
<td>0.56 (0.11)</td>
<td>0.56 (0.11)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

224 Microvascular obstruction and left ventricular thrombi after acute myocardial infarction are associated with an increased inflammatory response

C. Rischpler1, R.J. Dirschinger2, S. Nicolosi1, H. Kossmann2, A. Meinicke1, F. Hanus2, K. Goetze2, KL. Laugwitz2, M. Schwaiger1, SG. Nekolla1

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Purpose: Recently, research has focused on inflammatory processes after acute myocardial infarction. Preclinical studies have demonstrated that the inflammatory response after acute myocardial infarction can be imaged using F-18-FDG PET/MRI. In this study we aimed to investigate F-18-FDG PET/MRI as a novel biosignal in post-ischemic myocardium and investigated its relationship with the innate immune response in patients after acute myocardial infarction.

Methods: After percutaneous coronary intervention (PCI) 32 patients with first acute STEMI were prospectively enrolled and imaged 4.9 ± 1.3 days later using hybrid F-18-FDG PET/MRI. Patients were prepared for the scan by a low-carbohydrate, high-fat diet the day prior to the scan as well as by injection of unfractionated heparin before F-18-FDG injection. In 17 patients, Tc-99m-sestamibi SPECT with tracer injection before PCI was additionally performed in order to assess the area at risk. Imaging results were correlated with the cellular innate immune response, which was measured at different time points after acute myocardial infarction.

Results: In the postischemic myocardium an F-18-FDG signal was present in all patients. There was a substantial agreement (k=0.64) between the F-18-FDG uptake and the LGE signal when compared on a segmental basis (AHA 17-segment model). In the quantitative analysis, however, the F-18-FDG signal extent exceeded the LGE extent (29.3 ± 13.7 %LV vs. 20.4 ± 10.6 %LV, p<0.001) but did not differ from the area at risk assessed by Tc-99m-sestamibi SPECT (25.3 ± 10.3 %LV vs. 22.3 ± 17.4 %LV, p=NS). The infarct size determined by LGE showed a positive correlation with inflammatory CD14-high and CCR2+ monocytes in the peripheral blood (R=0.60, p<0.001 and R=0.57, p<0.001, respectively). The F-18-FDG uptake was highest in areas with transmural LGE, but did not correlate with monocyte counts in the peripheral blood.

Conclusions: Early after acute myocardial infarction hybrid PET/MRI demonstrated increased F-18-FDG uptake both in scarred and in post-ischemic non-scarred myocardium. This novel biosignal presumably represents a combination of postischemic viable myocardium and recruited monocytes. In order to clearly elucidate this phenomenon specific tracers targeting either postischemic myocardium or subsets of inflammatory cells are needed and may help to guide future immunomodulatory strategies after acute myocardial infarction.

Abstract 224 Figure. F-18-FDG PET/MR LV-Thrombus

225 Hybrid F-18-FDG PET/MI after acute myocardial infarction: characterization of a novel biosignal

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Purpose: Recent cardiovascular research has focused on inflammatory processes after myocardial infarction. Preclinical studies have demonstrated that the inflammatory response after acute myocardial infarction can be imaged using F-18-FDG PET/MRI. In this study we aimed to investigate F-18-FDG PET/MRI as a novel biosignal in post-ischemic myocardium and investigated its relationship with the innate immune response in patients after acute myocardial infarction.

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Abstract 224 Figure. F-18-FDG PET/MR LV-Thrombus

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F-18-FDG PET/MR of a patient showing a left ventricular thrombus. Note intense F-18-FDG uptake in the post-ischemic myocardium.