Combined functional MRI and µPET measurements in a mouse model of cardiac infarction

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Introduction

In cardiac research *in vivo* studies of mice are indispensable to gain an improved understanding of cardiovascular disease mechanisms and to develop novel diagnostic tools as well as surgical and therapeutic interventions. Imaging techniques, such as MRI and PET play an important role in determining global functional parameters as well as infarct size (1,2). There is a trend towards combining the strengths of different imaging techniques in order to obtain a full characterization of the functional and metabolic status of the diseased myocardium. However, often it is not clear how the different imaging techniques compare.

Aim

The goal of this study was to compare global functional parameters as well as infarct size, determined by CINE and contrast-enhanced (CE) MRI with respect to ^{18}F-FDG µPET, in a mouse model of myocardial infarction.

Methods and Materials

Mouse model: C57Bl6 mice (age, 3 months; weight, 25-30 g) were subjected either to permanent occlusion of the left anterior coronary artery (n=6; O) or temporal occlusion of 30 min. followed by reperfusion (n=5; IR). Healthy mice (n=12) were used as control.

MRI: MRI was performed, with a 6.3T scanner (Bruker BioSpin), two weeks after recovery bringing the infarct development to the end-stage (3). Measurements were performed under isoflurane anaesthesia. A stack of short-axis slices covering the heart from base to apex and two orthogonal long-axis slices were acquired to determine global functional parameters, using a ECG triggered and respiratory gated CINE FLASH sequence (α=15°, TR=7ms, TE=2.3ms, FOV=3x3cm^2, matrix=192x192, slice thickness=1mm, NA=6). Subsequently, 4 O and 4 IR mice received a bolus injection of Gd-DTPA (0.2 mmol/kg) in the tail vein for CE delineation of infarct size. For the CE MRI a time series of a modified multi-slice ECG triggered FLASH sequence was used (α=50°, TR=78ms, TE=2.2ms, FOV=3x3cm^2, matrix=256x256, slice thickness=1mm, number of slices=10, NA=6, acquisition time ±3 min), which incorporated an extra navigator echo slice placed perpendicular to the diaphragm to correct respiratory motion retrospectively (4). MR images were analyzed with Matlab 6.1 and CAAS MRV FARM (Pie Medical Imaging, Netherlands). Global functional parameters of the left ventricle: end-diastolic (EDEV) and end-systolic (ESEV) endocardial volumes, ejection fraction (EF), stroke volume (SV) as well as end-diastolic myocardial mass (without papillary muscles) were calculated following the Simpson's rule.

PET: Within three days following MR measurements, the mice were scanned in a 32-module quadHIDAC (Oxford Positron Systems) PET scanner using the MRI aneasthesia protocol. One hour before the measurement ^{18}F-FDG (15 MBq) in 100µL 0.9% saline was injected intravenously. List-mode emission data were acquired for 30 min. and subsequently reconstructed retrospectively into 16 equidistant ECG gates with image volumes of 110x60x60mm^3 (voxel size of 0.4x0.4x0.4mm^3) using dedicated in-house software. For infarct size assessment an additional ungated image volume was reconstructed similarly. For automated assessment of functional parameters a left-ventricular myocardial segmentation algorithm working in 3D was applied.Transmural infarct size as myocardium surface ratio was determined by a threshold of 50% of maximum myocardial activity to separate infarcted from viable tissue as described in (2).

Data analysis: The variability between MRI and PET of the global functional parameters was determined. Infarct sizes determined by PET as myocardium surface ratios were compared to MRI measurements of (i) infarct size volume ratios, (ii) infarct size surface ratios, and finally (iii) infarct size surface ratios determined by decreased wall thickening between diastolic and systolic heart phases (threshold <15%) observed in the CINE MR images. Statistical correlations were tested for significance by a paired student t-test.

Table 1: Variability between MRI vs. PET of control and myocardial infarction groups. (Mean value MRI-PET ± SD)

	Control (n=12)		Myocardial infarction (n=11)	
	Value	Percentage	Value	Percentage
EDEV [µl]	-8.0 ± 11.2	-12.5 ± 17.4	2.5 ± 18.9	2.2 ± 16.9
ESEV [µl]	-0.9 ± 7.6	-5.1 ± 41.3	7.5 ± 28.4	9.7 ± 36.7
EF [%]	2.7 ± 6.9	-3.8 ± 9.7	-0.6 ± 15.9	-1.6 ± 43.2
SV [µl]	-7.1 ± 6.5	-15.3 ± 14.0	-5.1 ± 18.0	-14.6 ± 52
LVM [mg]	45.6 ± 12.0	63.0 ± 16.5	29.8 ± 42.9	31.1 ± 44.6

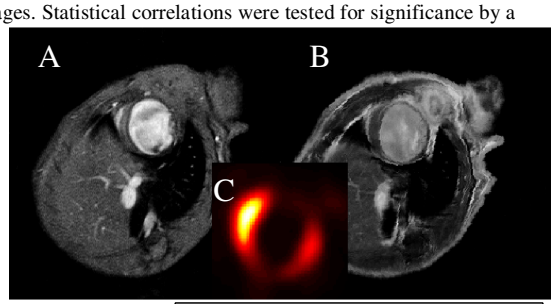

Figure 1: Images of the same short-axis slice of an occlusion mouse model: A) end-diastolic CINE MR image; B) CE MR image; C) µPET image.

Results

Figure 1 shows a short axis slice of an occluded mouse heart imaged by CINE MRI (A), CE MRI (B) and PET (C). Mean global functional parameters determined with MRI using long-axis correction were: EDEV=60.4±6.5µl; ESEV=18.1±3.0µl; EF=70.2±3.9%; SV=42.4±4.8µl; LVM=95.4±7.2mg for the control group and EDEV=113.3±57.3µl; ESEV=81.1±60.7µl; EF=36.5±18.3%; SV=32.1±9.0µl; LVM=111.1±13.3mg for the two myocardial infarction groups combined. The variability between the MRI and PET global functional parameters is listed in Table 1. Using long-axis correction for MRI, the variability was reduced by approximately 6% for the EDEV and EF and by 50% for the SV of the control group.

No significant linear correlations were found between infarct sizes determined by PET and the different MRI infarct size measures (MRI vs. PET): (i) volume ratio: y=0.53x+18.29 (R^2=0.05); (ii) surface ratio: y=0.34x+18.32 (R^2=0.07); (iii) surface ratio from CINE MRI: y=0.41x+16.34 (R^2=0.08) (Figure 2). Higher correlations were found between the EF and the infarct sizes measured by MRI. EF vs. infarct size: (i) volume ratio: infarct size=-0.47EF+39.34 (R^2=0.91); (ii) surface ratio*: infarct size=-0.81EF+64.34 (R^2=0.82); (iii) surface ratio from CINE MRI*: infarct size=-0.77EF+62.69 (R^2=0.83) (* P=0.96).

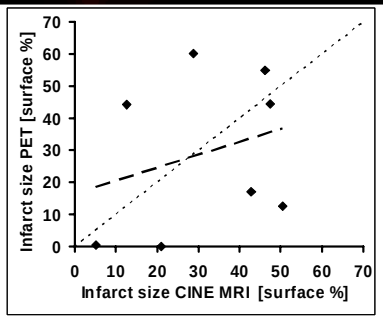

Figure 2: Infarct size correlation between MRI and µPET

Discussion and conclusion

Global functional parameters EDEV, ESEV, EF, and SV were comparable between PET and long-axis corrected MRI analysis. However, the standard deviations of the variability were considerable for control and both myocardial infarction groups. The LVM was considerably underestimated by PET compared to MRI, which is likely related to image resolution differences. Although the locations of the myocardial infarctions were clearly visible with PET as well as with contrast-enhanced MRI, infarct size measures did not correlate well between MRI and PET. This can be caused by the fact that the PET method is optimized to quantify transmural infarctions but not subendocardial infarctions due to the method's limited spatial resolution, whereas MRI can also visualize non-transmural infarctions very well. It might be possible to adjust the PET threshold level to account better for non-transmural infarctions. For MRI the EF correlated very well with infarct size, which suggests that the infarct size determined with MRI is functionally related to global performance of the heart, as expected (1).

We have shown that global functional parameters EDEV, ESEV, EF and SV determined by MRI and PET in a mouse model of myocardial infarction agreed well. LVM was systematically lower for PET than for MRI. The transmurality of infarcts is likely to influence the comparison of PET and MRI infarct size determination.

References: 1) Schneider JE, *et al*., J Magn Reson Imaging 2003;18(6):691-701; **2)** Stegger L, *et al*., J Nucl Med 2006;47(11):1837-1844; **3)** Ross AJ, *et al*., Magn Reson Med 2002;47(6):1158-1168; **4)** Nauerth A, *et al*., Proc Intl Soc Mag Reson Med 2006;14.