Relationship of Infarct Size and Cardiac Functions in the Hyper-acute Phase of Myocardial Ischaemia-Reperfusion in Rats

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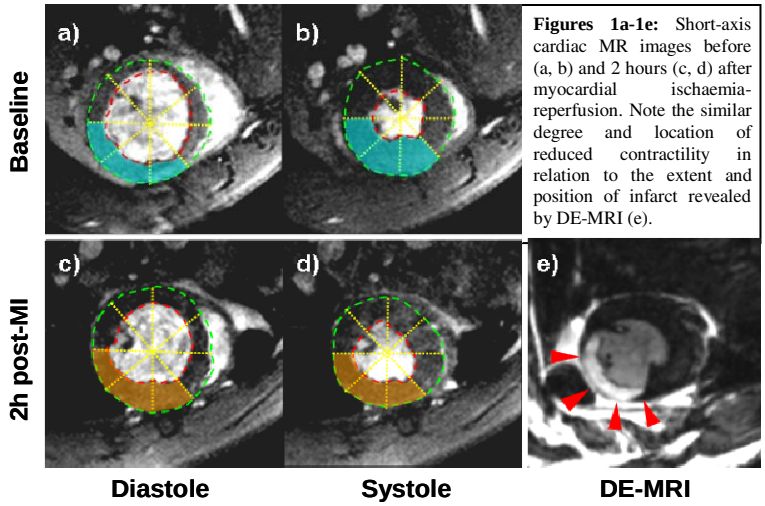
INTRODUCTION – Therapeutic studies in small animal models of myocardial infarction (MI) often rely on *ex vivo* infarct size as an efficacy endpoint. Recently, measurement of *in vivo* cardiac function using MRI has become a popular method to monitor treatment effects in addition to infarct size measurement. In chronic MI, infarct size has been shown to closely correlate to deterioration in cardiac functions, and is a predictor of poor prognosis in the long term[1,2]. However, the relationship between infarct size and cardiac functions in the hyper-acute phase (i.e. hours) following MI has not been fully explored. We aim to investigate this relationship using cardiac MRI with Gd-DTPA delayed-enhancement and *ex vivo* TTC-viability assay.

METHODS – Male Wistar rats (n=13) were anesthetised and imaged with a 9.4T Varian scanner before and 2 hours after sham operation or induction of myocardial ischaemia (30 minutes) by ligation of the left anterior descending coronary artery. A dual ECG/respiratory-gated gradient echo sequence was used to obtain long and short-axis cine images of the heart for cardiac function measurement (α=15°, TE=1.7ms, TR~7.5ms, FOV=40x40mm^2, 192x192, ΔZ=1mm, 15 slices). Infarct imaging was performed using Gd-DTPA (0.6mmol/kg) delayed-enhancement MRI with an inversion recovery sequence[3] (α=90°, TE=1.5ms, TR=3.6ms, TI~400ms, FOV=40x40mm^2, 192x192, ΔZ=1mm, end-systolic frame). Hearts were extracted following imaging for *ex vivo* infarct measurements by TTC staining and planimetry. MRI data (infarct size and global functional parameters) and *ex vivo* infarct size were quantified semi-automatically using Segment and ImageJ software respectively. Infarct size was normalised to the size of the left ventricle (In/LV). Relationships between infarct size and functional parameters including end-diastolic/-systolic volume (EDV, ESV), stroke volume (SV) and ejection fraction (EF) were analysed by linear regression using SPSS software.

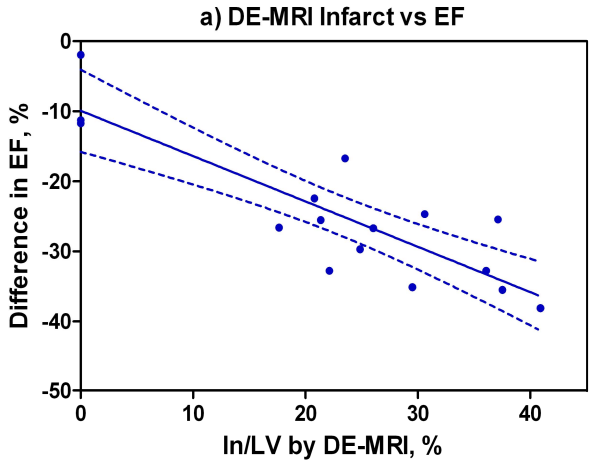
RESULTS AND DISCUSSION – Out of the four global functional parameters, EF demonstrated the strongest correlation to In/LV measurements by DE-MRI and TTC viability assay (EF vs In/LV, DE-MRI: R^2=0.736, F=39.0, p<0.0001; TTC: R^2=0.752, F=42.4, p<0.0001; see Figures 2a & b). The degree of variability within the correlation between infarct size and EF in the hyper-acute phase of MI was higher in comparison to existing literature of chronic MI studies (R~-0.94 for chronic MI[2]). The observed variability between EF and infarct size during the hyper-acute phase may be explained by transient physiological processes other than infarction: one possibility is myocardial stunning, where myocardium experiences significant contractile dysfunction despite being viable following ischaemia[4].

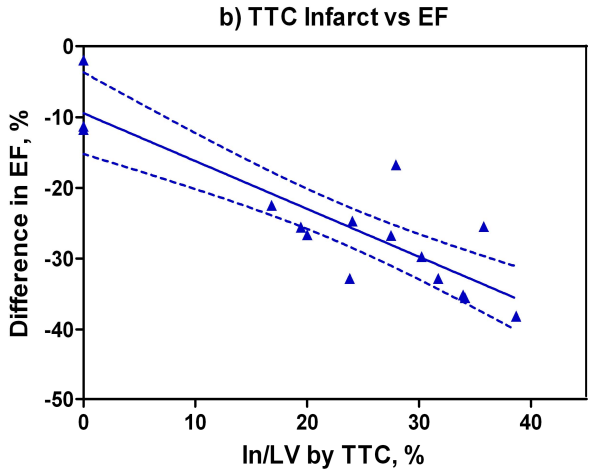
CONCLUSION – Cardiac functional parameters such as ejection fraction are becoming increasingly popular as efficacy endpoints for experimental therapeutic studies in MI, which has been shown to closely correlate to the extent of infarct in the chronic setting. However, in contrast to existing evidence from chronic MI studies, our results acquired during the early phases of MI suggest a higher variability between infarct size and EF, indicating changes in ejection fraction may not be solely dependent on the extent of infarct at this acute time point. Instead, other transient or reversible pathophysiological processes such as myocardial stunning may also affect EF, which may explain the observed variability in the correlation between infarct size and EF. It is therefore possible that the true efficacy of cardioprotective therapies may not be accurately reflected by assessing ejection fraction during the hyper-acute phase of MI.

REFERENCES – [1] Nahrendorf M. et al, *Am J Physiol Heart Circ Physiol* 2007;292(6):H3172-H3178; [2] Hu T.C.C et al, *NMR in Biomedicine* 2004;17(8):620-6; [3] Price A.N. et al, *Proc ISMRM* 2007; #2528; [4] Christian T.F. et al, *J Am Coll Cardiol* 1990;16(7):1632-8



Figures 1a-1e: Short-axis cardiac MR images before (a, b) and 2 hours (c, d) after myocardial ischaemia-reperfusion. Note the similar degree and location of reduced contractility in relation to the extent and position of infarct revealed by DE-MRI (e).





Figures 2a & b: Correlation between EF and In/LV measured by a) DE-MRI and b) TTC assay. Slope gradients were -0.65 and -0.68 respectively.