

Infarct size and extracellular matrix remodelling quantification using an elastin specific contrast agent (ESMA) in a model of permanent coronary ligation

Andrea Protti¹, Xuebin Dong¹, Ajay Shah¹, and Rene Botnar¹

¹King's College London British Heart Foundation Centre of Excellence, London, UK, United Kingdom

Introduction. The pathophysiological and molecular mechanisms of cardiac remodeling after the onset of MI have been widely studied with histochemistry [1] and imaging techniques such as echocardiography [2] and MRI. These studies collectively reported a degradation of the extracellular matrix and the creation of a collagen rich scar but also some elastin deposition [3]. Elastin is a structural protein important to provide tissues with elasticity. Recent studies suggest that elastin formation after MI leads to improved ejection fraction and decreased risk of myocardial rupture [3]. In this study we sought to investigate the merits of an elastin binding contrast agent, ESMA (Lantheus Medical Systems, USA) for the quantification of elastin in myocardial infarction in a mouse model of permanent coronary occlusion.

Method. Eight C57Bl6 mice underwent permanent left coronary artery ligation. Gadolinium DTPA (Magnevist, Bayer-Schering AG, Germany) and ESMA were administered intra-peritoneal (IP) and intra-venous (IV) respectively at a dose of 0.75 mmol/kg and 0.76 mmol/kg at time points of 3, 7 and 21 days after MI. To allow for complete clearance, ESMA was injected 24 hours post Magnevist injection. MRI images of the heart were obtained in the short axis view on a 7T horizontal MR scanner (Varian Inc., Palo Alto, CA) with an inversion recovery (Look-Locker) LGE sequence. At each time point Magnevist was studied 45min after injection while ESMA was studied at 2 hours, 2h 15min, 2h 30min and 2h 45min after injection, which were found previously to be good imaging time points for infarct visualization. Imaging parameters included: FOV=25x25mm², slice thickness=1mm, 30 phases, matrix size=128x128, 1 slice, flip angle=10°, IR = 2500ms, cardiac cycle≈120ms, acquisition time≈13min. R1 values were estimated for blood, remote and infarcted myocardium. Elastica van Giesson staining was performed to assess elastin content in the myocardium.

Results. ESMA uptake resulted in excellent delineation of the myocardial infarction at days 3, 7 and 21 post MI. Areas of enhancement with ESMA were compared to areas of enhancement with Magnevist (infarct size ESMA vs. infarct size Magnevist, P<0.05). ESMA and Magnevist R1 values for blood, infarcted and remote myocardium pre and post injection are reported in Figure 1. R1 values resulted in a significant difference between pre to post injection scans at all time points. R1 measurements also demonstrated a significant increasing uptake of ESMA in the infarcted myocardium at days 3, 7 and 21 and a similar but less pronounced behavior in the remote myocardium. The increasing R1 values at day 7 and 21 were related to increased elastin content in the myocardium as quantified with EvG staining and also some diffuse elastin deposition in the remote myocardium. At day 3, ESMA accumulation in the infarct zone is most likely non-specific and due to the increased extracellular volume. No elastin was detected by EvG staining at this time point. Magnevist diffuses in the infarcted area reporting higher R1 values at 3, 7 and 21 post MI when compared to ESMA. Values are: 3.7±0.91, 2.9±0.35 and 3.1±0.71 1/sec.

Discussion and Conclusions. ESMA and Magnevist areas of uptake resulted dissimilar one to each other at all time points as expected. R1 values of the infarct zone increased from day 3 to day 21 with ESMA while not significantly decreasing with Magnevist. Such behaviour was reflected by an increase in elastin in the infarct zone by histology. ESMA uptake at day 3 was most likely non-specific and related to the increased extracellular volume in the infarction. Further studies are now warranted to investigate the predictive value of elastin and its relationship to left ventricular function after 21 days.

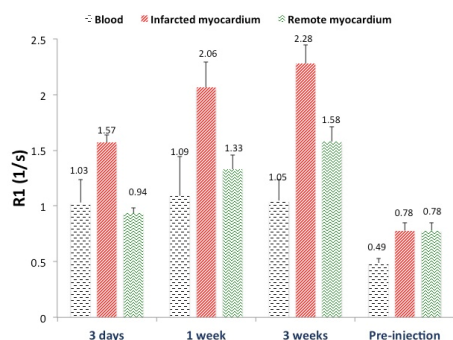


Figure 1. R1 values for blood, infarcted myocardium and remote myocardium at 3 days 1 and 3 weeks post MI 2h for ESMA post-injection. Pre-injection data are also reported.

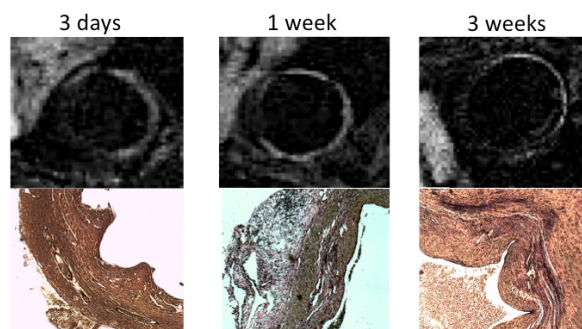


Figure 2. MRI images of ESMA 3 days, 1 week and 3 weeks post MI. ESMA areas are enhanced in LGE images. Elastica van Giesson staining for the 3 time points is shown in the row below.

References 1)Nahrendorf M, Swirski FK, Aikawa E, Stangenberg L, Wurdinger T, Figueiredo JL, Libby P, Weissleder R, Pittet MJ. *The healing myocardium sequentially mobilizes two monocyte subsets with divergent and complementary functions.* J Exp Med. 2007;204:3037-3047. 2)Kanno S, Lerner DL, Schuessler RB, Betsuyaku T, Yamada KA, Saffitz JE, Kovacs A. *Echocardiographic evaluation of ventricular remodeling in a mouse model of myocardial infarction.* J Am Soc Echocardiogr 15: 601-609, 2002. 3)Dobaczewski, M., C. Gonzalez-Quesada, and N.G. Frangogiannis, *The extracellular matrix as a modulator of the inflammatory and reparative response following myocardial infarction.* Journal of molecular and cellular cardiology, 2010. 48(3): p. 504-11.