Assessment of Post Infarct Remodeling in CCR2 knockout and wild type mice with an elastin-binding contrast agent

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Purpose: Myocardial infarction remains the leading cause of death in the western world despite advances in medical and interventional treatment. The subsequent biological processes that underlie myocardial remodeling and determine whether some patients develop heart failure are complex. Monocytes are believed to play an integral role in myocardial remodelling after infarction and are thought to be closely associated with de novo synthesis of the extracellular matrix by triggering the release of internal storage of elastin in myofibroblasts. We investigated the effect of monocytes on post infarct remodeling using in-vivo molecular imaging of elastin in a CCR2 knockout-model. We investigated how monocytes are related to long-term functional recovery and whether an elastin specific contrast agent (ESMA) may proof useful for the detection of remodeling and allow the assessment of functional recovery in the healing heart.

Methods: Permanent ligation was performed in the CCR2 knockout model and in wild type (WT) control mice. At day 7 and 28 after permanent ligation late gadolinium enhancement (LGE) and CINE MRI was performed with an elastin-binding contrast agent to assess LV remodeling, infarct size and function. 2D gradient echo CINE MRI (0.2x0.2x1mm) was acquired in the short axis and 2-chamber view to assess LV function and ejection fraction. 2 hours post elastin-binding contrast agent injection (0.6 mmol/kg), T1 weighted (T1w) 2D inversion recovery (IR) sequence (0.2x0.2x1mm) was acquired in the short axis to assess infarct size and extracellular remodeling (elastin synthesis). Histology was performed to compare ESMA uptake on LGE MR images with Elastica van Giesson staining and Masson's trichrome to assess the infarct area.

Results: Seven days after myocardial infarction, the infarct size was lower and the ejection fraction increased in C57Bl6 mice compared to CCR2 $^{(-/-)}$ (figure 2). One month after permanent ligation, the infarct size was lower and the ejection fraction was increased in C57Bl6 mice compared to CCR2 $^{(-/-)}$ mice.

Conclusion: Imaging of post infarct remodelling is feasible with an elastin binding contrast agent. In addition, we found less extracellular matrix synthesis in CCR2$^{-/-}$ compared to wild type mice seven days after permanent ligation by ESMA MRI and histology.

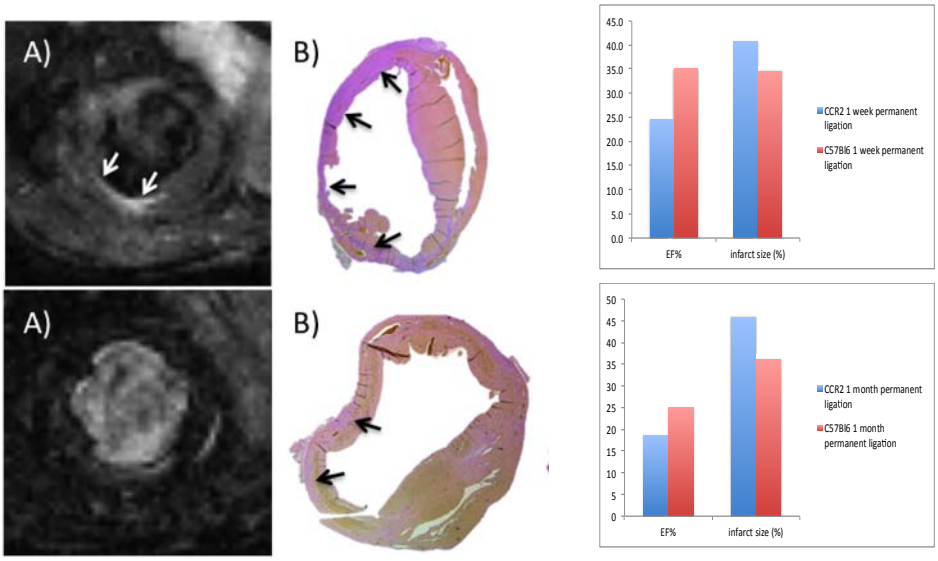

Figure 1: C57Bl6 mice (upper images): significant uptake of the elastin binding contrast agent on LGE MRI (A), visible Elastica van Giesson staining for elastin 7 days after permanent ligation (B), CCR2$^{-/-}$ mice (lower images): less uptake of the elastin-binding contrast agent on LGE MRI, less Elastica van Giesson staining 7 days after permanent ligation.

Figure 2): Ejection fraction seven days after myocardial infarction was less in CCR2 $^{(-/-)}$ mice compared to C57Bl6 mice. Also, the infarct size was increased in CCR2 $^{(-/-)}$ mice compared to C57Bl6 mice. (upper image). One month after permanent ligation, the ejection fraction was again less in CCR2$^{(-/-)}$ mice compared to C57Bl6 mice. Also, the infarct size was increased in CCR2 $^{(-/-)}$ mice compared to C57Bl6 mice (lower image).