$T_{1\rho}$ in infarcted mouse myocardium in vivo

Haja-Sherief N Musthafa[1], Galina Dragneva[1], Line Lottonen[1], Mari Merentie[1], Lyubomir Petrov[1,2], Tommi Heikura[1,2], Elias Ylä-Herttuala[1], Seppo Ylä-Herttuala[1], Olli Gröhn[1], and Timo Liimatainen[1]

[1]*AI Virtanen Institute For Molecular Sciences, University of Eastern Finland, Kuopio, Finland,* [2]*Ark Therapeutics Ltd., Kuopio, Finland*

Introduction After myocardial infarction, structural and physicochemical changes occur in ischemic cardiac tissue. In chronical phase, fibrotic tissue replaces necrotic tissue among other changes resulting compensatory dilation of left ventricle [1]. Severe myocardial infarction and the following loss of contractile myocardium lead to heart failure [2]. MRI methods based on longitudinal rotating frame relaxation time ($T_{1\rho}$) have been previously implemented successfully in detection of acute cerebral ischemia [3], anticancer therapy response [4] and chronic myocardial infarction in swine model [5]. In the current study, we measured $T_{1\rho}$ before and after myocardial infarction in mouse model.

Materials and methods Seven female C57BL/6J mice, which had infarction after left anterior descending artery (LAD) occlusion, were anesthetized using 1.5 % isoflurane. MRI experiments were performed at 9.4T using Varian DirectDrive console (Varian Inc., Palo Alto, USA) before and 1, 3, 7 days after LAD occlusion. MRI methods enclosed of gradient echo multi-slice (short axis) and single slice (long axis) cine sequences (TR/TE=10/2.7ms, 10 to 20 frames, slice thickness 1.2 mm, 7 to 8 slices, FOV=30x30 mm^2, and 128x128 matrix size), and continuous wave (CW) $T_{1\rho}$ measurements. CW spin-lock experiment consisted of adiabatic CW pulse [5] (spin-lock durations 0,18,36 and 54 ms, $\gamma B_1/(2\pi)$=1.25 kHz) between double (cardiac and respiratory) trigger, and spin-echo readout (TR/TE=2000/8 ms, FOV=30x30 mm^2, 128x128 matrix size, slice thickness 1.5 mm). $T_{1\rho}$ relaxation time maps were reconstructed based on mono-exponential decay model. The average $T_{1\rho}$ values were calculated on the infarcted and reference myocardium based on cine images. Two-way ANOVA was used for $T_{1\rho}$ comparison and one-way ANOVA was used for other comparisons. Histology of the heart, which was stained with Masson's trichrome, was performed to measure the infarction size.

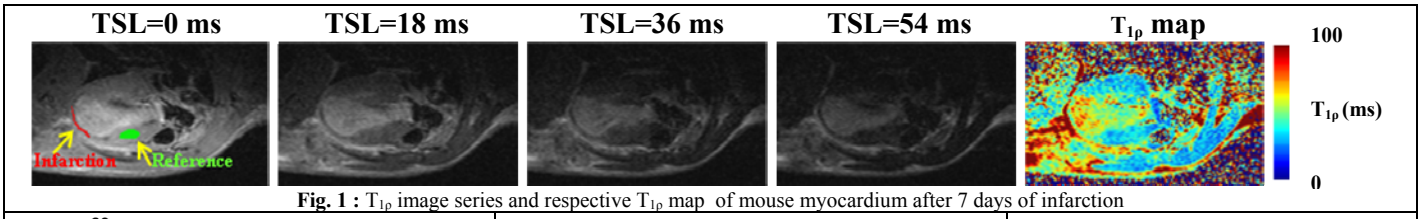

Fig. 1 : $T_{1\rho}$ image series and respective $T_{1\rho}$ map of mouse myocardium after 7 days of infarction

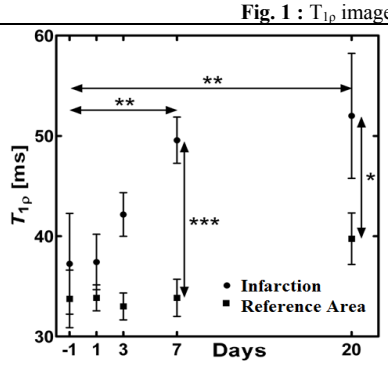

Fig. 2 : $T_{1\rho}$ time curve in infarcted and reference myocardium

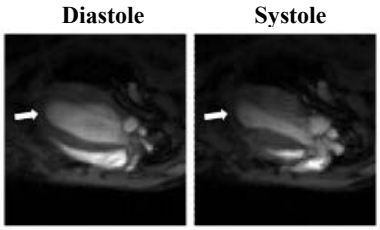

Fig. 3 : Cine images of infarcted heart at long axis (Arrow indicates infarction at apex of the heart)

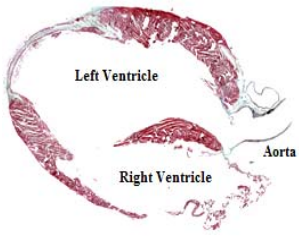

Fig.4 : Histology of Infarcted myocardium

Results and Discussion The increase of spin-lock duration results more signal loss in healthy myocardium than in infarcted area, which is clearly visible in $T_{1\rho}$ map (Fig.1). Significant increase in $T_{1\rho}$ was found at 7th day after infarction (Fig. 2) and $T_{1\rho}$ continued to increase until day 20 ($p<0.01$). An increasing trend was found in reference (noninfarcted) area ($p=0.09$). The significant difference in $T_{1\rho}$ was noticed between infarcted and reference myocardium at both 7th and 20th days after myocardial infarction ($p<0.001$ and $p < 0.05$). In earlier study, necrotic tissue was found to be replaced by granulation tissue completely 7 days after infarction in mouse myocardial infarction following by a formation of scar tissue [1]. The time scale of granulation and scar tissue formations fits with $T_{1\rho}$ increase serving most likely the reasons for $T_{1\rho}$ increase. The 20% decrease between before and 1 day after infarction ($p<0.05$) in ejection fraction together with the infarction size measured with MRI (32.6 ± 7.3% (mean±SEM) and with histology (27.6 ± 6.1%) confirmed infarctions. The presented data shows that, $T_{1\rho}$ can be mapped in mouse myocardium in vivo and $T_{1\rho}$ is shown to increase after infarction. The longitudinal characterization of $T_{1\rho}$ opens up possibilities to follow up the therapeutic agents' responses such as gene therapy responses and might provide diagnostic marker for tissue viability and damage.

References [1] Virag JK, Murry CE, AJP, 163: 6 (2003). [2] G Ertl, S Frantz, Cardiovas Res, 66: 22– 32 (2005). [3] Gröhn et al, JCBFM, 20: 1457-66 (2000). [4] Hakumaki et al, Cancer Gene Ther 9: 338-45 (2002). [5] Witchey et al., MRM 64: 1453-60 (2010). [5] Gröhn et al, MRM 49: 172–176 (2003).

Acknowledgements We like to thank for the support given by the funding agencies – Academy of Finland, Sigrid Juselius Foundation, Instrumentarium Science foundation and the Finnish Funding Agency for Technology and Innovation.