In vivo monitoring of anti-inflammatory Atorvastatin-effects in reperfused myocardial infarction using integrated cellular fluorine 19F-MRI and 1H-cardiac MRI

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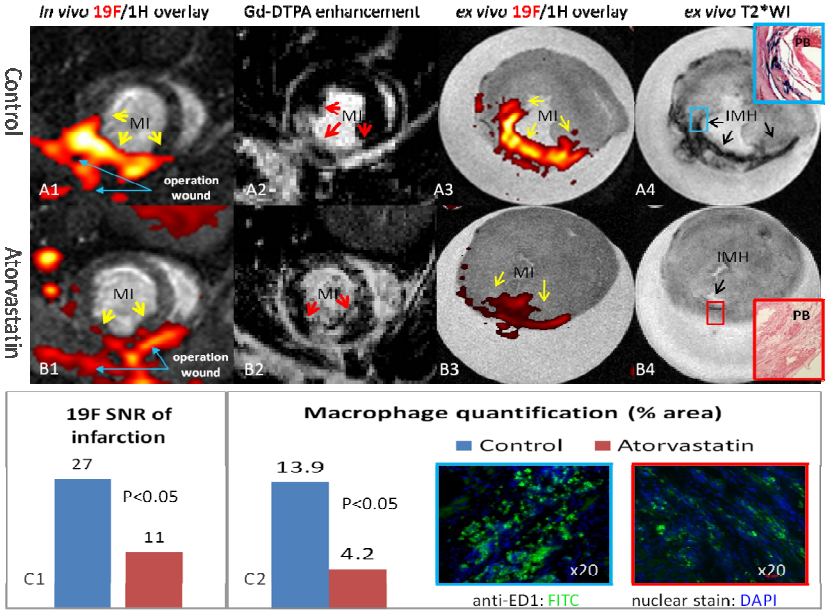
PURPOSE

In acute myocardial infarction (MI) blood monocytes play a key role in wound healing. They have been proposed as promising diagnostic and therapeutic targets in acute MI [1]. Non-invasive imaging strategies are required to better understand and translate this knowledge into clinics. Fluorine MR (^{19}F-MRI) is a novel method to visualize cell trafficking *in vivo*. Besides its unambiguous detection and quantitative nature [2], ^{19}F-MRI has the advantage to allow characterizing key pathophysiologic features e.g. edema, necrosis, and microvascular function by ^{1}H-MRI. In this work we investigated the diagnostic value of integrating ^{19}F-MRI cell trafficking with ^{1}H cardiac MRI to monitor an anti-inflammatory therapeutic approach in a reperfused MI rat model.

METHODS

Animal model: 5 rats with reperfused MI received Atorvastatin (*I.G.*100mg/Kg) 24h and 1h before 120min occlusion of left anterior descending coronary artery. 7 rats undergoing the same operation procedure receiving tap water served as controls. On day 1 after the operation, 650µL 20% perfluorocarbon (PFC) emulsion were injected *i.v.*. **Flow cytometry** was performed on day 3 to analyze the PFC-labeling efficiency of monocytes, T cells and B cells in blood. ***In vivo* MR** was performed with a 7T scanner on day 3, 7, and 14. Sequential monocyte recruitment was followed by ^{19}F-MRI (TSE). In ^{1}H-MRI, T2WI was used to assess edema, T2*WI to quantify intramyocardial haemorrhage (IMH), early and late Gd-DTPA enhancement to depict microvascular obstruction (MVO) and necrotic myocardium, respectively, and Cine MRI to analyze myocardial contractility. ***Ex vivo* ^{19}F/^{1}H MRI** was performed after the last *in vivo* MR. **Histology and immunohistochemistry (IHC):** H&E, Perl's Prussian blue (PB), and anti-ED1 IHC stainings were performed to analyze integrity of the myocytes, IMH and monocyte infiltrates, respectively. The signal to noise ratio (SNR) of ^{19}F in MI was compared between treated animals and controls. The relative area of anti-ED1+ cell in MI was quantified and compared with the ^{19}F-SNR. Effects of Atorvastatin were assessed with regard to (*a*) thinning of MI, (b) left ventricular dilatation (*c*) MVO occurrence, and (d) volume of IMH.



RESULTS & DISCUSSION

On day 3, 93.8±2.4% CD11b+ cells (mainly monocytes) in blood were labeled by PFC, while T and B cells were not labeled. *In vivo* ^{19}F-MRI convincingly depicted myocardial infiltration by blood monocytes (A1&B1). The ^{19}F signal correlated well with the amount of monocytes/macrophages detected by IHC (C1&C2) and revealed significantly less monocyte/macrophage infiltrates in treated (panel B) compared to untreated rats (panel A). A better preserved microvasculature in treated group was evidenced by the absence of MVO occurrence (43% in control, $p<0.05$) and significantly less IMH (A4&B4, $p<0.05$), an indicator of severe microvascular injury. There were also significantly less MI thinning ($p<0.05$) and less left ventricular dilatation ($p<0.05$) in treated rats. The ^{1}H MRI findings support the hypothesis that the Atorvastatin-associated beneficial effect of less cardiac muscle loss and inverse LV remodeling might result, at least partly, from the sustained microcirculation in the area at risk after ischemia-reperfusion. Whether less monocyte/macrophage infiltration in MI was a result of a better salvaged area at risk due to the effect of Atorvastatin on microcirculation, and/or it led to less endothelial and cardiomyocyte injury early after reperfusion still needs to be determined. In addition, the long term benefit of such treatment on cardiac remodeling needs to be investigated.

CONCLUSION

Our study demonstrates that combined ^{19}F/^{1}H MRI allows to monitor the modulation of myocardial monocyte infiltration and revealed a possible mechanism of an anti-inflammatory approach by Atorvastatin. Our platform might serve to provide a novel view on tissue injury and its innate immune response after ischemia-reperfusion, and thus contribute to gain new insights into the effects of anti-inflammatory therapy in MI, which in the future could be translated into acute MI patients.

REFERENCES [1] Nahrendorf M et al; Circulation 121: 2437-2445 (2010). [2] Ahrens ET et al; Nat biotechnol. 23 (8): 983-7 (2005).

ACKNOWLEDGEMENTS This work was in part supported by DFG (SFB688) and BMBF (GoBio-1, 01EZ0816 and Comprehensive Heart Failure Center).