Hemorrhage alters T2 BOLD response in remote myocardium following acute myocardial infarction in a porcine model

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Introduction: Hemorrhage, in association with microvascular obstruction (MVO), has been speculated to be a new independent predictor of adverse outcomes following acute myocardial infarction (AMI) [1,2]. Other studies have also suggested that in addition to infarct zone remodeling, the distal remote myocardium may experience alterations, including vasodilator dysfunction, edema, and extracellular matrix expansion [3,4,5]. The aim of our study was to investigate whether hemorrhage is related to remote myocardial remodeling using a novel preclinical model of myocardial hemorrhage. To this end, a blood-oxygen-level-dependent (BOLD) approach with T2 contrast was employed to evaluate vasodilator function using a stress agent.

Methods: Myocardial hemorrhage was artificially induced in a porcine model by direct intracoronary injection of collagenase (col) [6]. Animals (N=11) were subjected to ischemia-reperfusion injury in the LAD coronary artery and divided into three groups: Group 1 (N=3) 45 min occlusion with saline; Group 2 (N=4): 8 min ischemia with col; and Group 3 (N=4): 45 min occlusion with collagenase. Imaging was performed on a 3T MRI scanner (MR 750, GE Healthcare) at baseline (healthy) and day 1, week 1 and week 4 post-intervention. T2 mapping was performed using a previously validated T2-prepared spiral sequence: 12 spirals (3072 points), 5 TE's (2.9-184.2 ms) [4]; for BOLD response, the sequence was repeated with Dipyridamole (stress). Hemorrhage was identified by T2* using a multi-echo gradient-echo acquisition. Infarct and MVO were identified using early and late gadolinium enhancement imaging (EGE, LGE).

Results: Low infarct region T2* values confirmed the presence of hemorrhage in the collagenase groups 2 and 3 (16 ms vs. 33 ms at baseline, $p<0.001$) whereas group 1 was non-hemorrhagic (Figure 1). Infarct size was significantly greater in group 3 compared to group 1 at all time points ($p<0.0001$) and group 2 did not show any infarction on LGE images. MVO was present only in group 3 (1 of 4 animals). Figure 2 shows the plots for T2 alterations during the healing process. In group 1, remote T2 was significantly elevated under stress conditions at all time points and no changes were noted in the resting state. However, remote resting T2 was significantly elevated at day 1 and week 1 in groups 2 and 3 and this was associated with a transient vasodilator dysfunction (low stress T2) that resolved by week 4; the dysfunction was more persistent in group 3.

Discussion: Coronary vasodilator dysfunction has been demonstrated in infarcted as well as remote myocardium in patients post-AMI [3]. The BOLD mechanism exploits the paramagnetic properties of deoxyhemoglobin in blood and serves as an endogenous contrast agent to probe tissue perfusion. In groups 2 and 3, the subtle increase in remote resting T2 could potentially arise from either edema or hyperemia while the suppressed stress response may suggest an already-stressed or impaired state resulting from a systemic inflammatory response or neurohormonal sympathetic activity. Our study thus demonstrates that hemorrhage not only contributes to cellular and microvascular damage and inflammation [6] but may also be responsible for remote myocardial remodeling post-AMI. A mechanistic understanding of the pathophysiology of reperfusion hemorrhage will potentially yield improved management strategies for these high-risk patients who are prone to adverse long-term outcomes.

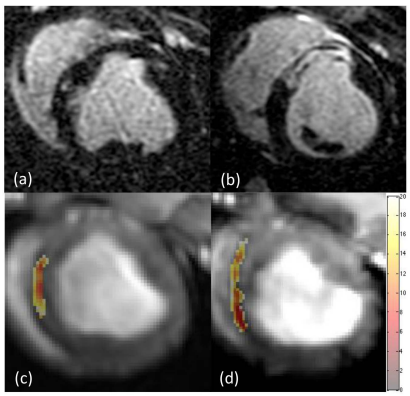

Figure 1: (a) and (b) are representative LGE images from animals in groups 1 and 3, respectively. (c) and (d) are representative T2-weighted images from animals in groups 2 and 3, respectively. The overlays show the hemorrhagic regions as identified by T2*<20 ms.

References:

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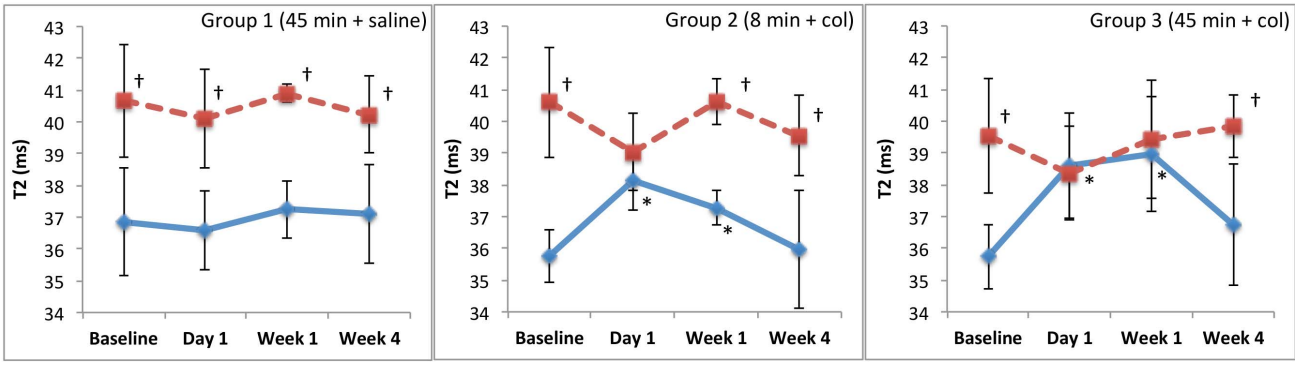

Figure 2: Evolution of T2 values in the remote myocardium under rest (blue) and stress (red) conditions in the three animal groups. (†: $p<0.05$ for stress values compared to resting values at the same time point; *: $p<0.05$ for rest values compared to rest baseline).