MICROVASCULAR OBSTRUCTION INHIBITS INFARCT HEALING AND ENHANCES COMPENSATORY VENTRICULAR HYPERTROPHY: EXPERIMENTAL CARDIAC MRI STUDY

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Hypothesis: MRI provides useful information on the pathophysiological processes associated with coronary revascularization, such as interstitial edema, intramyocardial hemorrhage and microvascular obstruction (MVO). Recently, Kloner (1) and Wu (2) hypothesized that MVO could inhibit the healing of myocardial infarct by limiting the delivery of inflammatory cells and nutrients essential for the healing process. Accordingly, the purpose of this noninvasive MRI study was to provide direct evidence that MVO may inhibit infarct healing and enhance structural LV remodeling.

Methods: Three groups of animals were used: group I control animals (no intervention, n=4), group II animals subjected to 90min LAD coronary artery occlusion/reperfusion (n=8) and group III animals subjected to 90min LAD occlusion/microembolization/reperfusion (n=8). Group III animals received 32mm^3, 80µm diameter) in the last 3min of the LAD occlusion while the angioplasty balloon was still inflated to avoid back flow. Coronary angiograms were acquired before, during and after occlusion. The animals were imaged at 3 days and 5 weeks after interventions, simulating the time window in clinical studies. MRI was performed with a 1.5T scanner (GE Medical Systems, Milwaukee, WI). For LV function, volumes and mass measurements, steady state free precession cine was used for measuring global and regional LV function. The imaging parameters were: TR/TE/flip angle=3.5ms/1.8ms/70°, slice thickness=6mm without gap, FOV=26×26cm; matrix size=160x152; NEX=1 and cardiac phases=16. For myocardial viability, inversion recovery gradient-echo sequence was used to delineate damaged myocardium. DE-MRI images were acquired at 10min after delivery of 0.15mmol/kg Gd-DTPA. The imaging parameters were: TR/TE/flip angle=5ms/2ms/15°; FOV=26×26cm; slice thickness=6mm without gap; read and phase matrix size=256x162, NEX=2 and TI=220-240ms.At the conclusion of the second imaging session, animals were euthanized and their hearts were excised. The entire LV was weighed and sliced into short axis rings (~6mm thickness) and stained with triphenyltetrazolium chloride (TTC) to macroscopically confirm the presence of myocardial infarct. All LV rings were fixed in buffered 10% formalin, divided into 2-7 segments, cut into 5µm sections and stained with hematoxylin-eosin and Masson trichrome to microscopically characterize the changes in myocardium.

Results: Persistent MVO at 10 min in the core of the infarct was larger and more frequent (n=8/8) in group III than group II (4/8) on DE-MRI (Table 1). At 5 weeks, however, there was a significant reduction in the extent of myocardial damage and an absence of visible MVO on DE-MRI in groups II and III (Table 1). Group II animals demonstrated significantly greater shrinkage in infarct mass (35±2%) compared with group III (24±2%, P<0.01). Cine MR images showed the structural and functional changes reflected by the increase in LV mass and chamber volumes over the course of the study. LV mass was not significantly different between the 3 groups (75±3g group I, 75±1g group II, 78±2g group III). At 5 weeks, LV mass was significantly lower in group I (93±4g), group II (100±3g, P<0.05) compared with group III (130±5g, P<0.001). Regression analysis showed moderate correlation between MVO zone measured at 3 days and LV mass measured at 5 weeks in group III (r=0.58), but not in group II (r=0.37). Group II showed acute drop in LV function followed by moderate recovery over the course of the study. Quantitative analysis of global LV function revealed a greater and persistent drop in ejection fraction and increase in end-diastolic and end-systolic volumes in group III compared with group II. Microscopically traces of inflammatory cells were observed in the contiguous infarct at 5 weeks in group III, but not II. In remote myocardium the myocytes were obviously larger (group III >, II, > I, but no quantitative measurements were obtained of these cells.

Conclusion: This MRI study illustrates the recently raised conjecture that MVO inhibits infarct healing, accentuates structural LV hypertrophy and LV dysfunction. Mechanical MVO caused persistent decline in ejection fraction and increase in LV volumes compared with MVO caused by reperfusion injury. Serial cine MR images showed that MVO in group III was associated with greater nonviable and viable (hypertrophied) mass compared with group II animals.

Table 1: Extents of microvascular obstruction and infarct as well as body weight of control animals (group I), animals subjected to LAD occlusion/reperfusion (group II) and LAD occlusion/microembolization/reperfusion (group III).

	MVO mass (g)		Infarct mass (g)		Body weight (kg)	
Group	3 days	5weeks	3 days	5 weeks	3 days	5 weeks
Group I	none	none	none	none	33±1	54±2*
Group II	1.6±0.8 (2.1%)	none	11.7±0.7 (15.5%)	7.6±0.5*	33±1	54±1*
Group III	3.9±0.3$^{\#}$ (5.0%)	none	12.9±0.5 (16.5%)	9.8±0.3*$^{\#}$	32±1	53±2*

MVO and infarct size data at 3 days are also presented in parentheses as % LV volume. *P< 0.001 compared with 3 days for the same cohort. $^{\#}P$< 0.02 compared with group II.

References: 1) Kloner RA. No-reflow phenomenon: maintaining vascular integrity. J Cardiovasc Pharmacol Therap 2011;16:244-250. 2) Wu KC. CMR of microvascular obstruction and hemorrhage in myocardial infarction. J Cardiovasc Magn Reson 2012; 14:68-84.