# CARDIOVASCULAR MR IMAGING IS A PLATFORM FOR PERCUTANEOUS TRANSENDOCARDIAL DELIVERY AND ASSESSMENT OF GENE THERAPY

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**INTRODUCTION:** Cardiomyopathy is the eventual scenario in patients with severe coronary disease. A candidate treatment for this condition is therapeutic angiogenesis (1). A percutaneous transendocardial approach to therapeutic angiogenesis in ischemic myocardium aims to achieve a locally effective concentration of therapy, minimize negative effects associated with systemic distribution, minimize the effect of blood enzymes on genes and eliminate open-chest surgery and extended hospitalization (2). Unlike the current study, the delivery of VEGF gene was performed in open chest swine model of reperfused infarction (3).

**PURPOSE:** To: 1) explore the utility of MR fluoroscopy in percutaneous transendocardial delivery of genes in canine model of occlusive infarction; and 2) evaluate the effect of plasmid VEGF gene on MR measurements of viability, perfusion and LV function.

**MATERIALS AND METHODS:** LAD was occluded distal to the first diagonal branch using surgical procedure. At 3 days MR fluoroscopy was used for guiding of the endovascular catheter and gene delivery. Plasmid VEGF contains a cytomegalovirus promoter deriving $VEGF_{165}$ cDNA (2mg) was delivered locally under MR guidance. Dy-DTPA-BMA was used in each animal to test the functionality of the catheter needle in delivery into intramyocardium. The animals were imaged at 3 days and 7-8 weeks after infarction. First pass perfusion, delayed contrast enhancement and cine MR imaging was employed for therapy assessment (3). Plasmid VEGF (n=6) or LacZ gene (n=6) was injected into the border and core of CE-MR region. At 7-8 weeks, tissue samples were stained with TTC, hematoxylin & eosin, Masson's trichrome and isolectin B4.

**RESULTS:** Three days after coronary artery occlusion, the infarction was visualized as a bright region on delayed contrast enhanced MRI (CE-MRI) (Fig. 1A) and the bright region was used as a target for delivering therapy. The signal derived from the active catheter allowed simultaneous visualization of the catheter and vascular wall. Precise placement of the catheter tip into the 4 target sites was made possible by rotating and deflecting the catheter (Fig. 1B,C). Treated, but not control, animals showed improved LV function as shown by increased ejection fraction and decreased the LV end systolic volume at 7-8 wks (Fig. 2). At 7-8 wks, signal intensity of infarcted myocardium in treated animals increased by 158% compared with 79% in control animals on first-pass perfusion imaging. Both groups showed a significant decrease in the extent of contrast enhanced regions compared with 3 days. VEGF gene caused a 9.4% greater reduction in the extent of the enhanced region than controls (8.5±0.9% vs. 11.3±0.9%, *P*=0.03) and comparable to TTC (8.5±2.0% vs. 12.5±0.8%).

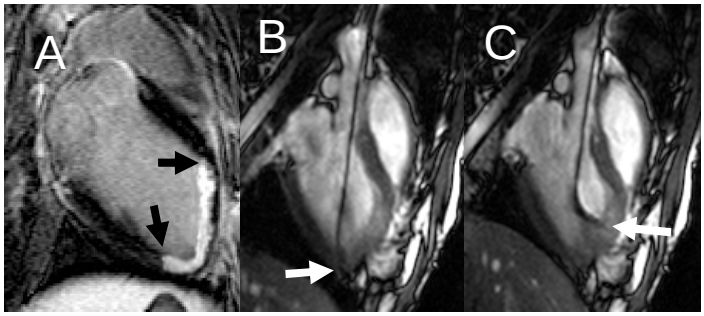


**Fig. 1.** CE-MR image (A) shows hyperenhanced infarcted myocardium as a target for delivering therapy (arrows). Real time images (B, C) show the endovascular catheter in LV (arrows).

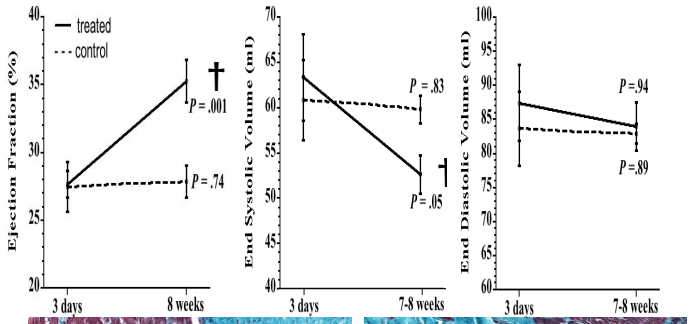


**Fig. 2.** Changes in global LV function. VEGF gene significantly increased ejection fraction and decreased end systolic volume. Bold= treated, dashed= control.

At 7-8 wks, infarcts from both groups showed few scattered thick walled arteries on Masson's trichrome stain. Furthermore, isolectin B4 delineated vascular endothelial cells with brown reaction product (Fig. 3). Lectin (brownish) stained capillaries were greater in the border region (498±94/mm$^2$, P=0.008) and the core (491±72/mm$^2$, P=0.0002) of treated compared with control animals (265±33/mm$^2$, 163±40/mm$^2$, respectively). Larger vessels showed a similar tendency in the border region (7±3/mm$^2$ P=0.05) and the core (4±1/mm$^2$, P=0.03) of treated compared with control animals (2±1/mm$^2$, 1±1/mm$^2$, respectively). There was no significant difference in capillary and arterial counts in normal remote myocardium between treated (760±70/mm$^2$, P=0.48, 2±1/mm$^2$, P=0.23, respectively) and control (706±77/mm$^2$, 1±1/mm$^2$, respectively).

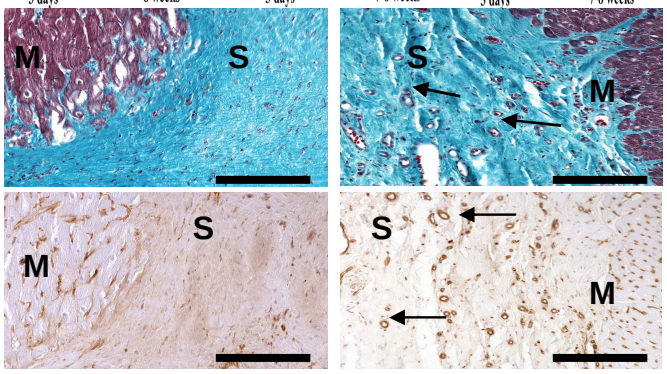


**Fig. 3.** Masson's trichrome (top) and isolectin B4 (bottom) of control (left) and treated (right) animals are shown. The healed infarct in treated animals contained numerous blood vessels (arrows), compared to few in control infarcts. New blood vessels were accentuated by isolectin B4 stain (brown) in treated infarcts. Calibration bars=80μ, M = viable myocardium (purple), S=scar tissue (blue).

**CONCLUSION**: The ability of MR imaging to define the target, guide endovascular catheter to the target and assess LV function and viability makes modality suitable for investigating the effects of angiogenic genes, cells and drugs. Percutaneous transendocardial delivery of VEGF gene into occlusive infarction is an effective technique for revascularization. VEGF gene improved myocardial perfusion and reduced the extent of infarction. The effectiveness of this approach most likely stems from the promotion of new blood vessels in the target.

**References**. 1) Folkman J. Circulation 1998,97:628-9, 2), Saeed M, et al Eur Radiol 2005,15:851-63, 3), Saeed M, et al Radiology 2007,243:451-60.

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