MR Value in the Assessment of the Efficacy of Cardiac Specific Gene Expression

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INTRODUCTION. Vascular endothelial growth factor (VEGF) proteins have been shown to improve LV function after infarction in experimental animals. Clinical studies, however, have not confirmed the benefit of VEGF in patients with ischemic heart disease. Recently, investigators have used adeno-associated viral (AAV) vector encoding VEGF gene to provide longer supply of VEGF (1). This AAV-VEGF is expressed only in ischemic myocardium, but not in extra-cardiac tissues or organs in mice. In this study, non-invasive MR imaging has been used to sequentially assess regional strain, global cardiac performance and infarct size.

MATERIALS AND METHODS. Myocardial infarction was produced by occluding the LAD coronary artery for 2h/ reperfusion. In 6 pigs the AAV-VEGF was injected 1h after reperfusion into 8 sites. A total of 10^{11} copies of AAV-VEGF was injected (500 µg) each. The other 6 animals served as control. Animals were imaged at 3 days and 8 weeks using 1.5T (Philips, The Netherlands). The imaging sequences were: 1) cine MR (TR/TE=8/5ms, cardiac phase=16), 2) tagged cine MR (TF-EPI: cardiac phases=16, CSPAMM=2line/acq.) and 3) inversion recovery gradient echo (TR/TE=4.4/2.1ms, TI=270-330ms) after administration of 0.1 mmol/kg Gd-DOTA (Guerbet Group, France). Regional all thickness and percent of systolic wall thickening were measured in 8 segments of the base, mid, apical levels of the LV. Regional end-systolic circumferential shortening was measured in infarcted, peri-infarcted and remote myocardium using Harp software. The extent of the infarcts was measured from delayed contrast enhancement images and triphenyltetrazolium chloride (TTC) stain. Tissue samples were obtained from infarcted, peri-infarcted and normal myocardium and stained with hematoxylin and eosin, Masson's trichrome and isolectin B4 to define scar tissue, myocytes diameters and vascular density.

RESULTS. No change in ejection fraction was observed in treated animals at 8 weeks. In contrast, significant deterioration in ejection fraction was detected in control animals (P=0.0005). Fig. 1 shows tagging cine CMR images in control and treated animals. Regional analysis showed improved systolic circumferential shortening in normal and peri-infarcts of treated, but not in control, animals at 8 weeks (Fig. 2). Myocyte diameter significantly decreased in peri-infarct zone of treated animals (23±0.1µm) compared with controls (28±0.1µm), suggesting lack of LV remodeling. Absence of hypertrophy in this territory of treated animals was associated with better vascularization.

CONCLUSIONS Injection of AAV-VEGF directly into infarcted myocardium improved systolic circumferential strain, wall thickening and prevented LV remodeling. This gene therapy prevented myocardial hypertrophy in peri-infarcted myocardium. A study using percutaneous MR guided delivery of this therapy is underway.

Reference: (1) Su H, et al. Proc Natl Acad Sci U S 2004;101:16280-5.

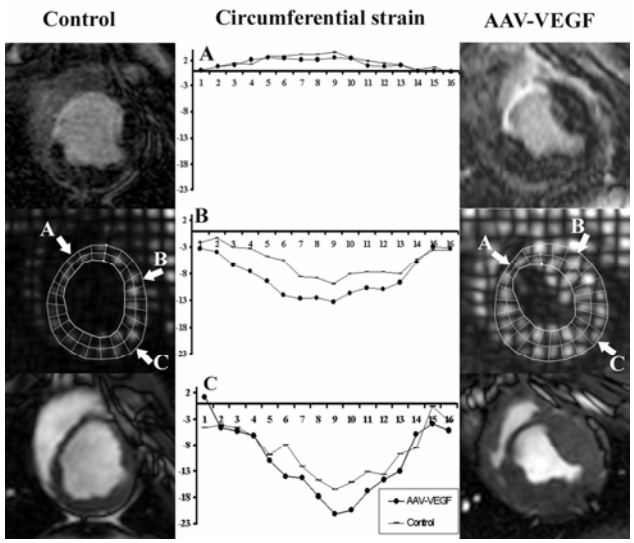

Figure 1. Representative images and circumferential strain profile at 8 weeks Anatomical co-registration between delayed contrast enhancement (top) tag (middle) and cine MR images (bottom) delineating the infarcted (A), peri-infarcted (B), and remote myocardium (C).

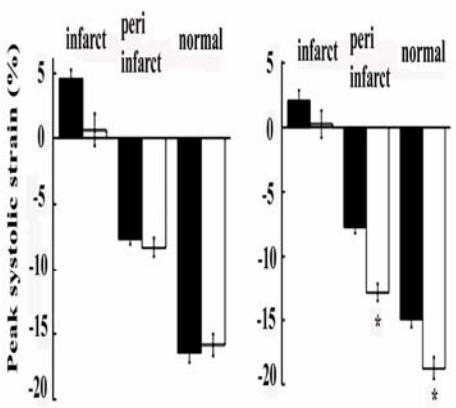

Figure 2. Systolic circumferential strain in the control animals (black bar) and AAV-VEGF treated animals (white bar) at 3 days (left) and 8 weeks (right). In the AAV-VEGF animals, the peri-infarcted and remote myocardium demonstrated improvement in strain at 8 weeks compared with control animals. * $P < .05$ compared to control animals at 8 weeks.