Repair of cardiac damage using intrapericardial drug delivery by means of MR-trackable alginate beads

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Introduction

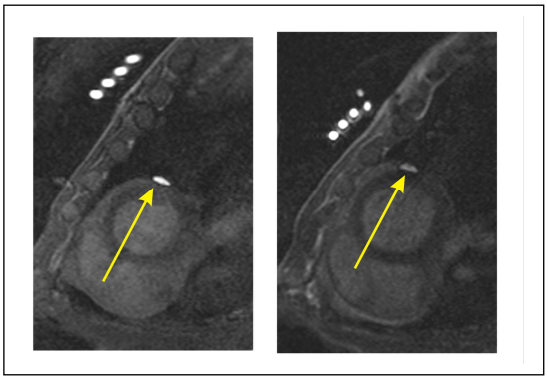
Re-establishment of a vascular network is an important step in the repair of damaged myocardium. For this purpose vascular growth factors (GFs) were applied at the site of injury. To prolong action of these peptides, GFs were incorporated in alginate beads. However, visualization of the beads is not an easy task.

Methods

The left ventricular (LV) anterior wall of pigs (15-20 kg) hearts was exposed to the tip of a 25-mm aluminum rod cooled in liquid N_2 to cause well defined cardiac damage. Alginate beads (d=3.2±0.2 mm) were hardened in 30 mM $CaCl_2$ + 1mM $GdCl_3$ and loaded with basic fibroblast GF (~0.1 mg) and vascular endothelial GF (~0.1 mg) + heparin (n = 5) or heparin alone (control, n = 3). Release rates of VEGF and bFGF were determined in vitro using an immunoassay and were low, ~3 and ~1%/day, respectively. A string of 6 beads was sutured to the cryo-injured epicardium after which the pericardium was closed.

In vivo cardiac imaging was performed on a 3T Siemens imaging system using a phased-array 16-element coil. Following breath-hold cine (FLASH) imaging of cardiac hemodynamics, T_1-weighted spin echo inversion-recovery short-axis images (12-13 slices, 5-6 mm thick) were acquired with ECG-gating. Typical acquisition parameters: TI = 500 ms, TE = 1.7 ms, TR = 700 ms, flip angle = 20 degrees, 192x 256 data matrix and a FOV of 210-225x280-310 mm^2.

MR imaging of the animals was performed at ~2.5 h and 1, 2 and 4 weeks after cryo-injury. Following baseline imaging GdDTPA was injected as a bolus (0.2 mmol/kg) and serial short axis images were acquired.



Cardiac short-axis images. The image on the left was acquired 2 h after surgery and placement of the alginate beads, containing $GdCl_3$, in the pericardium. The image on the right was acquired two weeks later from the heart of the same animal. Both images show the position of alginate beads, as indicated by the arrow. The four bright spots at the top of the image are from a reference (1mM $GdCl_3$ solution) mounted on the pig.

Results and Discussion

Alginate beads without contrast agent were not distinguishable from the background forcing the use of formulations containing contrast agent. Four weeks after cardiac injury, the infarcted area appeared uniformly hyperintense and was negative for viability stain (TTC). GFs prevented the thinning of the LV wall as observed in control animals. Throughout the experiments the beads appeared as bright spots on MR images and were recovered from the LV tissue after 4 weeks. Optical spectroscopy detected visible absorption bands characteristic to hemoglobin (Hb) and/or myoglobin (Mb) in the tissue surrounding the beads while in controls these bands were not detectable, implying the establishment of a capillary network filled with Hb and/or myocytes containing Mb.

Conclusions

Sustained intrapericardial release of vascular growth factors from alginate beads facilitated growth of vascularized connective tissue over the cryo-injured area.