MRI and micro-CT evaluate the effect of VEGF in a rabbit femoral artery chronic total occlusion

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Introduction

Chronic total occlusion (CTO) is common in diseased coronary and peripheral arteries. These occlusions are associated with myocardial infarction and ischemia in extremities that can lead to death and amputation, respectively. In many cases, revascularization has yielded beneficial outcomes. Percutaneous revascularization of chronic total occlusions is usually limited by failure of guidewire crossing (1). We propose that intravascular administration of Vascular Endothelial Growth Factor (VEGF) to the proximal end of the CTO would promote new microvascular growth in CTOs, and in turn would potentially increase the successful rate of guide wire crossing. MRI has the potential to identify the CTO non-invasively; it may also be helpful for treatment planning and monitoring. Particularly, the goal of this study is to examine its potential to monitor the development of microvasculature in the CTO with VEGF (2).

Methods

Thirteen New Zealand white rabbits (3 to 3.5 kg) were included in this study. Femoral arteries were occluded by thrombin injection (100IU, Millipore cat. No. 82-036-3, Kankakee, Illinos) (3). When the CTO formation had progressed for 12 weeks, contrast-enhanced magnetic resonance imaging (MRI) was performed. The rabbits were then divided into two groups randomly, seven for control with a bovine serum albumin (BSA) injection and six for injection to the CTO with a VEGF $-_{164}$ treatment (R&D Systems Cat#MMV00). Three weeks after the injections, MRI was performed again. The femoral arteries were then dissected from the animals after sacrifice and micro-computed tomography (m-CT) was conducted.

MRI: MRI studies were performed on a 3.0 T GE Excite Scanner (GE Healthcare, Milwaukee, Wisconsin) using a custom-made small receive-only surface coil for signal reception. An intravascular contrast agent, Clariscan (NC100150-injection, GE Healthcare) was used in this study. A 3-D spoiled gradient echo acquisition (SPGR) was performed (TE: min full, 30^o Flip Angle, BW=125kHZ, Matrix=320x320, FOV=8cm, Phase FOV=1 Slice Thickness=0.8mm) before and immediately after an intravenous bolus injection of Clariscan (0.2 ml/kg).

Micro-CT: Once the MRI study was finished, the animals were given 100 units of Heparin to prevent blood coagulation in the microvasculature prior to sacrifice. The abdominal aorta was then cannulated and flushed with 250 milliliters saline followed by a 50 ml injection of MicroFil (FlowTech, USA) perfusion. The femoral artery was excised about 90 minutes after microfil perfusion and stored in 10% formalin for 24 hours. The specimen was mounted in 10% gelatin and three-dimentional CT data sets were acquired using a microCT scanner (MS-8, GE Medical Systems, London, Ontario). The cone beam CT acquired projections of 1000 x 1000 pixels at 600 angular increments.

A ratio of signal intensity in the MR images from the region of interest at the proximal part of CTO and the patent femoral artery close to the entrance of CTO was defined as a relative blood volume index (BVI); BVI was calculated and expressed as a percentage.

Results

BVI measured pre- and post-intervention were compared between control and VEGF groups. Our results indicated that BVI increased significantly in the VEGF group compared to the control (Fig.1 P=0.037). The surface renderings of micro-vessels from micro-CT and contrast-enhanced MR images 3 weeks after intervention in control and VEGF groups are shown in Fig. 2 and 3 respectively. In the micro-CT data sets, there were clearly more micro-vessels in the CTO for the VEGF group, in agreement with MR measurement of BVI.

Discussions and Conclusion

BVI measured at the proximal end of the CTO can determine the development of new micro-vessels. VEGF therapy appears to improve significantly neovascularization. Non-invasive MRI may therefore be a feasible and practical way to evaluate and monitor such treatments in patients with CTO. The next step is to determine if improved microvascular volume in the proximal CTO following VEGF therapy will improve crossing rates and, ultimately, patient outcomes.

Fig. 1. Blood volume index pre and post interventions:

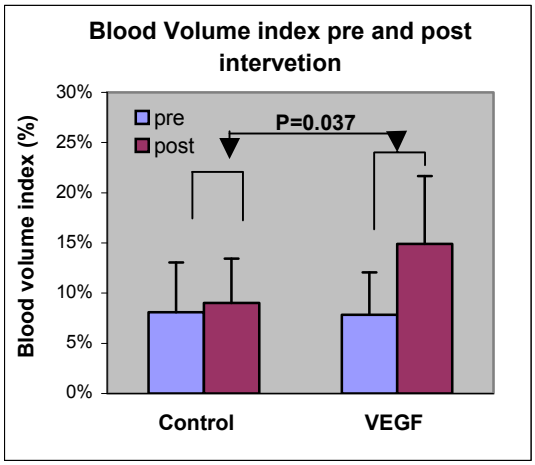


Figure 2. Micro-CT from ex-vivo samples and contract-enhanced MRI in vivo 3 weeks after intervention in Control group (bar=5mm)

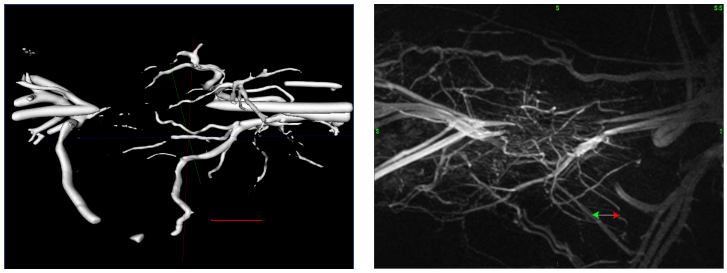
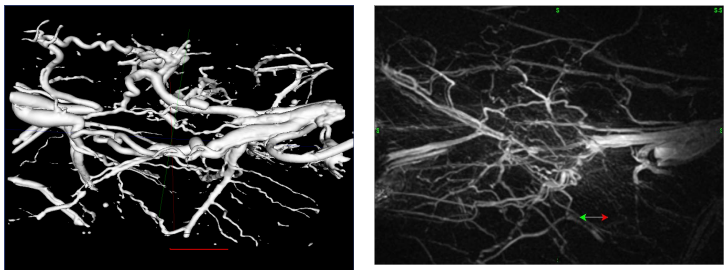


Figure 3. Micro-CT from ex-vivo samples and contrast-enhanced MRI in vivo 3 weeks after intervention in VEGF group (bar=5mm)



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