Towards an *In Vivo* Model of Complicated Atherosclerosis

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Introduction

The underlying cause of heart attack and stroke can be traced to atheromatous lesions. Lesions that are more likely to lead to clinical events are designated as vulnerable plaques. Intraplaque haemorrhage and plaque neovascularization are recognized as contributors to plaque vulnerability [1], but current animal models do not consistently or spontaneously produce these types of lesions. The results presented here are from a preliminary investigation into an improvement upon the commonly used hypercholesterolaemic rabbit model [2].

Methods

Two different interventions were performed on New Zealand white rabbits (n=6). In the first, a 3 MHz ultrasound probe (GE Logiq 700) was used to insonate a section of the abdominal aorta in conjunction with 1.5 ml of Definity microbubbles mixed with 100 ml of saline and infused at a rate of 0.25 ml/sec. In the second, the animals received a 2 μg/kg intramuscular injection of recombinant human vascular endothelial growth factor (rhVEGF) at 5 weeks.

All of the rabbits were fed a 6% peanut oil and 0.25% cholesterol diet. One group (n=2) underwent the ultrasound insonation only, another group (n=2) underwent both the ultrasound insonation and VEGF injection, and the final group (n=2) acted as a control. In each group, one rabbit was sacrificed at 10 weeks with the other sacrificed at 15 weeks. The animals were scanned on a GE 3.0T EXCITE MR system 20 minutes after sonoporation to obtain images from both before and after administration of Omniscan. Finally, the abdominal aorta was excised and stained with H&E.

Results

In the rabbits that underwent ultrasound sonoporation, the MR difference images indicate higher signal intensity in the portion of the vessel on which the ultrasound beam was incident versus the control rabbit images that do not show increased signal intensity (Fig. 1). These results suggest that permeability was elevated in the rabbits that received sonoporation. The histological sections point to intimal thickening in the aortas of these same rabbits (Fig. 2). Histology also reveals neovessel formation in the rabbits injected with rhVEGF.

Conclusions

The results from this preliminary study suggest that ultrasound sonoporation leads to increased aortic wall thickness and that a low, intramuscular dose of rhVEGF is enough to facilitate neovascularization around the aorta. An increase in permeability due to ultrasound sonoporation can be shown using contrast-enhanced MRI. These results are encouraging, prompting further investigation into the reproducibility and utility of this new *in vivo* model of atherosclerotic plaque.

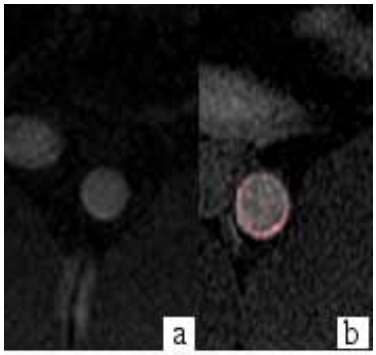

Figure 1: (Top right) Overlay of MR difference image and post-contrast image shows increased uptake of GdDTPA in vessel walls after ultrasound sonoporation (b) compared to no ultrasound exposure (a).

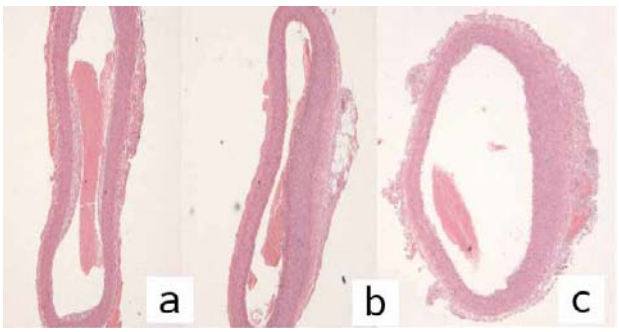

Figure 2: (Right) H&E stained cross sections of aorta in (a) hypercholesterolaemic (HC) control rabbits, (b) HC + ultrasound sonoporation (US) rabbits, (c) HC + US + rhVEGF injection rabbits. Increasing intervention produces increasing wall thickness.

References

[1] Virmani R et al. Arterioscler Thromb Vasc Biol 2005;25(10):2054-61.
[2] Kolodgie FD et al. Arterioscler Thromb Vasc Biol 1996;16(12):1454-1464.