Evaluation of Statin Therapy in a Rabbit Model of Aortic Valve Sclerosis Using High Resolution MRI

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Purpose: Aortic valve sclerosis (AVS) is a prevalent disease process affecting more than 25% of the population over age 65; it advances to aortic stenosis in 5% of people over age 75.[1] Aortic stenosis is coupled to an 80% 5-year risk of heart failure, valve replacement or death, but despite these severe clinical consequences there is currently no effective therapy other than surgical aortic valve replacement.[2] Increased knowledge on the progression of AVS has lead to the investigation of pharmaceutical therapies including statins (hydroxymethyl glutaryl coenzyme A reductase inhibitors).[3,4] Clinical trials of statin therapy have yielded conflicting results but have exemplified the need for early diagnosis in the development of useful aortic valve disease therapies. We propose that MRI can be used to identify AVS early in the sclerotic process such that statin therapy can cause significant improvements to the diseased valves that can also be monitored by MRI analysis.

Methods: Male New Zealand White rabbits were fed an AVS-promoting cholesterol-supplemented (0.125-0.25%; n=29) or control (n=6) diet. After 15 months on their respective diets, eight rabbits (5 cholesterol-fed and 3 control) were sacrificed for ex vivo analysis and the remaining rabbits were subdivided into one of 5 treatment groups: control (n=3), cholesterol to control (n=6), cholesterol (n=6), control plus statin treatment (n=6) and cholesterol plus statin treatment (n=6) for an additional 15 months (Figure 1). Rabbit aortic valve cusps were examined using MRI every 3 months, starting at 6 months. Images were obtained using a 1.5 T GE MR clinical scanner interfaced with a customized two-channel phased array RF coil. A retrospectively gated cine fSPGR sequence (FOV=8 cm, Matrix 256x128, Slice thickness=2 mm, NEX=6, FA=20 deg., BW=31.25 kHz) was used. A plethysmograph attached to the rabbit's ear provided the gating signal. Oblique sagittal images were acquired of each valve cusp in cross section. Image analysis was performed off-line using the OCCI Viewer.[5] Images were reviewed by three independent blinded observers and valve thickness was measured in the middle third of the cusp using digital calipers. Measurements from all three cusps were averaged to generate average valve thickness measurement for each treatment group. Results are shown at mean +/- SEM and were assessed by one-way ANOVA followed by a Tukey's post hoc test.

Results: Using retrospective peripheral gating we acquired high resolution images in which the aortic valve is clearly measurable (Figure 3). This in vivo monitoring technique allows us to examine and treat individual subjects over time. The aortic valves of all treatment groups were observed to thicken significantly compared to control (Figure 2). Valves were observed to continue to thicken despite treatment until 24 months at which point statin-treated valves, with or without cholesterol-feeding, were observed as not significantly different from control. Group 3 (long-term cholesterol-fed) rabbit valves were not observed to thicken to a great extent at later time points (Figure 2). This reflects the difficulty in delineating diseased valve cusps with bright blood imaging in the presence of regurgitant flow (Figure 3).

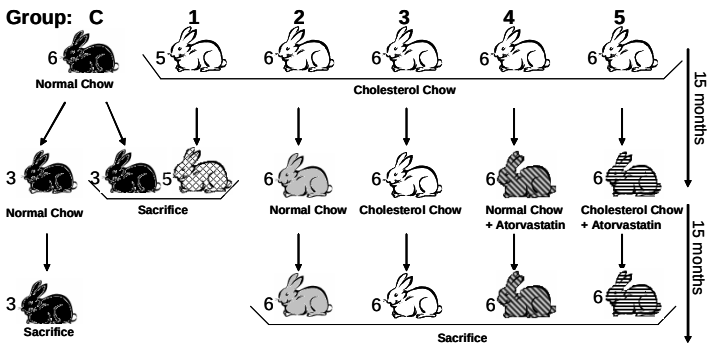

Figure 1: Rabbit feeding regime.

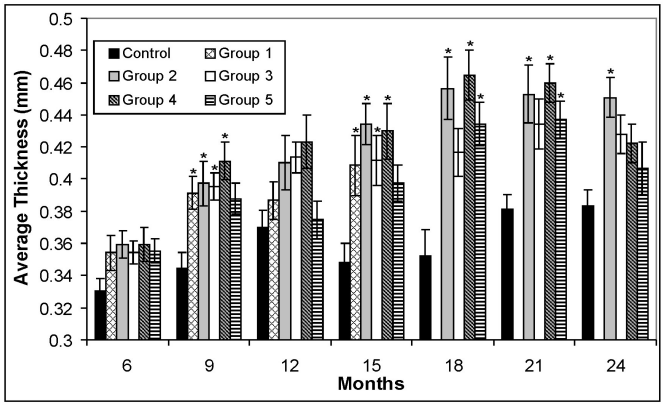

Figure 2: Average valve thickness of rabbit treatment groups over time. *P<0.05 compared to control.

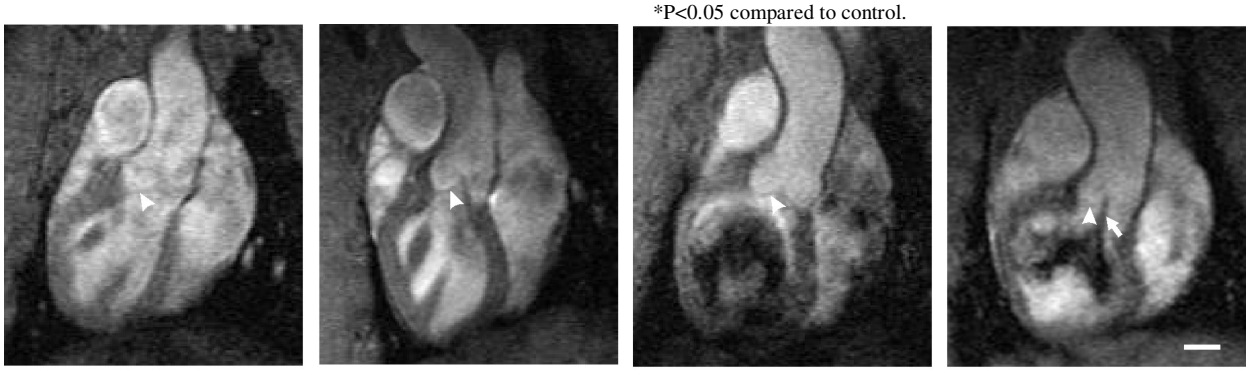

Figure 3: Oblique sagittal images of rabbit aortic valve cusps at 24 months. Arrowheads delineate the valve cusp. Arrow shows regurgitant flow. Scale bar = 5mm.

Discussion and Future Directions: Our current MRI technique allows us to examine the progression of the sclerotic process on a case-by-case basis and to investigate the efficacy of disease treatments in vivo. As cholesterol-induced AVS progresses, valves are observed to thicken in MRI analysis. This holds true until the valves become too diseased to fully close at which point regurgitant blood flow occurs and the valve cusps are not as easily identified with bright blood imaging. This valve failure, however, is also observable with MRI analysis and is seen as a distinct regurgitant black jet in bright blood images. Initial data suggests that statin therapy is modulating the sclerotic process in our rabbit model. All treatment groups will continue to be monitored at 27 and 30 months. At 30 months the rabbits will be sacrificed, aortic valves will be excised and examined ex vivo to validate the MRI data. To further improve the sensitivity of our technique we will also be investigating the use of gadolinium- and iron oxide-based contrast agents.

References: 1. Stewart MD *et al.* (1997) J Am Coll Cardiol. 29:630-4. 2. Otto CM *et al.* (1997) Circulation. 95:2262-70. 3. Chua D and Kalb K. (2006) Ann Pharmacother. 40:2195-9. 4. Cowell ST *et al.* (2005) N Engl J Med. 352:2389-97. 5. http://cardiacimaging.ca/technical_resources/occi_viewer.