MRI Evaluation of Inflammation and Tissue Healing Response to Glutaraldehyde-fixed Porcine Tissue Implant on Rodent Model

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Purpose

Development of new biomaterials for heart valves has been a significant area of research and development for the academic and industrial organization. When mosaic bioprosthesis implant, a porcine tissue commonly used in heart valves, is implanted, the tissue response can generally be described as a mild inflammatory reaction within the first week with localized inflammatory infiltrate at the host/implant interface[1, 2]. By 10 days after implantation, the fluid surrounding the implant and a vascularized fibrous capsule begins to develop. The foreign-body giant cell reactions have been seen to persist throughout 40-day long studies[3]. At the same time, the growth of new vessels around the implant tissue is a critical component of the wound-healing process. During this process, angiogenesis leads to increased endothelial permeability of the microvasculature, suggesting some similarities between wounds and tumors. The purpose of this pilot study was to investigate whether the process of inflammation and tissue healing around bioprosthetic implants in a rat subdermal model could be monitored by MRI techniques.

Methods

Fifteen healthy adult Sprague-Dawley rats were studied under the institutionally approved protocol. Animals were assigned to implanted (n = 8) and sham surgery groups (n = 7). In the experimental group each rat was implanted subdermally with two coupons of porcine valve tissue fixed in 0.2% glutaraldehyde. One coupon was taken from the leaflet part of the valve, while the other coupon was taken from the aortic root part of the valve. In the sham surgery group, identical surgical procedures were performed without implanting any test samples. Animals were studied longitudinally with MRI techniques on days 3, 7, 14, 21, and 60 after surgery.

MRI was performed on a 4.0 Tesla scanner equipped with Philips acquisition console. The anatomical image, T2-weighted images (TR=3500ms, TE=11.5, 20, 30, 50, 80, 140, 240ms, FOV/thickness=120/3mm, matrix=128x256) were acquired. After injection of Gd-DTPA-BMA (Omniscan®, 0.1mmol/kg), dynamic 3D FLASH sequence was used to acquire DCE-MRI images. After eliminating the contribution of the implanted material from the wounded tissue regions, the T2 measurement was performed in the healing tissue, and normal tissue adjacent to the wounded area in the implant and sham surgery groups. The signals obtained at a given pixel position as a function of echo time were fit to an exponential curve to determine the T2 at that location. With the method described by Su et al.[4], the percentage enhancement was computed with respect to the baseline signal obtained by averaging the four images before Gd-DTPA was injected.

Table 1. The T2 measurement (ms) of bilateral wound chamber tissues in the implant and sham surgery group *

	Implanted group					Sham surgery group				
	Left (aortic root implant)			Right (leaflet Implant)		Left			Right	
Time points	N	T2	ΔT2	T2	ΔT2	N	T2	ΔT2	T2	ΔT2
day 3	8	25.90 ± 4.60	-0.69 ± 4.21	25.00 ± 2.37	-1.19 ± 3.09	7	24.90 ± 1.20	-2.71 ± 0.76	25.00 ± 1.33	-2.48 ± 0.96
day 7	7	23.76 ± 3.38	-3.21 ± 3.04	24.26 ± 1.92	-2.07 ± 1.48	6	24.83 ± 1.62	-2.50 ± 0.84	23.61 ± 1.00	-3.72 ± 0.57
day 14	* p < 0.05	3.00	-1.17 ± 1.49	23.72 ± 2.73	-3.17 ± 2.50	5	31* p < 0.05	1.60 ± 1.82	30.93 ± 6.02	-1.40 ± 1.82
day 21	4	24.17 ± 2.27	-1.75 ± 1.20	23.17 ± 2.32	-3.17 ± 2.08	2	24.33 ± 1.41	-2.50 ± 0.71	24.33 ± 0.47	-3.00 ± 0.00
day 60	2	23.50 ± 0.24	-2.33 ± 0.0	22.17 ± 0.24	-3.17 ± 0.24	1	25.00 #	* 0.00 #	24.00 #	-1.00 #

* Data presented as mean ±SD # SD not applicable due to single measurement ΔT2 = T2(healing tissue) - T2(normal tissue)

Results

The measurement of T2 was more consistent but did not show any statistically significant longitudinal changes for either type of implant material as seen in Table 1. When comparing the T2 value of healing tissue in the sham animals on both sides, the values remain fairly constant with the exception of day-14. But in this case the change is similar for both sides suggesting some immune response or measurement error. Furthermore, there are no longitudinal differences in the difference in the relative T2 values between the healing and normal tissues (Table 1).

The dynamic contrast enhanced MRI results indicate that there is an increased amount of enhancement on day-7 for both types of implanted material. However, such an increased enhancement was not observed in the sham animals. When comparing the maximum enhancement observed at 15-minute post contrast injection as shown in Figure 1, there is a statistically significant difference on day-7 for both implant materials ($p < 0.05$), suggesting an increased angiogenic activity at that time.

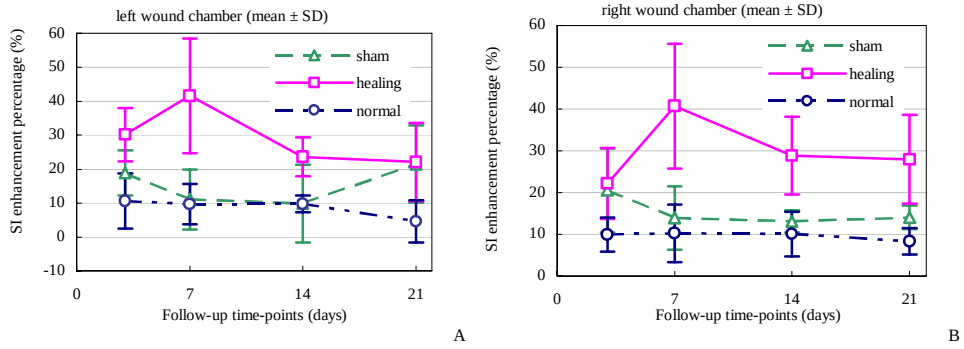

Figure 1. Comparison of the highest signal enhancement percentage (mean ± SD) of the bilateral (A: left; B: right) healing tissue and normal tissue regions in the implant group and the wounded tissue region in the sham surgery group.

Discussion

An increase in the contrast enhancement on day-7 for both implanted materials suggests an increased angiogenic activity and provides some evidence that an inflammatory reaction developed within the first week after the porcine tissue valve is implanted. These results demonstrate that contrast-enhanced MRI may be able to quantitatively assess the time-dependent changes of inflammation and angiogenesis in the wound-healing process after the implant. The measurement of T2, which is an indicator of edema, did not show any statistically significant longitudinal changes for either type of implant material. The standard deviation of measurements averaged over all participating animals is also fairly large making such changes insignificant. Our results are promising in terms of discovering a marker for wound healing by means of non-invasive MRI techniques, though the number of animals used in the study was too small to make further statistically definitive statement. A larger study using the protocol is certainly warranted to investigate whether such MRI techniques could be used to follow tissue healing after cardiac valve implant. If the outcome is positive, such techniques could also be used in humans as a non-invasive tool to monitor the resolution of inflammation after implantation or to help diagnose suspected endocarditis.

References

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