In vivo testing of an intra-annular aortic valve annuloplasty ring in a chronic calf model

J. Scott Rankin a,c,*, Jeff L. Conger b, Egemen Tuzun c, Jo Anna Winkler c, Kelly M. Harms b, L. Alan Beavanc, Terry Fossum d and William E. Cohn b

a Centennial Medical Center, Vanderbilt University, Nashville, TN, USA
b Texas Heart Institute, Houston, TX, USA
c Biostable S-E, Austin, TX, USA
d Texas A&M Institute for Preclinical Studies, College Station, TX, USA

* Corresponding author. Centennial Medical Center, Vanderbilt University, 320 Lynnwood Blvd., Nashville, TN, 37205, USA. Tel: +1-615-9691543; e-mail: jsrankinmd@cs.com (J. Scott Rankin).

Received 13 October 2011; received in revised form 21 November 2011; accepted 24 November 2011

Abstract

OBJECTIVE: To increase applicability and stability of aortic valve repair, a three-dimensional aortic annuloplasty ring has been developed for intra-annular placement. The goal of this study was to test the safety of this device with in vivo implantation in the calf model.

METHODS: In 10 chronic calves, the HAART annuloplasty ring was sutured to the aortic valve annulus using cardiopulmonary bypass. The animals were recovered and followed for 1–2 months. Serial echocardiography was used to evaluate valve competence, and contrast aortograms and CT angiograms were obtained in selected animals. After completion of follow-up, each animal was euthanized, and aortic endoscopy was performed under water distension in five. Full autopsies with histologic examinations were performed.

RESULTS: All animals survived surgery. Two were euthanized in the first week for complications, and the remaining eight calves were followed uneventfully for the 1–2 months. Serial echocardiography showed completely competent valves in all but one animal, in which the ring was intentionally up-sized to test the sizing strategy. Contrast aortographic and CT angiographic findings were similar to the echocardiograms. Postmortem examination showed proper seating of all rings with endothelialization at 1–2 months. All valves demonstrated good leaflet coaptation and no abnormalities.

CONCLUSIONS: In vivo testing of a three-dimensional aortic annuloplasty ring in a chronic calf model proved to be very successful and safe. Using the sizing and implant strategies developed, human trials seem indicated.

Keywords: Aortic valve • Aortic valve repair • Annuloplasty ring

INTRODUCTION

Aortic valve repair is being performed increasingly, and it is likely that effective valve repair will achieve superior results to prosthetic valve replacement over the spectrum of pathologies causing aortic valvular insufficiency [1–4]. Newer techniques for addressing leaflet prolapse, such as central plication, have been shown to be highly successful long term, solving one of the problems holding back aortic valve reconstruction. A need still exists, however, for a stable method of annuloplasty during aortic valve repair. Suture commissural annuloplasty and the various forms of sub-annular circumference reduction do not control the geometry of the entire aortic valve annulus and are likely to be associated with late repair deterioration. Like mitral and tricuspid annuloplasty, a three-dimensional ring-like device that restores the geometry of the entire aortic valve toward normal would be most likely to achieve this goal. This study reports in vivo evaluation of a newly developed ‘Hemispherical’ aortic annuloplasty frame for use in aortic valve repair [5–9].

METHODS

This study was designed to evaluate the safety of the Hemispherical Aortic Annuloplasty Ring Technology (HAART) device (US Patent No. 11/799,942) during chronic implantation in the calf model. In a consecutive series of 10 intact calves (75–106 kg), appropriately sized devices were implanted chronically in the aortic position using cardiopulmonary bypass. Final ring design was based on normal human aortic valve geometry [5–7] obtained with CT angiography (Fig. 1), with the assumption that restoration of annular size and geometry toward normal during repair would be associated with better long-term valve function. Design features included: elliptical 2:3 base geometry, 10° outwardly flared subcommissural posts, one-piece titanium frame construction and Dacron covering for endothelialization (Fig. 1). The rings were placed through complete transverse aortotomies and positioned adjacent to the undersurface of the annulus using an interrupted trans-annular suture technique (Fig. 2) [8]. According to previous models [5–7], frame size was determined
Minor variations in protocol were incorporated into the study to evaluate several concepts. In one animal (Study #1), a ring with a circular (rather than elliptical) base geometry was used to correlate with previous acute porcine experiments [5, 6]. This ring still had 10° outwardly flaring subcommissural posts. In another animal (Study #4), the ring was intentionally up-sized to evaluate the sizing strategy. The leaflet in this animal sized to a #19 ring, but a #21 ring was implanted to violate the sizing technique. An attempt was made to carry all animals to 1–2 months of survival. Valve morphology and competence were evaluated postoperatively with serial transthoracic echocardiograms in all animals, contrast aortograms in four animals and CT angiograms in two animals. At the conclusion of each study, each calf was euthanized, and a full autopsy was performed with histologic examination of the implant site. With the aortas pressurized by water, video aortic root endoscopy of the valves was performed in five studies. Specifically, attention was given to identifying any damage to root structures that the device might have caused, as well as the maintenance of normal valve geometry and competence. This protocol was approved by the Texas Heart Institute Animal Care and Use Committee.

**RESULTS**

In all 10 animals, the implant proceeded in an organized fashion, and all animals survived the operation (Table 1). Terminal transthoracic echocardiograms showed no valve leak in 9 of the 10 animals (Fig. 3), with good valve opening and no discernable valve abnormality. The one valve that was up-sized intentionally to evaluate the sizing method (Study #4) showed moderate leak, but the animal remained clinically stable for the 2-month follow-up. One animal was euthanized on the first postoperative day because of an air-induced neurologic defect and another at 7 days for purulent pericarditis with ventricular pathology.

Figure 1: The final HAART ring design was developed from high-resolution CT angiographic studies of 10 normal human aortic valves [7, 8]. (A) One-mm thick axial slices were analyzed to assess the anatomy of sinus-leaflet complexes for the right coronary cusp (green), left coronary cusp (orange) and non-coronary cusp (yellow). (B) After incorporating all vertical slices, the subcommissural and annular regions appeared as a three-pointed coronet with highly elliptical base geometry and outwardly flaring subcommissural posts. (C) A representative study shows the elliptical valve base geometry and flaring posts, with a 5–8° outward flare (tops of all three commissures are shown as green circles). The flare was always similar for the three posts, and average circumferential lengths between commissures were statistically equivalent. The post of the non-coronary/left coronary commissure was always located at the posterior minor axis diameter–circumference intersection (also the centre of the anterior mitral leaflet), with the right coronary cusp centred opposite. (D) The final design of the HAART ring was based on the average geometry of the 10 normal human valves, with an elliptical 2:3 minor–major diameter base geometry and 10° outwardly flaring posts. The size of each ring was denoted as the diameter of a circle with equivalent circumference, and the post heights were defined as the radius of the ‘equivalent’ circle [5–8].
arrhythmias. Both had competent valves with good frame seating by echocardiography, angiography and autopsy inspection. The seven remaining animals were studied after 30–60 days of implantation, and each had a fully competent valve by the study methods employed. A representative root aortogram is shown in Fig. 4, showing the delicate structure of the Titanium ring and no valve leak. On CT angiography (Fig. 5), the posts were buried well back into the subcommissural region (A) and beneath the annulus (B), and the leaflets opened well (C and D).

Each autopsy showed good device position and endothelialization of the Dacron-covered frames, with no significant leaflet of other root abnormalities by gross and histological examination. The one animal with circular ring geometry had a competent valve, but exhibited minor leaflet prolapse, similar to previous acute porcine experiments (Fig. 6). Full organ autopsies showed no significant abnormalities in any organ system. Pictures of all nine valves implanted with elliptical rings are shown from the ventricular aspect in Fig. 7.

**DISCUSSION**

In this study, chronic animal implantation of the HAART aortic annuloplasty ring in an intact calf model seemed safe and highly successful in maintaining normal valve geometry and competence. Elliptical ring geometry, ring sizing strategy and the

<table>
<thead>
<tr>
<th>Study animal</th>
<th>Implant date</th>
<th>Term (days)</th>
<th>Ring size</th>
<th>Angio</th>
<th>Base echo</th>
<th>Post echo</th>
<th>Term echo</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 (1765)</td>
<td>14 January 2010</td>
<td>33</td>
<td>21</td>
<td>–</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Circular ring, uneventful</td>
</tr>
<tr>
<td>#2 (1787)</td>
<td>28 April 2010</td>
<td>60</td>
<td>21</td>
<td>–</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>First elliptical ring, uneventful</td>
</tr>
<tr>
<td>#3 (1788)</td>
<td>29 April 2010</td>
<td>35</td>
<td>21</td>
<td>–</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Elliptical, uneventful</td>
</tr>
<tr>
<td>#4 (1826)</td>
<td>6 December 2010</td>
<td>60</td>
<td>21</td>
<td>2+</td>
<td>0</td>
<td>2+</td>
<td>3+</td>
<td>Elliptical, up-sized from 19 to 21</td>
</tr>
<tr>
<td>#5 (1827)</td>
<td>7 December 2010</td>
<td>7</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Elliptical, intra-operative stroke</td>
</tr>
<tr>
<td>#6 (1830)</td>
<td>4 January 2011</td>
<td>7</td>
<td>19</td>
<td>–</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>Elliptical, arrhyth./pericarditis</td>
</tr>
<tr>
<td>#7 (1831)</td>
<td>5 January 11</td>
<td>60</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Elliptical, uneventful</td>
</tr>
<tr>
<td>#8 (1832)</td>
<td>6 January 2011</td>
<td>60</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Elliptical, uneventful</td>
</tr>
<tr>
<td>#9 (796)</td>
<td>19 October 2010</td>
<td>30</td>
<td>21</td>
<td>–</td>
<td>0</td>
<td>1+</td>
<td>0</td>
<td>Elliptical, uneventful</td>
</tr>
<tr>
<td>#10 (882)</td>
<td>4 January 2011</td>
<td>30</td>
<td>19</td>
<td>–</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Elliptical, uneventful</td>
</tr>
</tbody>
</table>

Term: days after implant that study was terminated; Angio: root angiography performed; Base: baseline; Post: immediately after implant; Echo: transthoracic echocardiography; Term echo: echo performed just prior to termination. 1+ to 3+ is the degree of aortic valve leak. See text for other details.

**Table 1.** Details of 10 chronic calf implants

![2-Month echocardiogram](image)

**Figure 3:** Representative echocardiogram obtained after a 2-month calf implant. (A) Leaflet closure is symmetrical with good central coaptation. (B) All three cusps open freely with normal-appearing leaflet mobility. (C) No Doppler evidence of valve leakage is observed. (D) Systolic flow is laminar and undisturbed.
The surgical implant technique appeared ideal for clinical application. Based on these studies, the authors believe that the device is safe to begin human clinical trials of implantation in patients with aortic valve insufficiency. Like the mitral valve, long-term control of circumferential annular size and geometry could be important for increasing applicability and stability in most patients undergoing aortic valve repair. It should be emphasized, however, that this positive animal safety study does not necessarily imply efficacy, especially in human pathologic states for which no animal model exists. Careful and highly controlled human trials will be required to assess efficacy of aortic valve ring annuloplasty in patients with clinical disease. It should be possible to design a human procedure so that valve competence is assessed immediately after implant by cardioplegia infusion, and any problems could be corrected promptly by re-opening the aorta and re-repairing or replacing the valve. In this way, initial clinical trials should increase patient risk negligibly. Of course, the device would only provide the annuloplasty portion of the repair. Centralleaflet plication or other techniques would be necessary to correct leaflet abnormalities. However, it is likely that most patients with AI have some degree of annular dilatation and distortion, and restoration of the entire aortic valve annulus toward normal size and geometry could improve early and late leaflet coaptation. Specifically, re-establishment of normal elliptical base geometry and outwardly flaring commissures might produce more effective repair than current nonspecific 'constricting' annuloplasty methods.

From recent aortic valve repair outcomes assessments, the prognostic benefits of reconstructing the patient’s own aortic valve may be equivalent, or even superior, to those observed for

![Figure 4: Aortic root angiogram obtained just prior to study completion. (A) The delicate, low-profile design of the titanium frame is evident, with 10° outwardly flaring posts. (B) With contrast injection into the aortic root, no aortic valvar insufficiency is observed.](image)

![Figure 5: HAART annuloplasty ring at CT angiography after 2 months of implantation. (A) A diastolic cross-section showing the Titanium posts buried into the subcommissural areas and away from leaflet tissue. (B) A diastolic longitudinal view with the valve closed and the leaflets coapting normally. The frame body is positioned up under the leaflets and adjacent to the annulus to prevent leaflet abrasion by ring Dacron. (C) A systolic view showing good leaflet opening in cross section, and in (D), the leaflets are physiologically vertical during ejection.](image)

![Figure 6: Views of valves at autopsy. (A and B) Views of Study #1 in which a ring with circular base geometry was implanted. Although the valve was competent, circular geometry seemed to pull the leaflets apart and resulted in minor prolapse of the right coronary (RCA) cusp. These findings correlate with previous observations in isolated porcine valves [5, 7]. (C and D) The last nine animals with elliptical rings. Note the absence of cusp prolapse with the elliptical device and symmetrical coaptation of the leaflets. Having the RCA cusp positioned on the anterior minor diameter produced a broader appearance of the leaflet both from below (C) and above (D), although leaflet sizes and annular lengths were similar. This appearance correlated with the valve shape observed in normal humans (Fig. 1), and suggests that elliptical valve geometry may be important for maintenance of proper leaflet coaptation. Note the complete endothelialization of the ring and Dacron sutures/pledgets after 2 months of implantation.](image)
the mitral valve. Valve-related complications with current aortic valve repair techniques (including reoperation for repair failure) occur at a rate of $\approx 1\%$ per year (data that are similar to mitral repair), while complications occur in up to 3–5% per year with aortic valve prostheses [10]. From a recent analysis [11], raw unadjusted 10-year survival after aortic valve replacement approximated 50%, a value that is inferior even to mitral valve replacement [12]. With 10-year survival after current methods of aortic valve repair approaching 75–80% (unpublished data, Prof. H.-J. Schäfers), the survival benefits of aortic valve repair may be quite significant—but proper assessment will require appropriate risk adjustment using multivariable analysis. However, good evidence does exist to support efforts at increasing reparative procedures for the aortic valve. Current approaches utilize commissural suture annuloplasty or suture sub-annular reduction—methods that do not control the entire valve annulus. All studies of mitral and tricuspid valve repair have shown better stability with full ring annuloplasty when compared with suture annuloplasty [13], so development and clinical testing of a complete circumferential device for aortic valve annuloplasty seems justified. The low-profile appearance and rapid endothelialization of the HAART ring (Figs 6 and 7) would suggest similar safety to mitral rings, but of course, clinical data will be required to be certain.

Aortic ring annuloplasty is not a new idea. The problem has been trying to understand the geometry of the aortic valve annulus. The development of the ‘Hemispherical’ model of aortic valve geometry in studies of human cadaver valves [5], and then refinements to the model based on CTA studies of normal awake humans [7] have facilitated development of the current device. The observation that the aortic valve is quite elliptical in shape may be especially important. With the present positive animal safety studies, extension into humans will validate this geometric concept from the viewpoint of efficacy. Currently, the Coroneo ring is approved for use in Europe [14], and is applied to the exterior of the aortic root and valve during valve sparing root replacement. Clinical experiences with this device have been quite positive, and when combined with appropriate leaflet repair procedures, early and intermediate-term results have been improved over standard David-like techniques [15]. This finding suggests that inclusion of aortic valve annuloplasty may be of significant importance as the initial step of valve sparing root surgery, but internal rings may perform better than external rings [16]. Finally, the Coroneo device requires extensive dissection of the aortic root, similar to a David procedure, and does not address restoring the elliptical geometry of the aortic valve. Thus, it is possible that the HAART device will perform even better.

Potentially, the HAART ring can be implanted as the initial phase of a remodelling procedure [17], obviating extensive root dissection. After ring placement and completed valve repair, a scalloped graft could be sutured to the base of the coronary sinuses, incorporating the supra-annular pledgets from the ring. Thus, the procedure would not require external deep root mobilization. At the conclusion, the native valve would be firmly ‘sandwiched’ between the ring below, and the graft above, with the ring functioning as a permanent stent upon which the native valve leaflets are mounted. It is also possible that restoration of elliptical geometry of the pathologic valve could improve long-term valve coaptation and function, and certainly, the inclusion of a permanent three-dimensional ring would hold the

Figure 7: Autopsy appearance of the nine implanted elliptical aortic annuloplasty rings. There was generally good symmetry of leaflet coaptation and healing of the devices. Studies #5 and #6 were from the animals dying early, with refrigerator storage for a period of time. In study #10, the heart was immersed in formaldehyde prior to cutting. All three of these valves (#5, 6 and 10) were formally examined histologically by pathologists (James M. Anderson MD PhD, Cleveland, Ohio or Fred Clubb MD, College Station, TX, USA), and all of the thrombus on the three valves was determined to have occurred post-mortem, with no significant device abnormalities observed. Each of the more chronic studies looked good, with almost complete endothelialization of the Dacron ring by 1–2 months of implant.
geometry constant long term. The tri-leaflet HAART ring also could have applications in aortic insufficiency patients without root aneurysms, and a bicuspid variant is under development. In both tri-leaflet and bicuspid aortic valve repair, late lateral migration of valve sinuses after repair can be a cause of reoperation [18–20], and a permanent ring annuloplasty could prevent that occurrence. One limitation of the present study, however, is that this is a pure safety evaluation, since no efficacy data can be obtained in animals with human-like pathology. Thus, definition of device utility will await carefully conducted trials in patients with aortic valve disorders. In earlier animal implants, several avoidable complications of ring placement were identified. These included perforation of leaflets caused by long suture tails, abrasion of commissural leaflets by exposed posts and distortion of the native valve by skewed implantation of the ring. Using the technique described in this paper, each of these problems was avoided. Gentle handling of leaflets (if at all) is also important, and perhaps less traumatic forceps can be developed to minimize the chances of surgical leaflet damage.

In conclusion, by restoring the entire diseased aortic valve annulus to normal geometry and dimensions, the HAART annuloplasty frame has the potential for improving early and late results of aortic valve repair. The device seems safe in animal studies and potentially could be effective for surgical aortic valve repair. The device seems safe in animal studies and potentially could be effective for surgical aortic valve repair. J Heart Valve Dis 2008;17:179–86.

References


