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MYERS, Patrick Olivier, KALANGOS, Afksendiyos

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Valve repair using biodegradable ring annuloplasty: from bench to long-term clinical results

P.O. Myers, A. Kalangos
Cardiovascular Surgery, Geneva University Hospitals and School of Medicine, Geneva, Switzerland

ABSTRACT
Annulus remodeling and stabilization with a ring is a necessary step in mitral and tricuspid valve repair to maintain effective leaflet coaptation and improve long-term results. Although conventional rings meet the basic needs of adults, they do not preserve the changes in shape and size occurring during the cardiac cycle, and do not allow growth of the native annulus in children. The bioring annuloplasty ring was developed to allow for annular stabilization, while remaining biodegradable and allowing for growth. It is a curved “C” segment of poly-1,4-dioxanone polymer located on a non-degradable polyvinyl monofilament suture equipped with a stainless steel needle at each extremity. This ring is inserted subendocardially directly into the mitral or tricuspid annulus, away from blood contact. Animal model experiments have shown that it degrades within 12 months of implantation and is replaced by fibrous tissue, which stabilizes the annulus durably, while allowing for annular growth in children. We review the published data, from bench to bedside, as well as the early, mid and long-term clinical outcomes using the biodegradable ring, which shows that biodegradable rings remodel the annulus, reinforce the repair, restore the function of the atrioventricular valve and maintain the three dimensional dynamic motion and geometry of the mitral and tricuspid valves annulus. Growth potential is preserved in children. The mid- and long-term results showed that degradation of the device occurred without negative observable consequences.

Keywords: cardiac surgery, valve repair, annuloplasty, biodegradable, review.

INTRODUCTION
Annulus remodeling and stabilization with a ring have been demonstrated to be a necessary step in mitral and tricuspid valve repair to maintain effective leaflet coaptation and improve long-term results (1). After establishing the basic tools of valve repair and annuloplasty, Professor Carpentier envisioned biodegradable annuloplasty in his pioneering review of the state of the art of valve repair in 1983 (2) and predicted valvuloplasty using a “polyethyl-collagenol resorbable ring, which dissolves spontaneously in 12 months” and is “replaced by strong connective tissue by a process of creeping substitution”. The need for such a degradable device, beyond the science-fiction vision of a pioneer, stems from two areas in which non-permanent, biodegradable annuloplasty can theoretically fill a void: valve repair in infected tissues, such as endocarditis, to avoid colonization of permanent implanted materials and infection recurrence, and valve repair in children, where traditional annuloplasty
rings can’t be used due to the risk of acquired stenosis from lack of growth. Following in the footsteps of Prof. Carpentier’s vision for the future, Duran et al. (3, 4) and Chachques et al. (5) showed the feasibility of absorbable flexible ring or large bore suture annuloplasty in animal models, with degradation of the ring material within 1-2 months when comprised of fibrin (3), or 4 to 12 months when comprised of polydioxanone (4, 5). Duran et al. completed this with a clinical study on 73 patients with functional tricuspid regurgitation, who received the first De Vega “vanishing” annuloplasty using 2-0 polydioxanone (6). They concluded that this vanishing annuloplasty resulted in annular stabilization for 4 months, and had acceptable results after 2 years of follow-up.

Despite these promising laboratory and initial clinical results, little is known on the long-term outcomes of suture annuloplasty and in particular on the stability of annular remodeling after suture annuloplasty with a biodegradable suture or on the risk of annular re-dilatation with degradation.

Following in these footsteps, we were encouraged to develop a new biodegradable annuloplasty ring in 1994, which received the CE mark approval in 2005. Initially marketed by Bioring (Bioring S.A., Lonay, Switzerland), now it is being produced by Parvulus Suisse (Lonay, Switzerland) with renewed CE marking since 2011, and is undergoing clinical investigation by the US Food and Drug Administration (FDA) under a “humanitarian use exemption” for orphan drug products.

**Design of the biodegradable annuloplasty ring and initial animal models**

The biodegradable ring has a curved C segment comprised of a poly-1,4-dioxanone polymer, located at the middle of a non-degradable suture material equipped with stainless steel needles at each extremity. The suture material is 2-0 polyvinyl monofilament in adult-sized rings, and 3-0 polyvinyl in pediatric rings. The suture material increases the resistance to tensile re-dilatory stretch of the dilated mitral or tricuspid annulus. The specific molecular weight of polydioxanone polymers ensures structural memory against subsequent deformations (contrary to biodegradable sutures), and adds three-dimensional flexibility to the ring. The ring material is degraded by hydrolysis within 6 months of implantation. The product of hydrolysis (2-hydroxyethoxy-acetic acid) triggers inflammation, such that the implanted ring will disappear in six months, inducing fibrous tissue.

As with traditional annuloplasty rings, the rings are available in various sizes, ranging from 16 to 36. The rings are sized, using a specific sizer, according to the height of the anterior leaflet. There are separate mitral and tricuspid rings, differing in shape. The mitral ring is a symmetrically curved C shape, sized to remodel the posterior and both commissural annulus segments. The tricuspid ring is asymmetric and designed to remodel the anteroposterior annulus. Contrary to traditional annuloplasty rings, which are implanted onto the native atrioventricular valve annuli, the biodegradable ring is inserted directly into the native annulus underneath the endocardium using the needles and suture extensions at each extremity of the ring, similarly to De Vega suture annuloplasty. For mitral annuloplasty, insertion starts at the posterior commissure, approximately 2-3 mm from the insertion of the posterior leaflet and 2-3 mm in depth, advancing the needle along the posterior annulus, as far as the needle allows. Once the needle has been advanced through and out of the tissue, the suture is pulled on, in the same direction as the exit point so as to avoid ripping the endocardium, to advance the ring into the annulus until the
first exit point. Subsequent insertion of the needle is made through the previous exit point, allowing the ring to move forward into the annulus up to the next exit point. Complete insertion of the ring into the native mitral annulus is achieved by repeating the same steps in 2-3 bites past the anterior commissure. The ring is then fixed to the anterior trigone by passing the suture twice down from the anterior trigone to the anterior commissure, and tied onto itself. The posterior needle is finally passed twice through the first subendocardial entry point at the posterior commissure, up to the posterior trigone twice. Care should be taken to maintain tension on the first loop on the posterior trigone before tying down the suture on itself, as this completes the annular remodeling at the desired size.

In pathologies which require complete ring annuloplasty, such as ischemic mitral regurgitation, the partial ring can be converted to a complete ring by advancing the suture extensions on each extremity to the midpoint of the mitral annulus, after tying the sutures on themselves at both trigones as explained above, and then tying both extensions together at the mid anterior annulus.

For tricuspid annuloplasty, insertion technique is quite similar: ring implantation begins at the postero-septal commissure, advancing along the antero-posterior annulus to the antero-septal commissure, avoiding the conduction tissue along the septal annulus. The tricuspid ring is asymmetric, with two curves in the ring to allow it to follow the shape of the native antero-posterior annulus. The shorter curved segment should be placed at the antero-septal commissure, and the longer curved segment at the postero-septal commissure.

The biodegradable ring was first tested in a juvenile pig model (7). Histological analysis showed that the ring material was gradually degraded within 6 months after implantation, with gradual increase in thickness of annular fibrous tissue filling the space left by the degraded implant material, reaching the diameter of implant at 12 months after implantation.

**RESULTS**

The biodegradable ring has been reported in clinical use in several subsets of patients, which will be reviewed.

**Endocarditis.** One third of patients with infective endocarditis requires operative intervention. Given the superiority of valve repair over valve replacement in many indications other than endocarditis, there has been increasing interest and an increasing number of reports of excellent results of valve repair in acute infective endocarditis. Operative principles for infective endocarditis include complete debridement of infected tissues, drainage of abscess cavities followed by restoration of anatomic relationships.

It is tempting to avoid an annuloplasty ring when fixing limited leaflet destruction from mitral or tricuspid valve infective endocarditis, assuming that the underlying mechanism is acute regurgitation and usually doesn’t involve annular dilatation. Annuloplasty plays an important role in valve reconstruction, particularly if a significant infected leaflet segment must be resected, to relieve tension on the repaired leaflets and ensure long-term stability of the repair. Traditional annuloplasty rings and bands, predominantly made of polyester mesh, are susceptible to seeding and infection. Ciprofloxacin-coated polyester annuloplasty ring mesh was shown to confer infection resistance in a subcutaneous animal implantation model (8), however these devices haven’t been reported in clinical use to date. The theoretically ideal material for valve repair in this setting is non-perma-
nent, “vanishing” material, not at risk of seeding or colonization, such as the biodegradable ring. Infection resistance of the biodegradable was tested in a rat subcutaneous implantation model, looking at “clean” implantations and implantations associated with inoculation of *Staphylococcus Aureus* (M. Cikirikcioğlu, personal communication, to be presented at AATS mitral conclave 2013, May 2nd 2013; http://aats.org/mitral/abstracts/2013/E57.cgi). Compared to traditional Carpentier-Edwards rings, the biodegradable rings showed fewer positive cultures (2/16 vs 11/16, *p* = 0.003) and lower colony counts (181 ± 130 CFU/ml vs 7175 ± 5936 in conventional rings, *p* < 0.0005).

Clinical use of the biodegradable ring has been reported in infective endocarditis by Kazaz et al. (9) and by our group (10-12). We previously reported our initial experience of using this ring from 2004 to 2009 in 17 patients with acute infective endocarditis, 13 in the mitral, 3 in the tricuspid and 1 in both valves (10). There were 3 early deaths, and no late evidence of endocarditis recurrence, valve dysfunction, reoperations or deaths at a mean follow-up of 30 months. We updated this report with our experience in 8 children with infective endocarditis (11). There were no early or late deaths, reoperations or evidence of endocarditis recurrence at a mean follow-up of 56 months.

Valve repair for endocarditis often entails large debridement of infected tissue, followed by reconstruction. This is often done using pericardium, although mitral and tricuspid valve patch augmentation is associated with poor outcomes, due to retraction of autologous pericardium or early calcification of glutaraldehyde-fixed autologous or xenogenic pericardium (13). Biodegradable scaffolds used as patches, such as intestinal submucosa marketed as CorMatrix® (14), promise to extend the theoretical advantages advanced for biodegradable annuloplasty to leaflet reconstruction, and offer the potential for valve repair with entirely degradable materials. Their use in atrioventricular valve repair has been reported in a limited study by Boston Children’s Hospital, which didn’t include any patients with endocarditis (15), and further research is needed in this subject area.

**Congenital mitral regurgitation.** Preservation of the growth potential of the native atrioventricular annulus is critical to avoid acquired stenosis after valve repair in small children. In our experimental study in a model of fast-growing juvenile pigs, who increased their weight from a mean of 48 kg to 195 kg (+406%) during post-implantation follow-up, the growth potential of the tricuspid annulus was preserved (7).

Clinical experience with the biodegradable ring in this indication is still sparse. We reported our experience using the biodegradable annuloplasty ring in 22 patients with congenital mitral regurgitation, compared to 18 controls who had posterior biodegradable suture annuloplasty using 4-0 or 5-0 PDS, and 17 controls with posterior pericardial band fixed onto the native annulus by interrupted mattress polypropylene stitches. Unlike the two control groups, patients with a biodegradable ring showed homogeneous growth of the mitral anteroposterior and lateral annular diameters, similar to physiologic growth over a follow-up of 57 ± 12 months, with two patients developing moderate mitral regurgitation (16). The Boston Children’s Hospital reported their experience with the biodegradable ring in 6 young patients (median age: 5.4 years) with complex congenital heart defects (17). The atrioventricular valve anteroposterior and lateral diameters, areas, and related z-scores were significantly reduced in all 6 patients. This reduction was more pronounced in the anteroposterior di-
ameter, thus creating the more typical oval-shaped AV valve annulus. During a mean follow-up of 42 months, there were 2 atrioventricular valve reoperations, not linked to the biodegradable ring.

There have been limited case reports or series in other indications for mitral valve repair in children. Myers et al. reported the successful management of congenital ischemic mitral regurgitation associated with an ALCAPA (18). The biodegradable ring has also been used for left or right atrioventricular valve repair at or after atrioventricular canal repair defect repair (17, 19).

Rheumatic mitral disease in children. We recently reported our 13-year experience with mitral valve repair for rheumatic disease in children, comparing results with the biodegradable ring to traditional rigid Carpentier-Edwards annuloplasty rings (20). The aortic cross-clamp and cardiopulmonary bypass times were shorter by 10-12 minutes in the biodegradable ring group. The systolic left ventricular function, as assessed by shortening fraction, was also better preserved at 1 week after repair with the biodegradable ring, perhaps because this flexible ring better preserves the three-dimensional geometry of the mitral annulus. Mitral inflow gradients during the first post-operative year were lower with the biodegradable ring, with no significant difference in terms of recurrent regurgitation or reoperations.

Degenerative mitral regurgitation. We recently reviewed our experience with the biodegradable ring in mitral valve repair for degenerative mitral regurgitation (16). Between 2005 and 2007, we included 102 consecutive patients who underwent mitral valve repair with the biodegradable ring, and matched them to contemporaneous patients who underwent mitral valve repair with a traditional Carpentier-Edwards ring. During a follow-up of 3 years, the biodegradable ring group showed lower mitral inflow gradients (3.0 ± 1.2 mmHg, vs 5.2 ± 1.8 mmHg in controls) after 1 year. The inflow gradients continued to increase in the control group at 3 years post-operatively (5.2 ± 2.2 mmHg), while it gradually decreased for 2 years in the biodegradable ring group before reaching a plateau on the third year after repair (2.3 ± 0.4 mmHg). There was no significantly different rate of recurrent mitral regurgitation between groups. As in our study in children with rheumatic mitral regurgitation, we also found a significantly smaller decrease in shortening fraction early after surgery (3 weeks). Finally, we measured the dynamic annular diameters during follow-up, which showed that the anteroposterior diameter maintained a 15 ± 3 % variation during the cardiac cycle after biodegradable ring annuloplasty, which wasn’t the case in controls, and we didn’t see any late re-dilatation of the annulus.

Minimally invasive and robotic annuloplasty. One last area that hasn’t been investigated quite as much, is the applicability of the implantation technique of the biodegradable ring in minimally invasive cardiac surgery. Minimally invasive and robotic surgery is an emerging field in cardiac surgery. Although initially more complicated for the surgeon, these surgeries have been shown to be less traumatic for the patient and to provide a faster recovery, without compromising the quality of the repair (21, 22). Dedicated surgical instruments have been developed to fit these approaches, although traditional annuloplasty devices have not been adapted to minimally invasive surgery, and still require multiple suture placement and knot tying, which are somewhat difficult, tedious and time-consuming in minimally invasive surgery. The biodegradable ring, as outlined previously, can be inserted directly into the native annulus, using the suture extensions at each extremity. No further sutures are
required, thereby simplifying the implantation in minimally invasive cardiac surgery (23). We recently reported our experience in 10 consecutive patients who underwent successful tricuspid annuloplasty with the biodegradable ring (24).

**CONCLUSION**

Annuloplasty using a biodegradable ring has shown excellent early and mid-term results, with particular advantages compared to traditional annuloplasty rings in specific subsets of patients, namely children, endocarditis and minimally invasive cardiac surgery. Longer-term follow-up is currently being assessed and we look forward to expanding our current knowledge of these biodegradable devices.

**REFERENCES**