Biodegradable Semi-Rigid Mitral Valve Annuloplasty Ring Designed for Children

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Abstract: Descriptive information has indicated unsatisfactory outcomes associated with mitral valve plasty in the case of pediatric patients. Conversely, favorable outcomes have been consistently reported in adult cases, primarily attributed to the feasibility of prosthetic annuloplasty rings. Due to this notable distinction, we aimed to address the specific needs of small children by developing a semi-rigid annuloplasty ring for the mitral valve, employing biodegradable polymers. The expectation is that this approach would involve the gradual degradation and absorption of the developed semi-rigid annuloplasty ring, coinciding with the remodeling of the mitral annulus. The inner support medium was crafted from sutures composed of a blend of poly L-lactic acid and poly ε-caprolactone copolymer, mixed at a molar ratio of 3:1. Subsequently, this material was bundled together and coiled around a saddle-shaped mold rod. Following heat processing, a reinforced saddle-shaped rod with a diameter of 0.6mm was successfully created. The external cuff utilized a blade weaving technique made of polyglycolic acid, facilitating the smooth insertion of needles. A blade material was woven using 16 sets of polyglycolic acid sutures (size 50D), resulting in an internal diameter of 2mm and an area density of 0.55mg/mm^3. The internal rod was inserted within the polyglycolic acid blade, and both ends were subjected to heat processing at a temperature of 230°C for 10 seconds to prevent fraying. This device holds the potential to offer a solution for enhancing the outcomes of pediatric mitral valve plasty, and address the current challenges associated with unsatisfactory results in this patient population. Additionally, its applicability to adult patients could potentially eliminate the requirement for lifelong anticoagulation therapy.

Key Words: mitral valve, annuloplasty ring, biodegradable polymer, children

Introduction

The objective of mitral valve plasty (MVP) is to ensure lifelong prevention of regurgitation. MVP in children is estimated to be performed in approximately 300 cases annually nationwide in Japan. Descriptive information, however, unveiled unsatisfactory outcomes associated with pediatric MVP (1). Conversely, outstanding outcomes have been documented in adult cases, primarily attributed to the feasibility of prosthetic annuloplasty rings (AR) (2). AR restores the physiologic saddle-shape and normal size of the annulus, representing a fundamental principle of MVP in adults. Nevertheless, commercially available AR are frequently oversized for use in growing children.

AR have rigid, flexible, or semi-rigid variations. Specifically, the semi-rigid AR demonstrates notable efficacy in restoring a saddle-shaped annulus. Typically, it consists of an inner metal component, such as stainless steel or titanium, encased in fabric to provide a cuff for sutures. While materials like titanium exhibit strength, lightness, and corrosion resistance, it is important to note that titanium does not possess the ability to grow in size. Hence, even if a smaller-sized annuloplasty ring could be produced using a metal, it would impede annular growth and necessitate a second surgery for retrieval. On the other hand, if AR were manufactured using biodegradable polymers (BDP), they could potentially ensure both long-term prevention of regurgitation and stenosis. In the field of orthopedics, BDP have already been employed as an alternative to titanium as a material for implants. Following this concept, we tried to develop a semi-rigid AR for the mitral valve in small children, utilizing BDP. The expectation is that the semi-rigid AR made from BDP would undergo gradual degradation and

Table 1. Brief overview of the differences between Poly L-lactic acid, poly ε-caprolactone, and polyglycolic acid.

	PGA	PLLA	PCL
Source	Synthetic (petrochemicals)	Natural and synthetic (corn starch)	Synthetic (petrochemicals)
Mechanical Properties	High strength but can be brittle	High strength and stiffness	Flexible with a lower module than PLLA
Degradation Rate	Rapid degradation	Slow degradation	Slow degradation (slower than PLLA)
Applications	Sutures, tissue scaffolds	Medical implants, sutures, devices	Drug delivery, tissue engineering
Biocompatibilitye	Generally biocompatible	Generally biocompatible	Generally biocompatible

PGA, Polyglycolic acid; PLLA, Poly L-lactic acid; PCL, Polu ε-caprolactone

absorption while facilitating remodeling of the mitral annulus. This approach aims to prevent the development of stenosis over time. In this article, we conducted a literature review using the medical literature reference site PubMed to systematically explore potential BDP suitable for AR, and to examine the mechanical and degradation characteristics of these BDPs. Additionally, we detail the construction method of our newly developed AR specifically designed for children.

Potential BDPs to be used for AR
Recently, BDP have gained widespread use in the manufacturing of biomedical devices. They have been demonstrated to possess favorable biocompatibility, controlled degradability, excellent processability, and appropriate mechanical strengths. Advancements in fabrication techniques have enabled the swift construction of scaffolds using various BDPs, with the added advantage of not being restricted by specific shapes (3). Commonly used BDP are mainly alpha-hydroxy acids such as poly glycolic acid (PGA), poly lactic acid (PLA), poly ε-caprolactone (PCL), polydioxanone, polyhydroxylbutyratevalerate, polyacetyglutamic acid, polyorthoesters, polyethylene oxide, polybutylene terephthalate, and others. Among these, sutures made of PGA were the pioneering clinical devices crafted from BDP, appearing in the market during the 1970s. Several decades following the first PGA sutures, technological advancements have evolved, allowing for the customization of BDP to fulfill specific requirements for emerging fields, notably in the development of tissue-engineered products. Throughout these advancements, PLA, PGA, and PCL continue to be the cornerstone of synthetic BDP used in the fabrication of clinical products (4). PLA is a chiral molecule which exists in two enantiomeric forms: L-lactic acid (PLLA) and D-lactic acids (PDLA). PLLA is predominantly crystalline and therefore could be a substrate for medical devices, as opposed to PDLA which is chiefly amorphous. These polymers are appealing due to their outstanding biocompatibility, degradability, and versatile physiochemical and mechanical properties.

These are the reasons PLLA have been extensively used in the field of orthopedic, dermatological (5), and cardiovascular medicines encompassing biodegradable stents (6). A brief overview of the differences between PGA, PLLA, and PCL is listed on table 1.

Degradation rate of BDP
The strategic arrangement of various polymers, aimed at regulating biodegradation time, holds particular significance in facilitating the normal growth of the mitral valve annulus. The degradation rate of BDP is primarily influenced by their hydrophilicity. For example, PLLA is relatively hydrophobic, and thus is highly biostable. In the in vivo study, the geometrical shape and original height of the PLLA cage were preserved throughout the six-month follow-up period. The mechanical strength was also maintained for a period of six months in vitro. At 12 months, the PLLA cage had been disintegrated into multiple fragments with signs of absorption (7). This is in contrast to PGA, which, being less hydrophobic, undergoes faster degradation within 5-12 months compared to PLLA, despite the latter's higher crystallinity (8, 9). PCL is a semi-crystalline material, initiating degradation primarily in the amorphous regions, while the crystalline regions remain intact for a more extended period. This characteristic contributes to the prolonged maintenance of mechanical properties. Following the degradation of the amorphous segments, the cellular activity proceeds to degrade the crystalline regions, leading to fragmentation and a subsequent decrease in mechanical properties. Depending on its molecular weight, PCL as a homopolymer exhibits degradation times ranging from 2-4 years. Due to its slow rate of degradation, PCL is well-suited for use in long-term implantable devices (8).

The strength of BDP
BDP changes their shape by different temperature. It starts melting above the melting temperature (Tm). Below the glass transition temperature (Tg), the polymer chain assumes a more rigid, glassy state, contributing to the material's plasticity. Tg is proportional to the stiffness of the polymer chain: the softer the polymer chain, the

lower the Tg. The Tm and Tg of PLLA are about 70 and 67 degrees, respectively. The strength of a polymer is characterized by the collective resistance from both internal and external molecular interactions against external forces, leading to the initiation of molecular displacement. Generally, higher interaction forces correlate with a higher Young's modulus, which is represented by the slope of the initial linear elastic deformation in the stress-strain curve. The tensile strength for PLLA is reported to be 11.4 to 72 MPa, while flexural strengths were 45 to 145 MPa. The initial tensile strength and modulus are reported to be 60.3 MPa and 3.7 GPa. The Tm and Tg of PGA is reported to be 225-230°C and 35-40°C, resulting in a high tensile modulus. The strength of PGA and PLLA, therefore, could be comparable with that of pure titanium, whose Young's modulus of elasticity is about 100GPa (10). On the other hand, PCL has a low tensile strength ranging between 10 and 27 MPa, but an extremely high elongation at breakage (>700%) (11). It is a semi-crystalline polyester and properties of low Tg (-60°C), low Tm (56-65°C), and high thermal stability (12).

Blending of BDP (Copolymerization)

Both PLLA and PCL have the capability to copolymerize with other monomers or blend with additional polymers, allowing for the enhancement of certain material properties. In particular, composites involving PCL blended with other polymers have found wide application in various settings, notably in tissue engineering, owing to the material's processability that facilitates the creation of diverse scaffold architectures (13), and has been used for many biomaterials (14). It offers an advantage in the construction of implants with specific shapes through the 3-dimensional melt-plotting technique, primarily due to its thermal stability in the molten state (12), possessing porous structure which allows cell anchoring and vascularization (15). Furthermore, its mechanical properties are recognized to be modifiable through the incorporation of other biodegradable fibers. Particularly, there have been thorough investigations into the synthesis and degradation behavior of the copolymer composed of PLLA and PCL. Blending PCL with PLLA is acknowledged to enhance the fracture strength of PCL (16). In the study, the tensile strength of PCL was reported to be 19.3 MPa. Additionally, the tensile strengths of copolymers consisting of 50%, 75%, 85%, and 95% PLLA were measured at 0.6, 19.0, 22.1, and 47.6 MPa, respectively (17). Conversely, blending with PCL is recognized to enhance the flexibility of PLLA (18). Moreover, this copolymer demonstrated an accelerated degradation rate when contrasted with the PCL homopolymer. Research has shown that initially, PLLA segments undergo degradation, leaving behind segments of PCL. This phenomenon results in PCL maintaining its structural integrity for a prolonged period (19). The PLLA-PCL copolymer, akin to the PCL homopolymer, has demonstrated the ability to form 3-dimensional structures without restrictions in shape. Furthermore, its surfaces exhibit decreased platelet adhesion and an enhanced proliferation of fibroblast cells (20).

Design of the biodegradable ring (Figure 1-3)

Based on the insights discussed above, we endeavored to fabricate an AR replicating the configuration of commercially available counterparts. This involved utilizing 3 commonly employed biodegradable polymers: PGA, PLLA, and PCA. Concerning the inner support medium, a copolymer of PCA and PLLA was selected. This choice was motivated by the fact that using PLLA as a homopolymer would not confer the flexibility
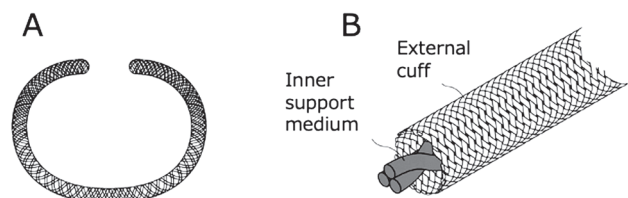

Figure 1. Diagram illustrating the ring configuration: The inner support medium is composed of a copolymer of poly ε-caprolactone and L-poly lactic acid. The external cuff is a blade material woven with 16 sets of polyglycolic acid sutures.
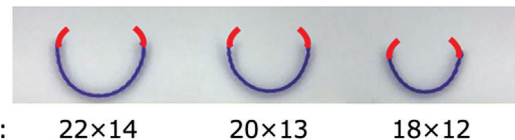

Figure 2. Image of annuloplasty rings featuring various sizes, dyed with two colors. The orange segment has undergone heat processing to prevent fraying and does not contain an inner support medium. This section is pliable, potentially efficient in preventing erosion to the aortic tissue, and can be trimmed if redundant. The purple segment contains the inner support medium.
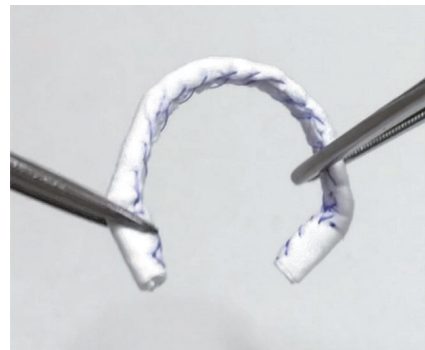

Figure 3. Image of an annuloplasty ring showcasing a certain degree of flexibility.

comparable to metals like titanium. Hence, our objective was to copolymerize PLLA with PCL, the softer material, to attain a balance of flexibility, sufficient strength, and suitability for tissue ingrowth. Drawing from the preceding discussions, we extrapolated that the assumed absorption rate of the PLLA-PCL copolymer should extend beyond 6 months. This duration is deemed sufficient to ensure the remodeling of the valve annulus. We hypothesized that a favorable mean molecular weight of the copolymer should be within the range of 200 to 800kDa. We also hypothesized that the size of the reinforcing rod should be within the range of 0.3 to 0.8 mm. Based on these assumptions, we decided to employ 3 sutures sized #2 (as per the United States Pharmacopeia standards). These sutures were crafted from a PLLA/PCL copolymer blend at a molar ratio of 3:1. The aforementioned sutures were bundled together and coiled around the saddle-shaped mold rod. Following heat processing at a temperature of 120°C for 3 hours, a reinforced saddle-shaped rod with a diameter of 0.6mm was successfully produced. For the external cuff, we employed the blade weaving technique—a distinctive method to produce a soft and bulky suture material crafted from PGA. This choice was made to facilitate smooth needle insertion. As discussed earlier, it is known that PGA degrades at a faster rate compared to the PLLA/PCL copolymer. We believe that the complete absorption of the outer cuff should precede that of the inner rod. This sequencing is deemed necessary to prevent irregular scar formation around the ring. A blade material weaved with 16 sets of PGA sutures (size 50D), resulted in an internal diameter of 2mm and area density of 0.55mg/mm^3. The internal rod was placed inside the PGA blade, and both ends were heat processed at a temperature of 230 C° for 10 seconds to prevent fraying.

Utilizing this AR, we initiated an in vitro experiment employing the following method. Initially, we detached the porcine mitral valve with attached chordae tendineae and papillary muscles, installing it in a simulator tank to create an explanted heart test model. Subsequently, we elongated the posterior leaflet in the longitudinal direction, resulting in the development of a mitral valve regurgitation model with an approximate regurgitation fraction of 40% when integrated into a pulsatile circuit. Through the application of the present AR, we conducted MVP and identified the device's effectiveness through the reduction of the regurgitation fraction.

Future prospect of the clinical use

The mechanical properties and degradation rate of this AR should be assessed using animal models, followed by necessary modifications based on the observed outcomes. Extrapolating from the data on PGA, PLLA, and PCL, it is anticipated that the present AR will undergo absorption over a period ranging from 6 months to several years. The adequacy of this time period to ensure

remodeling of the annulus remains uncertain due to the absence of objective data from MVP cases in growing children. Nevertheless, it is worth noting that this AR should not impede the growth of the annulus, given its expected absorption within several years. Moreover, an ideal biodegradable artificial ring should exhibit mechanical properties, including radio force, that are comparable to those of a metal ring. For example, flexibility range of titanium is 7.6mm and 2.4mm in the septal-to-lateral and commissure-to-commissure direction in a size 32 Physio I Annuloplasty ring (Edwardes Lifesciences, Irvine, CA, USA.) (21). This flexibility is particularly crucial for stress adaptation, helping to mitigate the risk of ring dehiscence. On the other hand, the elastic modulus of BDP materials can differ from that of metals. For instance, there is a report indicating that a PLLA composite possesses a flexural modulus that is 62% of that found in stainless steel (22).

Hence, additional adjustments to the mechanochemical characteristics of the AR may be necessary. For instance, the degradation rate of BDP can be altered by adjusting their size and shape (23), and the strength loss during a specific period is often considered to be proportional to the diameter of the material (24). Also, the strength of BDP can be modified through various methods beyond copolymerization. For example, polymers can be reinforced by incorporating other fibers, such as carbon or calcium phosphate. Also, the reinforcing fiber can be the same polymer itself (self-reinforcement) (25).

Finally, the potential for an inflammatory reaction to the product is a crucial concern, as it could lead to tissue overgrowth and scar formation. This, in turn, has the potential to fix the annulus and result in stenosis or clot formation. Clinical experience with devices implanted inside the cardiovascular system has been primarily focused on biodegradable stents (26, 27). Prototypes of biodegradable stents were produced from PLLA. The mixed results in inflammatory response and endothelial hyperplasia observed in both in vivo and in vitro studies highlight the complexity of evaluating the performance of biodegradable stents (28-31). Nevertheless, elucidating the absence of inflammation and tissue proliferation is crucial in ensuring the safety and efficacy of the present AR. Conducting a series of in vitro mechanical studies and in vivo microscopic evaluations is also essential for thoroughly assessing the performance and biocompatibility of this AR. While there are challenges to address before clinical use, the development of a biodegradable AR holds promise as a potential solution to enhance outcomes in pediatric MVP. In addition, the potential for eliminating the need for lifelong anticoagulation therapy with the use of this AR could offer significant advantages, not only in the pediatric population but also in adult patients.

Conflict of Interest

The annuloplasty ring presented in this paper was manufactured by Gunze Ltd. (Ayabe, Kyoto, Japan). The first author is the advisor for the product, but there is no conflict of interest for the author, and the work is not funded by the company.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors employed the assistance of the AT tool ChatGPT to enhance language and ensure grammatical accuracy. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's substance.

Abbreviations

AR, Annuloplasty ring; BDP, biodegradable Polymer; MVP, Mitral valve plasty; PCL, Poly ε-caprolactone; PGA, Polyglycolic acid; PLLA, Poly L-lactic acid; Tg, glass-transition temperature; Tm, melting temperature

References

1. Ando M, Takahashi Y: Durability of mitral valve repair performed before the age of 5 Years. Circ J 2016; **80:** 124-9.
2. Jassar AS, Vergnat M, Jackson BM et al: Regional annular geometry in patients with mitral regurgitation: Implications for annuloplasty ring selection. Ann Thorac Surg 2014; **97:** 64 - 70.
3. Vaquette C, Cooper-White J: A simple method for fabricating 3-D multilayered composite scaffolds: Acta Biomater 2013; **9:** 4599-608.
4. Gunatillake P, Mayadunne R, Adhikari R: Recent developments in biodegradable synthetic polymers. Biotechnol Annu Rev 2006; **12:** 301-47.
5. Leenslag JW, Pennings AJ, Bos RR et al: Resorbable materials of poly (L-lactide). VII. In vivo and in vitro degradation. Biomaterials 1987; **8:** 311-4.
6. Bittl JA: Deconstructing stent polymers. J Am Coll Cardiol 2014; **63:** 308-9.
7. van Dijk M, Tunc DC, Smit TH et al: In vitro and in vivo degradation of bioabsorbable PLLA spinal fusion cages. J Biomed Mater Res 2002; **63:** 752-9.
8. Middleton JC, Tipton AJ: Synthetic biodegradable polymers as orthopaedic devices. Biomaterials 2000; **21:** 2335-46.
9. Nakamura T, Hitomi S, Watanabe S et al: Bioabsorption of polylactides with different molecular properties. J Biomed Mater Res 1989; **23:** 1115-30.
10. Brown SA. Vandergrift J: Healing of femoral osteotomies with plastic plat fixation. Biomater Med Devices Artif Organs 1981; **9:** 27-35.
11. Nair LS, Laurencin CT: Biodegradable polymers as biomaterials. Prog Polym Sci 2007; **32:** 762-98.
12. Chandra R, Rustgi R: Biodegradable polymers. Prog Polym Sci 1998; **23:** 1273-335.
13. Sun B, Long YZ, Zhang HD et al: Advances in three-dimensional nanofibrous macrostructures via electrospinning. Prog Polym Sci 2014; **39:** 862-90.
14. Woodruff MA, Hutmacher DW: The return of a forgotten polymer—polycaprolactone in the 21st century. Prog Polym Sci 2010; **35:** 1217-56.
15. Seyednejad H, Gawlitta D, Dhert WJ et al: Preparation and characterization of a three-dimensional printed scaffold based on a functionalized polyester for bone tissue engineering applications. Acta Biomater 2011; **7:** 1999-2006.
16. Shibata A, Takase H, Shibata M: Semi-interpenetrating polymer networks composed of poly(L-lactide) and diisocyanate-bridged 4-arm star-shaped ε-caprolactone oligomers. Polymer 2014; **55:** 5407-16.
17. Wehrenberg RH: Lactic acid polymers: strong, degradable thermoplastics. Mater Eng 1981; **94:** 63-6.
18. Li S: Hydrolytic degradation characteristics of aliphatic polyesters derived from lactic and glycolic acids. J Biomed Mater Res 1999; **48:** 342-53.
19. Huang MH, Li S, Vert M: Synthesis and degradation of PLA-PCL-PLA triblock copolymer prepared by successive polymerization of ε-caprolactone and DL-lactide. Polymer 2004; **45:** 8675-81.
20. Kim SI, Lim JI, Lee BR et al: Preparation of lotus-leaf-like structured blood compatible poly(ε-caprolactone)-block-poly(L-lactic acid) copolymer film surfaces. Colloids Surf B Biointerfaces 2014; **114:** 28-35.
21. Skov SN, Ropcke DM, Tjornild MJ et al: Semi-rigid mitral annuloplasty rings improve myocardial stress adaptation compared to rigid rings: insights from in vitro and in vivo experimental evaluation. Eur J Cardiothorac Surg 2017; **51:** 836-43.
22. Zimmerman M. Parsons JR, Alexander H: The design and analysis of a laminated partially degradable composite bone plate for fracture fixation. J Biomed Mater Res 1987; **21:** 345-61.
23. Mauduit J, Bukh N, Vert M: Gentamycim/poly(lactic acid) blends aimed at sustained release local antibiotic therapy administered per-operatively. I. the case of gentamycin base and gentamycin sulfate in poly(DL-lactic acid) oligomers. J Control Release 1993; **23:** 209-20.
24. Pellinen M. Pohjonen T, Tamminmaki M et al: The in vitro degradation of biodegradable self-reinforced (SR) polyglycolide rods. Trans Soc Biomater 1988; **11:** 562.
25. Laiho J. Mikkonen T. Tormala PA: Comparison of in vitro degradation of biodegradable polyglycolide (PGA) sutures and rods. Trans Soc Biomater 1988; **11:** 564.
26. Gao R, Yang Y, Han Y et al: Bioresorbable vascular scaffolds versus metallic stents in patients with coronary artery disease: ABSORB China Trial. J Am Coll Cardiol 2015; **66:** 2298-309.
27. Arroyo D, Cook S, Puricel S: Mechanisms of late and very late bioresorbable vascular scaffold thrombosis: is it only about flow? J Am Coll Cardiol 2016; **67:** 1259-60.
28. van Nunen LX, Zimmermann FM, Tonino PA et al: Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. Lancet 2015; **386:** 1853-60.
29. Tamai H, Igaki K, Kyo E et al: Initial and 6-month results of biodegradable poly-l-lactic acid coronary stents in humans. Circulation 2000; **102:** 399-404.
30. Onuma Y, Piazza N, Ormiston JA et al: Everolimus-eluting bioabsorbable stent–Abbot Vascular programme. EuroIntervention 2009; **5 Suppl F:** F98-102.
31. Verheye S, Ormiston JA, Stewart J et al: A next-generation bioresorbable coronary scaffold system: from bench to first clinical evaluation: 6- and 12-month clinical and multimodality imaging results. JACC Cardiovasc Interv 2014; **7:** 89-99.